Leading Article

The Chianciano Conference to redefine chronic liver disease

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Introduction

The Fogarty International Center was established in 1968 as a memorial to Congressman John E. Fogarty of Rhode Island, who wished to extend the internationalism of medicine based on the high academic standards of Bethesda's National Institutes of Health. One of their many projects was to standardize the nomenclature, diagnostic criteria and diagnostic methodology of diseases of the liver and biliary tract. This study produced an outstanding monograph, which led to international agreement and enabled the world to compare disease incidence, results of preventive measures, and responses to treatment on an international scale not previously possible.^{1,2} But this seminal publication was as long ago as 1976, and much has happened since then. It was therefore, time for another conference with modern nomenclature and criteria for the world. This was the task given to 24 world experts on the liver meeting in September 1989 in Chianciano Thermal Spa, Italy. They were divided into small groups of five persons, and each group contained a clinician, histologist and a chemical pathologist or immunologist. Each group went into secret session to analyse just one topic but in exhaustive detail. The Chairman of each group then presented an updated profile to all 24 liver specialists so that they could analyse and criticise each update. This consensus is reported here in broad outline for the general reader. The details will appear as an international monograph and as the voice of authority for the 1990s.

Chronic autoimmune hepatitis CAH

CAH is a form of chronic hepatitis distinguished by the presence of significant titres of circulating tissue autoantibodies. It occurs most frequently in amenorrhoeic females aged 15 to 25 years and there

is also a menopausal form of the disease. It presents as asymptomatic jaundice or it may mimic acute virus hepatitis (Table 1). Hyperbilirubinaemia is accompanied by serum transaminase levels which are increased tenfold, by a polyclonal gammopathy, and by antinuclear antibody titres of 1:40 or above, homogenous in type. An interesting variant is distinguished by the presence of circulating antibody against liver-kidney microsomes (LKM1).³ Histology reveals non-specific inflammation with a predominance of plasma cells, submassive necrosis, liver cell rosettes, and there may be a coexistent hepatic cirrhosis. There is a rapid good response to corticosteroid therapy, a fact which is diagnostically helpful. With treatment, jaundice disappears, menstruation is often re-established, the serum transaminase level falls, but progression to cirrhosis is not halted. Its aetiology is unknown, but there may be several background factors, particularly the soil or terrain in which it develops. It is more frequent in females, suggesting an endocrine factor, and it has affinity with HLA-DW3. A virus may be a trigger factor, it is associated with high titres of circulating measles antibody and measles nucleic acid in hepatocytes. It may be associated with or overlap with other autoimmune diseases, such as Hashimoto thyroiditis, diabetes, ulcerative colitis, pulmonary infiltrates and allergic capillaritis. Finally the LKM1 variant is associated with derangement of P450 in the liver, pointing to yet another genetic factor in its background.

Primary biliary cirrhosis (PBC)

PBC is a chronic liver disease of unknown aetiology characterized by chronic granulomatous destruction of the small intrahepatic bile ducts, leading towards cirrhosis. It occurs most frequently in women of the childbearing years of life, and it is characterized by high titres of mitochondrial antibodies, twofold elevation of alkaline phosphatase and raised IgM. It may be asymptomatic

Table 1 A comparison of autoimmune (lupoid) and chronic viral hepatitis

<i>Features</i>	<i>Autoimmune</i>	<i>Viral</i>
History of blood transfusion	No	Yes
Sex	Predominantly female	Either
Age (years)	15 to 25 or menopausal	Any
Amenorrhoea	Frequent	No
Tenfold elevation of serum transaminase	Yes	No
Yo-yo transaminases	No	Yes
Autoantibodies	> 1:40	Absent
LKM antibody	May be present	Absent
Viral hepatitis markers	Absent	Positive
Overlap autoimmune disorders	Thyroiditis Diabetes Ulcerative colitis Rashes Pulmonary infiltrates	No
Corticosteroid therapy	Rapid Good but transient	None or modest
Histology	Plasma cells Liver cell rosettes	Mononuclears Polymorphs Lymphocytes Kupffers + +
Prognosis	Dead in five years – Untreated 60% – Treated 15%	Hepatitis B progresses to cirrhosis and hepatocellular carcinoma

or present with jaundice and pruritus. It may overlap with other autoimmune disorders including scleroderma, the sicca syndrome, Raynaud's phenomenon, thyroiditis and autoimmune hepatitis. There may be granulomatous involvement of lungs, bone thinning and skin xanthomas. There are two histopathological stages, namely precirrhotic and cirrhotic. The precirrhotic stage is characterized by focal destruction of small intrahepatic bile ducts, lysis of basement membrane, periductal granulomas, biliary piecemeal necrosis with cholestasis, bile accumulation, pseudoxanthomatous changes, and copper accumulation. At the cirrhotic stage, there is micronodular cirrhosis with portal-to-portal bridging, marked absence of bile ducts (pseudoxanthomatous change) and marked changes of chronic cholestasis. The diagnosis is established by the presence of mitochondrial antibodies which are increasing in variety and significance. They may be recognized by immunofluorescence, but special techniques are now also delineating anti-dot nuclear antibody, anti-M2, anti-PDC and anti-lamin antibodies. Predictors of a poor outcome are rising serum bilirubin, development of portal hypertension, hepatic decompensation, and association of anti-M2 with other complement-fixing antibodies against cytoplasmic antigens.

