Serum glutamate dehydrogenase as a marker of hepatocyte necrosis in alcoholic liver disease

P R MILLS, R J SPOONER, R I RUSSELL, P BOYLE, R N M MACSWEEN

Abstract

Serum glutamate dehydrogenase concentration was assessed as a marker of the degree of hepatocyte necrosis found at liver biopsy in 95 patients suspected of having alcoholic liver disease. Although the serum concentration was raised in 54 patients, no relation between it and the severity of hepatocyte necrosis could be established. Glutamate dehydrogenase was therefore not confirmed to be a useful indicator of hepatocyte necrosis in patients with chronic alcoholism.

Introduction

Serum glutamate dehydrogenase concentration has been reported as a reliable marker of liver-cell necrosis in the alcoholic.¹ Screening of populations of chronic alcoholics might therefore be easily undertaken with a view to early detection of liver damage. As a first step we assessed the relation between serum glutamate dehydrogenase concentration and hepatocyte necrosis in chronic alcoholics thought to have liver disease.

Patients and methods

Over an 18-month period we undertook a prospective study to measure simultaneously serum concentrations of glutamate dehydrogenase and assess histological evidence of hepatocyte necrosis in 95 consecutive patients who were suspected on clinical grounds of having alcoholic liver disease and were therefore undergoing liver biopsy. Although glutamate dehydrogenase is predominantly hepatic in origin, care was taken to exclude patients known to have myopathy, cardiac disease, or pancreatic disease. Blood was drawn just before percutaneous liver biopsy, for which the Tru-Cut needle was used, and serum stored at -20°C . Glutamate dehydrogenase was assayed in batches at monthly intervals using a standard technique with a control on each occasion²; we had first ensured that storage for one month did not alter the concentration. Liver biopsy specimens were stained with haematoxylin and eosin and the degree of hepatocyte necrosis assessed, without knowledge of patient details, on an arbitrary scale of 0 (nil), 1 (mild), 2 (moderate), and 3 (severe).

Results

The 95 patients were categorised into the following histological classes according to the result of the liver biopsy: normal liver (five patients), fatty change (28), alcoholic hepatitis (27), and alcoholic cirrhosis (35). The degree of hepatocyte necrosis in these patients was assessed as nil (31 patients), mild (21), moderate (23), and severe (20).

Gastroenterology Unit and Department of Biochemistry, Royal Infirmary, Glasgow G4 0SF

P R MILLS, BSC, MRCP, senior registrar in medicine and gastroenterology
R J SPOONER, BSC, senior biochemist
R I RUSSELL, MD, PHD, consultant physician and gastroenterologist

West of Scotland Cancer Surveillance Unit, Ruchill Hospital, Glasgow G20 9NB

P BOYLE, BSC, senior statistician

University Department of Pathology, Western Infirmary, Glasgow G11 6NT

R N M MACSWEEN, MD, FRCPATH, titular professor in pathology

Serum concentrations of glutamate dehydrogenase were above the upper limit of normal (4 U/l) in 54 patients. The figure, however, shows that there was no relation between raised serum concentrations and severity of hepatocyte necrosis. By using analysis of variance no significant difference was noted between the four group means ($F = 0.42 < F(3,91)$; $p > 0.1$); there was also no significant linear trend between the serum concentration and severity of hepatocyte necrosis ($F = 0.45 < F(1,91)$; $p > 0.1$).

Relation between serum concentration of glutamate dehydrogenase and severity of hepatocyte necrosis in 95 chronic alcoholic patients. (Upper limit of normal for glutamate dehydrogenase concentration is 4 U/litre.)

Discussion

The increasing incidence of chronic alcoholism has stimulated interest in the early detection of and concentration of resources on patients with evidence of associated liver damage. While serum γ -glutamyl transpeptidase and α -amino-*n*-butyric acid may provide objective evidence of recent heavy drinking,³ no satisfactory screening test for liver damage is available, with the result that patients often first present with clinical evidence of advanced hepatic disease. Van Waes and Lieber suggested that measurement of serum glutamate dehydrogenase concentration might be the first simple objective screening test for alcohol-related hepatic necrosis, but, unfortunately, we have been unable to confirm their initial results.¹

Glutamate dehydrogenase is a mitochondrial enzyme found predominantly in the liver. Our experience (RJS) has shown a high incidence of abnormal serum concentrations of the enzyme in all categories of hepatic and biliary tract disease.⁴ In particular, patients with extrahepatic biliary obstruction and little hepatocyte necrosis showed high concentrations. The 59 patients with non-cirrhotic alcoholic liver disease and 116 patients with cirrhosis (mostly alcoholic) in this previous study⁴ showed

concentrations closely similar to the range found in our present study. A conspicuous early ultrastructural feature of alcoholic liver damage is large, swollen mitochondria, suggesting that mitochondrial damage may be an important factor in the pathogenesis of alcoholic liver disease. Enzyme analysis of isolated hepatocyte mitochondrial fractions from patients with alcoholic steatosis, however, has failed to show evidence of mitochondrial damage.⁵ Concentrations of enzymes associated with mitochondrial membranes were unchanged but concentrations of enzymes in the mitochondrial matrix, including glutamate dehydrogenase, were significantly raised in alcoholic steatosis. This suggests that raised serum concentrations of glutamate dehydrogenase might be due to either hepatocyte damage or alcohol induction of liver mitochondrial enzyme activity.

