RECENT ADVANCES IN HEPATOLOGY

Edited by
Howard C. Thomas
Roderick N.M. MacSween

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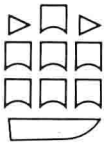

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Recent Advances in
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Preface

The disciplines of clinical science, pathology, biochemistry, immunology and molecular biology all impinge on the rapidly developing field of hepatology. It is therefore not surprising that clinicians find difficulty in evaluating the original publications and must increasingly rely on review articles written by experts within each discipline. For this, the first of a *Recent Advances in Hepatology* series, we have selected a group of contributors who are actively engaged in research in the topics on which they have written. We have asked them to review recent advances not only in the understanding of the pathogenesis of various liver diseases, but also in diagnostic techniques and management. We hope the monograph will provide a practical update for physicians, surgeons and pathologists involved in patients with liver disease, and will, in addition, stimulate interest in the research frontiers of hepatology.

London and
Glasgow, 1983

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Ian R. Mackay

INTRODUCTION

There are many chronic liver diseases in which genetic predisposition operates as an important contributing risk factor for disease, although in most instances this predisposition is multi-factorial and difficult to dissect, and the *modus operandi* of known genetic determinant(s) is usually poorly defined.

Of more particular importance, in terms of persons at risk, are the diffuse liver diseases of adult populations, chronic hepatitis and cirrhosis. The major contribution to these in developed countries is made by alcohol abuse, and in developing countries by chronic infection with hepatitis B virus (HBV), with co-factors such as undernutrition and mycotoxins being of possible relevance. Accordingly it might seem that the determinants of chronic liver disease, either in developed or developing countries, are predominantly environmental, yet it is clearly evident that only a proportion of individuals exposed to environmental hazards actually succumb to liver disease: hence ascertainment of the relative contribution of various genetic component(s) is a necessary, albeit formidable task. The autoimmune type of chronic hepatitis which affects Northern Caucasian populations exhibits the interesting association with HLA alleles B8 and DR3 of the major histocompatibility complex but genetic insights derived from study of this disease unfortunately cannot be extrapolated to chronic hepatitis affecting other populations in which such associations are lacking.

Of lesser importance numerically, but more clearly defined genetically, are the numerous liver diseases associated with metabolic errors, referable in most instances to an enzyme deficit preventing the assembly, degradation or excretion of a particular metabolite. Undegraded and often toxic metabolites may accumulate in extra-hepatic sites causing systemic diseases, with relative sparing of the liver or, less frequently, accumulate in the liver causing severe dysfunction and possibly provocation of a secondary inflammatory response with fibrosis, cirrhosis and eventual liver failure.

CHRONIC ACTIVE HEPATITIS (CAH)

HLA and disease associations: introductory survey

The major histocompatibility complex (MHC) on chromosome six in man is a segment of extraordinary interest and importance for theoretical and applied immunology — as witnessed by the attraction to this research area of the Nobel prize for Medicine in 1980. The reasons for this are the experimentally-defined associations in inbred animals (especially mice) between the magnitude of immune responses to antigens of limited heterogeneity and genes (immune response, Ir genes) of the MHC,[9] and the association in man between certain immunopathic diseases and HLA specificities.[25]

The more striking HLA associations with immunopathic diseases in Caucasians have involved a limited number of the B and DR locus antigens notably (i) HLA-B27 with ankylosing spondylitis and related spinal arthropathies (ii) HLA-B8 and DR3 with numerous organ-specific autoimmune diseases with a female predominance, these including chronic active hepatitis (CAH), and with coeliac disease which is due to an abnormal intestinal response to gluten, (iii) HLA-B7 and DR2 with multiple sclerosis, and (iv) HLA-DR4 with rheumatoid arthritis. In general, the HLA gene influence accounts for only a proportion of the risk for the associated disease, so that other genetic determinants acting independently of, or interactively with MHC alleles, together with environmental risks including infection, must be taken into account.