Primary sclerosing cholangitis (PSC)

PSC is a chronic hepatobiliary disease of unknown aetiology characterized by inflammation and fibrosis of the intra- and extra-hepatic bile ducts; it may progress to cirrhosis. It is most frequently observed in young men with inflammatory bowel disease complicated by mild jaundice. There may also be associated chronic pancreatitis, cholecystitis, cholelithiasis, retroperitoneal fibrosis, and thyroiditis. It is a premalignant condition for it predisposes to cholangiocarcinoma. Serological criteria include possible elevation of alkaline phosphatase, transaminases, IgG, IgA and IgM. Intermediate filament antibodies may be present in low titres, but mitochondrial antibodies are not observed. Cholangiographic imaging reveals characteristic beading. Histology shows narrowing of the lumen and marked fibrosis and inflammation of the extrahepatic bile ducts, progressive sclerosis of intrahepatic bile ducts with ultimate obliteration of the lumen. There may be duct ectasia, periportal fibrosis, periportal cholangiolar proliferation, biliary piecemeal necrosis and copper accumulation, micronodular cirrhosis with marked chronic cholestasis. The course may remain asymptomatic and benign for many years, or may be complicated by infective cholangitis, fluctuating progression,

presinusoidal portal hypertension and complicating cholangiocarcinoma.

Drug-induced chronic liver disease

Drugs may cause several different patterns of liver disease, such as fibrosis due to methotrexate, hypertrophy of ITO cells by hypervitaminosis A and alcohol-like hepatitis by amiodorone. However, two patterns of drug-induced chronic liver disease predominate, namely chronic active hepatitis (CAH) and chronic cholestasis (CC). CAH occurs following protracted administration of the drug in the course of months or years, whereas CC tends to occur within a month of drug administration. Cessation of the drug is usually followed by a slow recovery, and in the unfortunate event of incidental and unwitting rechallenge there is a discernible relapse of liver injury. Pointers to drug-induced liver disease include hypersensitivity skin reactions, eosinophilia, hepatic granuloma formation or the presence of giant cells. A positive lymphocyte transformation test is evidence incriminating the drug but a negative test does not exclude it from blame. Antibodies to nuclei or to smooth muscle may be present in low titres. LKM2 (liver, kidney, mitochondrial) antibodies are specific for tienilic acid-induced liver injury.

Alcoholic cirrhosis

Alcoholic cirrhosis develops in 10% of persons taking 160 grams of pure alcohol daily for 10 years and in 50% of those taking this quantity daily for 20 years. A daily dose of 10 grams is equivalent to 30 ml whisky, 100 ml wine or 250 ml beer. Women are more sensitive to alcohol than men so chronic liver disease is more readily discernible with smaller amounts of alcohol, say 100 grams daily. Women are also more likely to progress from alcoholic hepatitis to cirrhosis even if they stop drinking.⁴

Chronic viral hepatitis

New markers have been of great value in delineating chronic viral hepatitis and carriers, and in redefining a previously grey obscure zone of the

many different causes of chronic active hepatitis. There are several helpful serological markers (Table II). In the bad old days of last year, the term non-A and non-B (NANB) hepatitis covered those cases of virus hepatitis which were not due to hepatitis viruses A or B. This year the term hepatitis C (HCV) is now preferable since there is a specific anti-HCV serum antibody test. It will serve to define more accurately this type of chronic viral hepatitis, and it may reclaim patients who had hitherto been regarded as having chronic autoimmune hepatitis. Hepatitis C occurs in patients of all ages and both sexes, often following blood transfusion. Its progress is characterized by fluctuating levels of transaminase which rise and fall so often that the course has been aptly called 'Yo-yo transaminases'. The anti-HCV antibody test is a very lonely single marker at present and its presence must be interpreted with caution. It could mean past or present infection or a carrier state. It is hoped that it will soon be followed by a serological test for HCV antigen which will then help to clarify the significance of anti-HCV antibody.

Table II Significance of serological markers of viral hepatitis (after Sherlock 1989)²

Marker	Significance
Anti-HAV IgM	Acute hepatitis A
Anti-HAV IgG	Recovered from hepatitis A
HBsAg	Hepatitis B
Anti-HBe IgM high titre	Acute infectious hepatitis B
Anti-HBe IgM low titre	Chronic hepatitis B
Anti-HBc IgG	
- with negative HBsAg	Past exposure to hepatitis B
- with positive HBsAg	Chronic hepatitis B
Anti-HBs	Recovered from hepatitis B
HBsAg	Acute hepatitis B
Anti-HBe	Convalescence or continued infectious state
HBV DNA	Continuing infection
	Viral replication
HDV	Delta hepatitis
Anti-delta IgM	Chronic delta infection
Anti-delta IgG	Past delta infection
Anti-HCV	Chronic hepatitis C
	(not acute infection)
Anti-CMV IgM	Chronic cytomegalovirus hepatitis
Anti-EBV IgM	Chronic Epstein-Barr hepatitis

References

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