Our study has therefore failed to confirm the usefulness of

serum concentrations of glutamate dehydrogenase as an indicator of liver damage in patients with chronic alcoholism.

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Dissemination of resistance plasmids among gentamicin-resistant enterobacteria from hospital patients

SIDONIE KNIGHT, MARK CASEWELL

Abstract

Out of 184 patients who were infected or colonised with gentamicin-resistant enterobacteria, 17 (9%) harboured more than one strain. Single antibiotic-resistance plasmids were common to more than one of the different organisms isolated from nine patients, strongly suggestive of in-vivo conjugation. An "epidemic" plasmid with a molecular weight of approximately 110 megadaltons was found in 11 distinct strains isolated from four patients. Seven of the organisms harbouring this plasmid were *Klebsiella aerogenes*.

Spread of multiple-resistance plasmids among endemic gentamicin-resistant enterobacteria is not uncommon, and these organisms provide a reservoir of plasmids that may ultimately spread to more pathogenic genera.

Introduction

Interbacterial transfer of antibiotic-resistance plasmids by conjugation is a theoretically potent mechanism for limiting the clinical efficacy of many antimicrobial agents. Although the spread of plasmids from epidemic strains of multiply-resistant coliforms to other Gram-negative bacilli is recognised¹⁻³ little is known about the frequency of plasmid spread among hospital bacteria during endemic colonisation and infection.

We therefore sought evidence for the spread of single plasmids among gentamicin-resistant enterobacteria isolated from patients in our hospital during a non-epidemic period.

Patients and methods

Between 20 February 1979 and 27 March 1980 we identified all inpatients at St Thomas's Hospital whose bacteriological specimens

received by the diagnostic microbiology laboratory yielded more than one strain of gentamicin-resistant enterobacteria. Three strains from one patient at another hospital (case 9) were provided by D G White. Bacteria were identified by standard methods⁴ and controlled disc-diffusion was used for sensitivity testing.⁵ *Klebsiella capsular* (K) typing was as described.^{6,7}

Gentamicin-resistant enterobacteria from patients with more than one such strain were tested for plasmids that were transferable to *Escherichia coli* K12.⁸ Transconjugants were tested for resistance to chloramphenicol (Cm), tetracycline (Tc), ampicillin (Ap), carbenicillin (Cb), cephaloridine (Cr), cephalothin (Kf), cephalexin (Cfx), cefuroxime, cefoxitin (Fox), sulphamethoxazole (Su), trimethoprim (Tp), streptomycin (Sm), kanamycin (Km), neomycin (Nm), gentamicin (Gm), tobramycin (Tm), amikacin, nitrofurantoin, and nalidixic acid. Plasmid molecular weights were determined by single-colony lysate agarose-gel electrophoresis.⁹

Results

During the 13 months 184 patients at St Thomas's Hospital were found to have gentamicin-resistant enterobacteria; 17 (9%) harboured more than one strain, and the isolates from 14 of these patients possessed plasmids that were transferable to *E. coli* K12. Eight of the St Thomas's Hospital patients with multiple strains of gentamicin-resistant enterobacteria and the patient from another hospital were found to harbour two or more strains with common plasmids which were recognisable by their transferable resistance pattern and indistinguishable electrophoretic mobility. The table shows the resistance patterns and approximate molecular weights of these plasmids, together with the identification of their host bacteria and the clinical sources.

Klebsiella aerogenes was among the clinical isolates from eight of these patients and was the first gentamicin-resistant species isolated from seven patients. All but two of the patients had at least two distinct strains in their urine.

K. aerogenes K21, bearing a transferable plasmid of approximately 110 megadaltons which conferred the resistance pattern ApCbCm-TcSuTpSmKmNmGmTm, was isolated from four patients; this plasmid was found in 11 epidemiologically distinct strains belonging to four different genera (see table).

Discussion

Our finding that as many as 9% of patients with clinical isolates of gentamicin-resistant enterobacteria were infected or colonised by more than one strain, and that almost half of these

Department of Microbiology, St Thomas's Hospital Medical School, London SE1 7EH

SIDONIE KNIGHT, BSC, research assistant

MARK CASEWELL, MD, MRCPATH, senior lecturer in microbiology (now senior lecturer in medical microbiology, The London Hospital Medical College, London E1 2AD)