Who gets alcoholic liver disease : nature or nurture ? (Summary of the discussion)

P.P. Michielsen[1], D. Sprengers[2]

(1) Division of Gastroenterology, University Hospital Antwerp, Belgium ; (2) Division of Gastroenterology, St Augustinus Hospital, Antwerp, Belgium.

The State of the Art lecture of C.P. Day was essentially dealing with mechanisms of susceptibility to alcoholic liver damage. In the discussion, diagnostic and therapeutic management of alcoholic liver disease (ALD) was dealt with.

1. Susceptibility of women to alcohol

It is well recognised that women are more susceptible to alcohol than men. Men and women have similar sized livers, and when the rate of alcohol metabolism is normalised to liver mass, men and women have similar metabolic rates. However, blood alcohol levels after comparable doses of alcohol will usually be higher in women than in men because of their lower volume of distribution for alcohol. This is due to their lower body mass index and to fat consisting a higher percentage of their body mass than in men. Evidence from animal models has suggested that oestrogen increases gut permeability to endotoxin and accordingly upregulates endotoxin receptors of Kupffer cells leading to an increased production of tumour necrosis in response to endotoxin (1). Most worrisome, however, are recent reports that alcohol intake is increasing in adolescents, teenagers and young women, with the latter group particularly vulnerable to developing ALD.

2. What quantity of alcohol is toxic for the liver ?

One drink or unit contains between 10 and 15 g alcohol. It has been shown that significant liver disease can develop over time if more than 40 g alcohol per day in men or 20 g in females is taken (2). The time delay between start drinking and development of cirrhosis is usually in the order of 20 years. “Safe” limits of alcohol consumption for the liver are up to 2 drinks per day for women and up to 4 drinks per day for men with at least a three alcohol free days per week. The precise cut-off values for alcohol intake used to distinguish between alcoholic vs. non-alcoholic fatty liver disease (NAFLD) remain controversial. North American purists have used 0-7 units per week as cut-off, whereas European centres consider a use of up to 28 units per week still compatible with NAFLD. A cut-off of 14 units per week for both men and women can be considered as reasonable (3).

3. Evaluation of ALD

Although findings on the physical examination and laboratory tests may provide clues, the diagnosis of alcoholism depends on the history provided by the patients and their relatives.

Taking a full alcohol history can be time consuming. Fortunately, practical screening tests for alcohol dependence and abuse consisting of only a few questions (4) have been developed. One of the most commonly used questionnaires is the CAGE. It consists of only four items :

1. Have you ever felt you should **C**ut down on your drinking ?
2. Have people **A**nnoyed you by criticizing your drinking ?
3. Have you ever felt **G**uilty about your drinking ?
4. Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (**E**ye opener) ?

The acronym makes it easy for practitioners to remember the items that constitute it and to integrate them into a clinical interview. In general, the cut-off for the CAGE is two positive responses, but some authors recommend a cut-off at a single affirmative response. A limitation of this questionnaire is that while it is sensitive for alcohol dependence it is less sensitive for non-dependent heavy drinking.

Biochemical tests are widely used in diagnosis of liver diseases. In early ALD the AST/ALT ratio is > 2, whereas patients with NAFLD without fibrosis have a AST/ALT ration < 1. A AST/ALT ratio > 1 in NAFLD points to fibrosis (5,6).

Carbohydrate-deficient transferrin (CDT) is increased by excessive drinking. Its use as biochemical marker of heavy drinking was promising in early reports (7), however, recently it was found to be no more accurate

Expert : C.P. Day, Centre for Liver Research, Medical School, Newcastle upon Tyne, UK.
Moderators : O. Le Moine (ULB, Erasme), P. Michielsen (University of Antwerp).
Correspondence : P.P. Michielsen, M.D., Ph.D., Division of Gastroenterology, University Hospital Antwerp, Wilrijkstraat 10, B-2650 Edegem, Belgium. E-mail : peter.michielsen@uza.be.

than γGT, MCV and alcohol history. The specificity for CDT was 91%, a value substantially higher than γGT (18%) and MCV (66%), but the sensitivity was less for CDT (61%) than for γGT (85%) and MCV (70%) (8).

Mallory bodies have long be recognized as a cardinal feature of alcoholic hepatitis, but are also found in NASH.

4. Medical treatment of severe ALD

Many therapeutic agents have undergone clinical testing for alcoholic hepatitis.

- Colchicine has been suggested as a treatment for ALD because of its anti-fibrotic effects. Despite initial enthusiasm and biochemical rationale for use of this drug, it does not appear to be effective in ALD (9,10).
- Pentoxyfylline (Torental®) is a nonselective phosphodiesterase inhibitor which decreases the production of proinflammatory chemokines/cytokines, including TNF-α. A prospective randomised, double-blind clinical trial of pentoxyfylline 400 mg tid for 4 weeks in patients with severe alcoholic hepatitis improved survival and reduced the occurrence of the hepatorenal syndrome (11).
- Silymarin (Legalon®) has antioxidant activities, protects against lipid peroxidation and has anti-inflammatory and anti-fibrotic effects. In controlled clinical trials varying results were obtained. In a first study on 170 patients with cirrhosis (of which 92 alcoholic) a beneficial effect was observed (12). On the other hand, a recent study of 200 patients with alcoholic cirrhosis) found no beneficial effect (13). Both of these trials had major shortcomings including high drop-out rates and compliance issues.
- The rationale for steroid use is to inhibit the immune response and the proinflammatory cytokine cascade. The most recent meta-analysis on clinical studies performed (14) reported significantly improved survival at 28 days (85 vs. 65%) in severely ill alcoholic hepatitis patients having a Maddrey's Discriminant Function (DF) > 32. Importantly the long-term survival at two years is not different between patients treated with or without steroids. The modified DF is calculated as follows (15) :

  4.6 × [patient's prothrombin time – control time(s)] + serum bilirubin (mg/dL).