Heterogeneity of chronic active hepatitis

In considering the risk for disease attributable to any given genetic determinant, the problem of diagnostic homogeneity and subsets of disease assumes great importance. Examples include diabetes mellitus, divisible into insulin dependent (DR3 and DR4 associated) and non-insulin dependent types with further subgroups existing within these categories, myasthenia gravis, into young females with thymitis (B8 associated) and older males with thymoma, Sjögren's disease, into types without rheumatoid arthritis (B8 associated) and with rheumatoid arthritis, and CAH is a further example.

Chronic active hepatitis became identified in the 1950s, with extreme hyperglobulinaemia and later non-organ specific autoantibodies being early leads to immunological contributions to pathogenesis.[61] Most of the early (circa 1960) descriptions of the disease involved females derived from populations of Northern Caucasian origin, hinting even then at racial-genetic factors in pathogenesis. This classical or prototype form of CAH with immuno-serological abnormalities provided the basis for text-book descriptions, and for the definition adopted by the Fogarty-IASL nomenclature group even as late as 1976.[55] However the discovery of the hepatitis B surface antigen (HBsAg) and its association with acute and chronic hepatitis indicated that other types of CAH existed and indeed CAH is now considered to represent a spectrum of diseases: the similar histological appearances for all components of the spectrum of CAH[47] represent the composite 'white light', and the separate components of the spectrum are recognized by their disease-specific markers. Major subgroups of CAH include autoimmune, HBV-associated and cryptogenic categories; the proportion of cases in each category will vary considerably, primarily according to geographical area and, secondarily, by the interests of and referral patterns to a particular diagnostic centre.[45]

Autoimmune chronic active hepatitis

Autoimmune CAH is characterized serologically by high levels of IgG in serum, 25–80 g/l, and non-organ-specific autoantibodies. Antinuclear antibody (ANA) is present in most cases, with reactivity to double-stranded DNA in some 10% of cases,[100] and also frequent is anti-smooth muscle antibody (SMA), for which the main reactive constituent is actin.[65] There are no agreed-upon levels to separate 'background' from 'diagnostic' titres of ANA and SMA, although titres of 1/20 to 1/80 are often cited. A liver-specific autoantibody has not yet been identified but two candidates exist. One is liver-specific lipoprotein (LSP), a complex chromatographically-derived liver cell membrane preparation, and the other is an uncharacterized liver

membrane antigen (LMAg) which is separable chromatographically from LSP.[74] The frequency of reactivity and serum titres of anti-LSP were similar in HBsAG positive and negative cases of CAH,[50] but anti-LMAg has greater specificity for autoimmune CAH.[102]

Genetic determinants of autoimmune CAH

These include (a) female sex, (b) genes of the MHC expressed as HLA antigens, (c) Gm (immunoglobulin) allotypes, and (d) undefined inherited factors.

FEMALE SEX

Autoimmune CAH occurs most frequently and most typically in females aged 10–30, with a second peak of incidence among females aged 50–70.[60] The overall female sex excess of about 6 : 1 is equivalent to that for most other autoimmune diseases, and is in accord with evidence in humans and other species for a generally augmented humoral immune responsiveness in females,[68] exemplified by higher immunoglobulin levels, especially IgM, greater immunological responses to antigenic challenge, and higher 'background' frequency in normal populations of various autoantibodies. These various effects could be determined by an immunoregulatory gene on the X chromosome,[13] but are more probably attributable to modulating influences of estrogens or other sex hormones on the magnitude of immune responses.[106]

HLA ANTIGENS

HLA A and B. Mackay and Morris[66] reported a strong association between HLA-A1 (60%) and HLA-B8 (68%) among 37 patients with CAH (type unspecified, but mostly autoimmune), with the A1 effect attributed to linkage disequilibrium with B8. The significantly increased frequencies of these antigens compared with frequencies in 'other liver diseases' and/or healthy controls was corroborated for other populations of European origin.[62] Studies in Melbourne were later extended to include 48 cases, all specified as autoimmune-type CAH: 69% carried HLA-B8.[77] Freudenberg et al[32] from West Germany reported on 108 adult cases fulfilling criteria for autoimmune CAH and found a frequency of HLA-B8 of 82% and, relating this to the frequency of B8 among 5046 controls (19%), the relative risk (RR) for disease of HLA-B8 was 15.4. Eddleston and Williams[27] from England corroborated the increase in HLA-B8 and reported changes in frequency of other HLA specificities, in particular a significant decrease in HLA-B12 and an increase in HLA-B7; this decrease in B12 could in part be explained by the increase in B8, but the frequency of B12 decreased according to time from diagnosis, implying association with prejudiced survival, whilst the increase in B7 was among the longer surviving cases. Thus there could be multiple MHC-linked gene effects associated both with susceptibility to, and outcome of the disease.

