Who gets alcoholic liver disease : nature or nurture ? (extended abstract)

C.P. Day

University of Newcastle, Centre for Liver Research, Newcastle upon Tyne, UK.

Alcoholic Liver Disease (ALD) represents a considerable burden to the practising Clinician. Between 1988 and 2000, ALD was the commonest indication for orthotopic liver transplantation in Europe and remains the commonest reason for admitting patients with liver disease to hospital. Despite this burden, surprisingly little consensus exists in the field. In particular there is no consensus on disease pathogenesis and, as a result, on the factors that determine susceptibility. Most heavy drinkers will develop some degree of steatosis (fatty liver) but only about a third go on to develop alcoholic hepatitis and only between 1 in 4 and 1 in 12 progress to cirrhosis. The most obvious explanation for susceptibility to ALD is the dose and pattern of alcohol consumed. Epidemiological studies have certainly demonstrated that there is a linear correlation between the number of alcohol units consumed per day and the risk of liver disease and cirrhosis. However, in these studies, less than 6% of those taking the highest number of drinks per day had cirrhosis. Several other studies have shown that the pattern of intake is important, with disease risk increased by drinking alcohol away from meal times, drinking several rather than a single type of alcoholic beverage and drinking daily rather than weekend drinking. There has also been recent evidence that wine drinkers may have a lower risk of ALD than consumers of other alcoholic beverages but this may be due to confounding factors.

Mechanisms of liver injury and fibrosis related to alcohol intake can be divided into those involving increased gut permeability to endotoxin and subsequent release of intrahepatic cytokines, oxidative stress, arising as a result of alcohol metabolism and immune mechanisms directed at neoantigens arising as a result of alcohol metabolism and oxidative stress. With respect to exogenous factors based on these mechanisms, animal studies have provided some evidence that dietary factors are important, with diets high in polyunsaturated fat and iron and low in carbohydrates increasing risk, however this has yet to be reproduced in humans. A more obvious role for dietary risk has been suggested by two recent studies showing that obesity and associated type 2 diabetes increased the incidence of all stages of alcoholic liver disease in heavy drinkers. This was most striking for fatty liver, leading to the hypothesis that the association between obesity, type 2 diabetes and cirrhosis risk is likely attributable to the role of steatosis in the pathogenesis of more advanced liver disease. Further evidence supporting a role of steatosis in advanced disease has come from studies showing that the severity of steatosis on index biopsy predicts the subsequent risk of fibrosis and cirrhosis and from recent studies in animal models showing that a fatty liver is more sensitive to the effects of oxidative stress and endotoxin, suggesting that steatosis may be the "first hit" sensitising the liver to these "second hits". This suggests that genetic and environmental factors determining the degree of fatty liver would also be risk factors for advanced disease and there has been preliminary report that a low activity promoter polymorphism in the gene encoding microsomal triglyceride transfer protein, the principal protein for the export of fat from the liver, is associated with an increased risk of advanced ALD.

With respect to genetic factors, female gender is the most obvious "genetic" factor determining ALD risk with females developing ALD at a lower alcohol intake than men. This has been attributed to women having a lower volume of distribution for alcohol, although evidence from animal models has suggested that oestrogen may increase gut permeability to endotoxin. Evidence from twin studies has however suggested that non-gender-linked genetic factors may be important. This observation has lead to several case control studies of polymorphisms in candidate genes. Thus far there have been no replicated associations, however there is some supportive evidence for an association with a promoter polymorphism in cytochrome P450 2E1. Patients with this mutation and ALD have drunk considerably less alcohol in their lifetime than ALD patients with the wild type allele. This is consistent with the mutant allele increasing gene transcription. With respect to the endotoxin/cytokine cascade, there have been unconfirmed reports of an association between ALD and a polymorphism in the endotoxin receptor CD14, and, an as yet unconfirmed report of an association between ALD and the "loss-of-function" promoter polymorphism in the interleukin 10 (IL10) gene. This association is biologically plausible since IL10 is anti-inflammatory, anti-immune and anti-fibrotic. There has also been a weak association reported between alcoholic hepatitis and a

Correspondence : C.P. Day, Professor of Liver Medicine, University of Newcastle, Centre for Liver Research, Floor 4 William Leech Building, The Medical School, Franlington Place, Newcastle upon Tyne NE2 4HH, UK. E-mail : c.p.day@ncl.ac.uk.

polymorphism in the TNFα promoter region. Again this association has yet to be confirmed. The immunoregulatory role of IL10 has recently prompted studies of other "immune" genes and ALD susceptibility. There have been preliminary reports of an association between ALD and a "loss-of-function" mutation in the T cell molecule CTLA-4. This mutation has been associated with classical autoimmune diseases suggesting that the mutation is associated with an increased immune response. Supporting evidence that this association plays a role in pathogenesis has come from recent data that the presence of the polymorphism correlates with the degree of lymphocyte infiltration in liver biopsies from patients with ALD.