  In most trials the steroid used has been prednisolone 40 mg per day for 4 weeks. It is then abruptly stopped (Beaujon, Newcastle) or tapered over 2-4 weeks.

- Enteral nutrition for patients with severe ALD is of utmost importance. A major randomised study of enteral nutrition versus steroids in patients with alcoholic hepatitis showed similar overall initial outcomes and less long-term infection in the nutrition group (16).
- Insufficient data are available at this moment to judge the use of anti-TNF-α monoclonal antibodies (Infliximab – Remicade®) in alcoholic hepatitis (17).

References

1. ENOMOTO N., YAMASHINA S., SCHEMMER P., RIVERA C.A., BRADFORD B.U., ENOMOTO A., BRENNER D.A., THURMAN R.G. Estriol sensitizes rat Kupffer cells via gut-derived endotoxin. *Am. J. Physiol.*, 1999, **277** : G671-677.
2. YOUNOSSI Z.M. Epidemiology of alcohol-induced liver disease. *Clin. Liver Dis.*, 1998, **2** : 661-671.
3. JAMES O.F.W. NASH/NAFLD management. *Acta Gastroenterol. Belg.*, 2002, 65 :, 200-203.
4. MAYFIELD D., MCLEOD G., HALL P. The CAGE questionnaire : validation of a new alcoholism instrument. *Am. J. Psychiatry*, 1974, **131** : 1121-1123.
5. MC CULLOUGH A.J. Insulin resistance, obesity and fatty liver. In : AASLD Postgraduate Course, Boston, Nov 1-2, 2002, p. 134-143.
6. SANYAL A. Evaluation and management of non-alcoholic fally liver disease. In : AASLD Postgraduate Course, Boston, Nov 1-2, 2002, p. 144-150.
7. STAUBER R.F., STEPAN V., TRAUNER M. *et al.* Evaluation of carbohydrate-deficient transferring for detection of alcohol abuse in patients with liver dysfunction. *Alcohol Alcohol.*, 1995, **30** : 171-176.
8. BELL H., TALLAKIN C., SJAHEIM T. *et al.* Serum carbohydrate-deficient transferring as a marker of alcohol consumption in patients with chronic liver disease. *Alcohol Clin. Exp. Res.*, 1993, **17** : 246-252.
9. MORGAN T.R., NEMSCHAUSKY Y., SCHIFF E., ANAND B.S., BLOOR J., KIDAO J., CECIL B., MENDENHALL C., NELSON D., LIEBER C., PEDROSA M., LUMENG L., MISHA G., MARSANO L., SIMON F., CHEDID A., FRENCH S., KANEL G., TAYLOR D., WEISS D.G. Colchicine does not prolong life in patients with advanced alcoholic cirrhosis : results of a prospective, randomized, placebo-controlled, multicenter Va trial. *Gastroenterology*, 2002, **122** (suppl) : A641 (abstract).
10. CORTEZ-PINTO H., ALEXANDRINO P., CAMILO M.E., GOUVEIA-OLIVEIRA A., SAN P.M., ALVES M.M., MOURA M.C. Lack of effect of colchicines in alcoholic cirrhosis : final results of a double-blind randomized trial. *Eur. J. Gastroenterol. Hepatol.*, 2002, **14** : 377-381.
11. AKRIVIADIS E., BOTLA R., BRIGGS W., HAN S., REYNOLDS T., SHAKIL O. Pentoxyfylline improves short-time survival in severe alcoholic hepatitis : a double-blind, placebo-controlled trial. *Gastroenterology*, 2000, **119** : 1637-1648.
12. FERENCI P., DRAGOSICS B., DITTRICH H., FRANK H., BENDA L., LOCHS H., MERYNE S., BASE W., SCHNEIDER B. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *J. Hepatol.*, 1989, **9** : 105-113.
13. PARÉS A., PLANAS R., TORRES M., CABALLERÍA J., VIVER J.M., ACERO D., PANÉS J., RIGAU J., SANTOS J., RODÉS J. Effects of silymarin in alcoholic patients with cirrhosis of the liver : results of a controlled double-blind, randomized and multicenter trial. *J. Hepatol.*, 1998, **28** : 615-621.
14. MATHURIN P., MENDENHALL C.L., CARITHERS R.L. JR., RAMOND M.J., MADDREY W.C., GARSTIDE P., RUEFF B., NAVEAU S., CHAPUT J.C., POYNARD T. Corticosteroids improve short term survival in patients with severe alcoholic hepatitis (AH).. Individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. *J. Hepatol.*, 2002, **36** : 480-487.
15. MADDREY W.C. Alcoholic hepatitis : Clinicopathologic features and therapy. *Semin. Liv. Dis.*, 1998 , **8** : 91-102.
16. CABRÉ E., RODRÍGUEZ-IGLESIAS P., CABELLERÍA J., QUER J.C., SÁNCHEZ-LOMBRAÑA J.L., PARÉS A., PAPO M., PLANAS R., GASSULL M.A. on behalf of the Spanish Group for the Study of Alcoholic Hepatitis. Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition : a multicenter randomized trial. *Hepatology*, 2000, **32** : 36-42.
17. SPAHR L., RUBBIA-BRANDT L., FROSSARD J.L., GIOSTRA E., ROUGEMONT A.L., PUGIN G., FISCHER M., EGGER H., HADENGUE A. Combination of steroids with infliximab or placebo in severe alcoholic hepatitis : a randomised controlled pilot study. *J. Hepatol.*, 2002, **37** : 448-455.