Natural History and Factors Influencing the Course of Alcohol-Related Liver Disease

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Although alcohol-related liver disease (ALD) may be seen to have a single clear precipitant in the consumption of alcohol, its pathogenesis is very much that of a complex disease with genetic, environmental, and behavioral factors influencing its clinical course. The clearest example of this is the fact that only a minority of those consuming hazardous quantities of alcohol develop clinically overt liver dysfunction. For instance, in an Italian cohort of unselected heavy drinkers, 20% to 30% had evidence of steatohepatitis on liver biopsy and only 10% had cirrhosis, with even fewer experiencing symptoms.¹ This does not mean that the majority of heavy drinkers are safe from the hazards of alcohol excess. Although liver disease has the closest association with alcohol, it accounts for a minority of the total morbidity attributable to drinking, which includes cancer, neuropsychiatric disorders, physical injury, cardiovascular disease, and stroke.²

For those who do develop ALD, ongoing heavy drinking is the primary determinant of clinical progression, and abstinence from alcohol offers the best chance of slowing, halting, or even reversing that progression. This was demonstrated in a large-scale epidemiological study of cirrhosis deaths in France in the 1930s and 1940s showing that cirrhosis mortality fell almost immediately when war interrupted the supply of alcohol.³

Histological History. The histological spectrum of ALD encompasses steatosis, steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) (Fig. 1). However, these features can coexist and are largely asymptomatic so do not correlate with distinct stages in clinical disease progression. A small number of serial biopsy studies tell us that patients with simple steatosis have an approximately 10% risk of cirrhosis and an 18% risk of fibrosis or cirrhosis after a median of 10 years, with the risk increasing to 30% to 40% if

alcohol intake remains above 320 g/week.⁴ Those with steatohepatitis have an approximate 50% risk of cirrhosis over a similar period.⁵

Clinical History. Once ALD patients have developed clinically overt disease, prognosis depends on the degree of liver dysfunction and associated complications but can still be improved by abstinence. In a Danish cohort of 466 patients with ALD cirrhosis, those with no complications had a 1-year risk of 12% for developing ascites, 6% for developing variceal bleeding, 4% for developing encephalopathy, and 10% mortality. The 5-year risk figures were 27%, 15%, 7%, and 22%, respectively. Patients with established complications had a higher mortality (31% at 1-year for ascites and variceal bleeding and 64% for encephalopathy).⁶ The 5-year risk of HCC is 7% to 16%, rising to 29% at 10 years.⁷

For patients who present with acute alcoholic hepatitis, the short-term outcome depends on the degree of liver dysfunction (discriminant function or Model for End-Stage Liver Disease), nutritional support and the response to any pharmacological therapy (Lille score) with mortality up to 75% in the most severe cases.⁸ In patients who survive an episode of alcoholic hepatitis, the natural history depends on abstinence from alcohol, the presence of cirrhosis, and persisting liver dysfunction. Sex also appears to play a role, as males who achieve abstinence have a low risk of progression to cirrhosis, whereas females have demonstrated progression even in the face of abstinence.⁹

Environmental Factors Influencing the Course of ALD

The most obvious environmental/behavioral determinant of ALD is the total dose of alcohol consumed. This has been demonstrated on an international level with a 1 L per capita

Abbreviations: ALD, alcohol-related liver disease; GWAS, genome-wide association study; HCC, hepatocellular carcinoma.

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FIGURE 1. Histological spectrum of ALD.

FIGURE 2. Environmental factors influencing the course of ALD.

difference in alcohol consumption correlating with a difference in cirrhosis prevalence of 14% for males and 8% for females.^{10,11} On an individual level, alcohol intake also correlates with risk of histological and clinical ALD, but the relationship is not simply a dose-dependent one, as only a minority of heavy drinkers have evidence of progressive disease.¹ This study identified an additional contribution from the pattern of alcohol intake, with those who drank only on the weekends displaying less advanced disease than daily drinkers, and those who drank with meals apparently protected relative to those who drank equivalent quantities outside mealtimes.

An effect of the type of alcoholic beverage has also been observed with wine drinkers shown to have a lower prevalence of advanced ALD than beer drinkers.¹² An elegant study of supermarket till receipts showed that this difference may not be due to the beverages themselves but rather due

FIGURE 3. Genetic polymorphisms implicated in the development of ALD. ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; GABRA2, gamma-aminobutyric acid receptor subunit alpha-2; IL-1 β , interleukin-1 β ; IL-10, interleukin-10; MTHFR, methylenetetrahydrofolate reductase; NF κ B1, nuclear factor of kappa light polypeptide gene enhancer in B cells 1; PNPLA3, patatin-like phospholipase domain-containing 3; SOD2, manganese superoxide dismutase; TNF α , tumor necrosis factor α .

to the differing dietary habits of wine and beer drinkers with those who purchased beer tending toward a higher-fat diet.¹³ High-fat/low-carbohydrate diets have been shown to associate with more advanced ALD,¹⁴ and all stages of alcohol-related liver injury are more common in patients with obesity.¹⁵ As with other fibrotic liver diseases, epidemiological evidence suggests that the risk of cirrhosis is increased by smoking and is reduced by drinking coffee, with four cups a day reducing the relative risk of cirrhosis to 0.2.¹⁶

ALD mortality has been observed to be higher in areas of increased social deprivation with differences that cannot be accounted for by alcohol intake alone.¹⁷ It is likely that some or all of the factors above contribute to this difference (Fig. 2).

Genetic Factors Influencing the Course of ALD

The increased risk of advanced ALD in women may be partially accounted for by a lower total volume of distribution leading to higher blood alcohol concentrations from equivalent consumption, but there is also evidence that estrogens can enhance inflammatory signaling mechanisms in alcohol.¹⁸ Evidence for non-sex-linked genetic determinants of ALD progression comes from twin studies which suggest that 50% of the risk is heritable, particularly when studied in younger cohorts^{19,20}; a proportion of this heritable risk is due to genetic determinants of alcoholism, but it is likely there is also a genetic predisposition to liver injury that would account for the observed ethnic differences in ALD susceptibility.²¹

FIGURE 4. Routes by which physicians may influence the course of ALD.

To date, all genetic studies in ALD have been case-control gene association studies where candidate genes were selected for study on the basis of their relevance to known mechanisms of alcohol-related liver injury. These fall into categories of alcohol consumption, oxidative stress, inflammatory response, fibrosis, and HCC and are summarized in Fig. 3. The associations identified by this strategy are generally weak and have not been reproduced in different cohorts.²² The more powerful technique of genome-wide association study

(GWAS) has yet to be applied to ALD, but a GWAS in non-alcoholic fatty liver disease identified an association between the I148M mutation in the PNPLA3 gene and advanced liver disease. A similar association has been demonstrated in four separate ALD cohorts, but the mechanism by which the polymorphism (which causes gain of function in the lipogenic enzyme adiponutrin) influences disease progression has yet to be elucidated. Interestingly, two studies have also demonstrated an association between this polymorphism and the development of HCC in ALD patients with cirrhosis.^{23,24}

Future studies are likely to explore the influence of gene-environment interactions (epigenetics) and the intestinal microbiome on the natural history of ALD.

Relevance to Clinical Practice

Although our understanding of the genetic influences on ALD might aid the development of future therapies, the environmental influences can inform clinical practice immediately (Fig. 4). These findings provide physicians and patients with further strategies to slow disease progression in addition to minimizing alcohol intake.

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