HLA-C. HLA-C locus antigens were examined by Lepage et al[57] with the finding of an association between Cw7 and autoimmune CAH. Patients with HLA-Cw7 and DR3 had CAH and extrahepatic autoimmunity, whereas those with Cw7 but lacking DR3 had 'hepatitis-related' autoantibodies but lacked extrahepatic features.

HLA-D and DR. Opelz et al[81] reported on Dw antigens in 38 patients with 'chronic active liver disease' of whom 32 appeared to have autoimmune-type CAH; whilst there

was only a minor increase in HLA-B8 among their cases, the frequency of Dw3, 68%, was greatly increased over that, 24%, among the 91 controls, suggesting that the primary HLA association in CAH was with HLA-Dw3 rather than HLA-B8.

Serologically-defined DR locus antigens in CAH were first analysed in the 7th International Histocompatibility Workshop,[15] with cases (mostly of autoimmune type) contributed from Melbourne and London; the frequency of WiA3, later specified as DRw3 (now DR3), was significantly increased. Mackay and Tait[67] found the frequency of DR3 in 48 cases of autoimmune CAH to be significantly increased (74%, controls 32%), and DR2 was decreased. There was a high degree of co-occurrence between HLA-B8 and DR3, in that 31 of 33 cases positive for either antigen carried both B8 and DR3, representing a much stronger linkage disequilibrium than that existing in the normal population. Moreover, in 14 patients with CAH and positive for B8 and DR3, family studies showed that a haplotype containing B8 and DR3 was present in all 14, and an A1-B8-DR3 haplotype was present in 10. It remains uncertain, as for other DR3 and autoimmune disease associations, whether the DR3 gene product itself is the 'disease susceptibility gene' or whether this gene exists in linkage disequilibrium with the B8 and DR3 alleles.

There have been studies to ascertain whether the presence of HLA-B8 or DR3 per se would identify a particular subtype of CAH. In two studies, cases positive for HLA-B8 or Dw3 tended to be female and younger, and showed greater evidence for immunological disturbance and dependence on prolonged corticosteroid drug therapy, but differences from cases lacking these specificities were not definitive.[77, 81]

Subsequently data from the 8th Histocompatibility Workshop[104] indicated, in autoimmune CAH, that HLA-B8-DR3 had a considerably higher frequency (82%) among females aged less than 30 years with positive tests for 'hepatitis-related' autoantibodies, ANA and SMA, than among older females with autoimmune CAH, and a similar conclusion was reached at the 2nd Asia-Oceania Histocompatibility Workshop.[105] Thus autoimmune CAH itself may be heterogeneous, with a group of young females with a very high frequency of B8-DR3, and a less typical group of older females with a lower frequency of B8-DR3.

Explanations for the HLA associations with disease. Such explanations must accommodate the wide range of immunopathic disorders involved, and the antigens, extrinsic or 'self', of greatly differing specificities with which these diseases are associated. For HLA-B27 associated diseases which predominate in males and appear to be associated with a lacunar type of immune deficiency, the idea of molecular mimicry or cross-tolerance is attractive.[25] For HLA B8-DR3 associated autoimmune diseases which predominate in females and are associated with immune dysregulation the activity of an 'immune response gene', represented by the HLA-DR gene product, could provide the basis for an explanation, along one of the two following lines. *First*, such gene(s) could express on the surface of antigen-presenting cells a product (Ia molecule) with which a disease-provoking antigen becomes associated, and this stimulates T helper cells to respond to that antigen, on the basis that deletional tolerance of T cells to the disease-provoking autoantigen had failed to occur. *Second*, there is defective immunoregulation in at least certain of the diseases associated with high frequencies of HLA-B8-DR3, so that these specificities could be associated with inherited and possibly familial defects in the activity of suppressor T cell regulation of immunological responses.[1, 27]

The latter possibility has been investigated in relation to CAH, but with indecisive results. Galbraith et al[35] reported on magnitude of titres of antibodies to viral antigens (rubella, measles), bacteria (E. coli) and tissue antigens (nuclei, smooth muscle) in 57 patients with CAH, mostly HBsAg negative. Except for antibody to E. coli, titres of these antibodies were higher in cases positive for HLA-B8 and/or B12, attributable to a genetically determined increase in immunological responsiveness for which HLA-B8 and B12 were markers, or to the association of HLA-B8 with defective immune suppressor cell activity. Lindberg et al[59] reported on 43 cases of mostly HBsAg negative CAH compared with healthy controls for antibody titres against various viral antigens and tetanus toxoid and found significantly higher titres against measles and polio type 2 and 3, but no differences for various other viral antibodies including rubella; there was no correlation between antibody levels and HLA-B8 and/or B12. Krawitt et al[52] studied 32 patients with CAH, of different aetiologies; there was a low overall frequency of HLA-B8, only 5/24 for HBsAg negative cases; suppressor T cell activity did not differ significantly from controls, and neither HLA-B8 nor B12 influenced the suppressor activities studied.

Possibly of more relevance to CAH would be antigen specific modulatory effects associated with HLA alleles, but information on this is scanty. Vogten et al[109] reported a significant association between HLA-A1, B8 and Dw3 and cellular immunity to LSP measured by a rather unconventional assay, lymphocyte-mediated cytolysis of LSP-coated avian erythrocytes. In a study in our own laboratories (Frazer and Mackay, unpublished) no association between HLA-B8 or DR3 and the magnitude of the humoral response to LMAg could be shown.

GM ALLOTYPES — INTERACTIVE EFFECTS WITH HLA

Heavy chains of the immunoglobulin G molecule show allotypic variation due to amino-acid substitutions in the Fc portion of the molecule: the gene loci are known as Gm and specify a number of allelic variants. In mice, genes coding for the constant regions of Ig heavy chains may be linked with genes, V genes, which code for the variable (V) region of the immunoglobulin molecule to determine antigen-binding specificity[69] and, in man, genes coding for Gm allotypic variants could likewise be in linkage with V genes which specify antibody reactivity. There are two studies in which Gm types were correlated with the magnitude of responses to bacterial antigens, flagellin and S. typhi, cited by Mackay et al,[68] and there are associations between particular Gm types and immunopathic diseases, notably myasthenia gravis,[79] thyrotoxicosis,[31] multiple sclerosis[82] and autoimmune CAH.[110]

In autoimmune CAH, Gm phenotypes of serum IgG molecules were established by haemagglutination-inhibition in 50 patients and 180 controls; the markers tested for were G1m (f, z, a, x) and G3m (b0, b1, b3, b5).[110] In this study the statistical analysis of the association of HLA and Gm antigens with disease involved log-linear models fitted to multidimensional contingency tables, and procedures were developed to analyse the three factor interaction of disease risk affected by non-additive effects of HLA and Gm. The series was 'typical' in that females predominated five to one, 80% of the 50 patients were positive for HLA-B8 compared with 26% of 180 healthy controls (RR = 11.6), and 85% of 39 patients typed were positive for DR3 compared with 32% of 119 healthy controls (RR = 11.7). There was an excess of patients with the Gm phenotypes a + x + b +, with an RR for the Gm a + x + haplotype of 2.3; further

analysis showed that the association of disease with Gm a + x + b + was confined to patients positive for HLA-B8, observed = 16, expected = 5.2. Statistical analyses showed that the effect of Gm a + x + on disease was highly significantly influenced by HLA-B8, and vice versa.

Interactive effects of HLA and Gm gene products on susceptibility to disease could be explained at the cellular level by suggesting that the magnitude of an immune response depends upon the association of antigen with cell membrane structures coded by MHC (Ir) genes expressed on antigen producing cells and stimulatory to helper T cells, and recognition of antigen by lymphocyte receptors on B cells coded by immunoglobulin V genes. Thus, the specificity of the interaction of HLA-B8 with Gm a + x + in CAH may reflect the specificity of recognition of separate determinants on the antigen molecules presumed to initiate the autoimmune process. In other words, products of genes linked to the HLA-B8-DR3 haplotype associate on the surface of antigen-presenting cells with certain determinants of initiating antigen(s) in such a way as to facilitate an appropriate recognition of other antigenic determinants by products of Gm a + x + linked immunoglobulin V genes.

UNDEFINED INHERITED FACTORS

Family studies to ascertain immune dysfunction. Although multiple cases of CAH within families are quite infrequent, there is good evidence based on case studies for a familial disturbance in immune function in chronic hepatitis,[19] and there are several reported pedigrees (cited by Mackay[63]) wherein patients and family members had various non-hepatic immune-mediated diseases. In two studies, from England[35] and Finland,[92] first-degree relatives of patients with CAH and primary biliary cirrhosis were investigated for associated diseases and various autoantibodies, anti-mitochondrial antibody (AMA), SMA, ANA and microsomal antibodies of thyroid and gastric parietal cells: the mild excess of some of these autoantibodies in the CAH relatives is indicative of an inherited instability of general tolerogenesis or immunoregulatory control. Studies are needed on CAH relatives to ascertain whether autoantibodies are associated with specific HLA types, and for the existence of suppressor cell defects as in SLE.[75]

Hepatic determinants. Genetically-determined characteristics within the liver itself might represent susceptibility factors for chronic liver disease by rendering the liver more vulnerable to injury, since studies in mice show that there are marked differences among strains in susceptibility to the hepatotoxin, carbon tetrachloride (CCl_4).[10, 42] Detailed genetic studies using recombinant mice point to H-2 and non H-2-linked determinants of the different suceptibility of mouse strains to CCl_4-induced liver damage.[7]

HBV-associated chronic active hepatitis

The clinical expression of HBV-associated CAH is similar to that of the autoimmune type of CAH, except for a greater frequency of indolent or subclinical forms of the disease and a less predictably favourable response to treatment with prednisolone. Histological appearances are similar, with the only indication of the origin of the disease being histological evidence of HBsAg in hepatocytes.

Male sex

This is the major genetic determinant for HBV-associated CAH, with males comprising 80–90% of cases.[39]

HLA antigens

Studies on HLA in HBV-associated CAH have been a little inconsistent; reports, reviewed by Mackay[62] and Penner et al,[85] cited normal frequencies of HLA phenotypes. HLA-B8 may be decreased, in contrast to the increased frequency in autoimmune CAH, and the population frequency of HBV-associated CAH is certainly greatest among those populations in which HLA-B8 is lowest. Italians with HBV-associated CAH had an increased frequency of A3 and B35, with the phenotypic association of A3-B35 being increased from 6% to 28.5%[71] whilst increased frequencies of HLA-Bw15, Bw17 and Bw35 were found among HBsAg-positive haemodialysis patients not grouped according to liver histology.[43] Giani et al[36] failed to show significant associations of HLA among Italians with HBV-associated CAH but did find a definite increase in Bw15 (RR 5.8) in asymptomatic HBsAg carriers, suggesting an association of Bw15 with non-clearance of HBsAg but not with development of CAH. Penner et al[85] reported on 16 Austrians with HBV-associated CAH and found an increase in HLA-B35, 56% compared with 21% in controls, RR 4.79, and an increase in Cw4 which is in linkage-disequilibrium with B35; these authors also noted the raised frequency of B35 among German cases.[32]

Gm allotypes

Barr et al[5] found no association between Gm allotypes and the HBsAg carrier state, but reports on association between Gm types and HBV-associated CAH are lacking.

Familial predisposition

There may be genetic determinants for HBV-associated CAH other than male sex and HLA in view of the well-recognized aggregations within families of persons who are either carriers of HBsAg or have various types of HBV-associated liver disease, but such aggregations can readily be attributed to intrafamilial cross-infection, excluding the necessity to invoke inherited predisposition.

Cryptogenic chronic active hepatitis and cirrhosis

This category is certainly heterogeneous and may include cases related in some way to HBV infection, 'burnt out' cases of autoimmune CAH, undisclosed alcoholics and others; hence little comment can be made on genetic determinants. Cirrhosis per se may have familial determinants[70] but the nature of these is uncertain.

A small series of 17 cases of non-classified CAH was typed for DR specificities by Williams et al[112] and, since there were only three ANA positive cases, this could be regarded as a cryptogenic group. The frequencies of HLA-B8 and DR3 did not differ from controls, but the frequency of DR4 was highly raised, 70.6%.

Geo-epidemiology of CAH

The expression of liver disease among populations may be partly explained by genetic determinants such as genes for alpha$_1$-antitrypsin (vide infra) and HLA. Thus HLA-B8 exists in highest frequency in populations of Northern European origin,[91]

among which the autoimmune type of CAH occurs with the greatest prevalence, representative figures being 50–80 per million population based on data from Iceland[12] and Melbourne.[64] Southern European, African and Asian populations which lack the HLA-B8 and DR3 alleles have much higher carrier rates for HBsAg and presumably higher attack rates of, or susceptibility to HBV, and higher frequencies of the HBV-associated and cryptogenic types of CAH, and much higher frequencies of hepatocellular cancer. The expression of CAH was examined among two geographically and racially different populations, Australian cases of Northern European background and Yugoslav cases from Zagreb, of Southern European background.[84] The Australian cases were mostly of the autoimmune B8-DR3 positive type, whereas the Yugoslav cases were mostly cryptogenic or HBsAg positive, and their HLA profile resembled that of the normal population for HLA-B8 and DR3, but there was a mildly increased frequency of HLA-B35.

DRUG-INDUCED LIVER DISEASE: TOXICITY AND HYPERSENSITIVITY

A variety of damaging reactions in the liver can follow exposure to medicinal drugs, and these are broadly classified into those resulting from a directly toxic effect of the drug and those resulting from one or another type of idiosyncratic reaction, including hypersensitivity. For either type there are very few genetic studies available in man, although data are available from studies in animals pointing to genetic determinants of toxic liver injury.[7, 10, 42]

Drug-induced acute hypersensitivity

An interesting pointer to genetic predisposition to acute hypersensitivity hepatitis exists for halothane hepatitis which occurred in three pairs of closely-related women, mother-daughter, sister-sister and cousin-cousin, all with a Mexican-Indian or Mexican-Spanish ancestry;[46] in the discussion of the paper, a fourth pair (mother-daughter) was cited. No genetic markers were reported on in this study. Genetic determinants operative in hepatitis induced by halothane and other drugs could include female sex, and pharmacogenetic differences in drug metabolism.

Drug-induced chronic active hepatitis

This infrequently occurring subgroup of CAH is characterized by resolution of the disease on withdrawal of the inciting drug, with those incriminated including oxyphenisatin (now generally unavailable), alpha methyl dopa, nitrofurantoin, isoniazid, and sulphonamides.[65] By anaology with drug-induced SLE, genetic associations would be expected since hydralazine-related lupus is associated with slow-acetylator status and the HLA phenotype DR4.[86] There are similar associations for the drug-induced and autoimmune types of CAH, in that Lindberg et al[58] found a predominance of females (10:3), and a slightly raised frequency of HLA-B8 (41.7% controls 23.2%) for 13 patients and, in single case studies (to which little weight can be given), HLA-B8 was present in liver disease induced by nitrofurantoin[41] and by perhexiline maleate.[23]

PRIMARY BILIARY CIRRHOSIS (PBC)

Primary biliary cirrhosis (PBC) is an autoimmune disease of the liver which occurs characteristically in middle-aged females and which affects the bile duct epithelium