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Relation between lupus anticoagulant and splanchnic venous thrombosis in cirrhosis of the liver

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While angiographic studies have indicated that splanchnic venous thrombosis rarely occurs in patients with cirrhosis of the liver, a postmortem study has shown that it may occur in up to a fifth.¹ We have shown that patients with cirrhosis have lupus anticoagulant, which predisposes to venous and arterial thrombosis.² In this study we determined whether splanchnic venous thrombosis is associated with lupus anticoagulant in patients with cirrhosis.

Patients, methods, and results

From October 1990 to November 1991, 73 consecutive patients (43 men) aged 35-77 with cirrhosis of the liver that had been diagnosed by liver biopsy entered the study. Liver failure was categorised as mild, moderate, or severe according to Child-Pugh's classification.

Twenty nine patients had markers of hepatitis B virus infection, 30 had markers of hepatitis C virus infection, 11 had a history of alcohol misuse, and in three the cause of cirrhosis was unknown. Patients with cancer or acute inflammation who needed immediate plasma or blood transfusions were excluded.

Ultrasonography showed thrombosis in nine patients (portal vein thrombosis in eight, mesenteric vein thrombosis in one). These findings were confirmed by enhanced computed tomography.

Blood samples taken within 48 hours of the patients' admission and mixed with 3.8% sodium citrate were checked for lupus anticoagulant with four coagulation tests. Lupus anticoagulant was regarded as being present if the coagulation time was prolonged in at least two of these tests and if a further, fifth test yielded a positive result.² Anticardiolipin antibodies were measured as described elsewhere.²

Characteristics of 73 patients with cirrhosis of liver with and without splanchnic venous thrombosis. Figures are numbers (percentages) of patients unless stated otherwise

Variable	Patients with splanchnic venous thrombosis (n=9)	Patients without splanchnic venous thrombosis (n=64)	χ^2 Test or (if n $\leq$ 5) Fisher's test	P value
Mean (SD) age (years)	51 (6)	56 (11)	1.33*	>0.05
Men	4 (44)	37 (58)	1.02	>0.05
Grade of liver failure†:				
Mild		19 (30)	4.90	>0.05
Moderate	7 (78)	27 (42)		
Severe	2 (22)	18 (28)		
Cause of liver failure:				
Hepatitis B virus infection	1 (11)	28 (44)	3.70	>0.05
Hepatitis C virus infection	5 (56)	25 (39)		
Alcohol misuse or unknown	3 (33)	11 (17)		
Positive for:				
Anticardiolipin antibodies	5 (56)	10 (16)	5.45	0.015
Lupus anticoagulant	5 (56)	4 (6)	13.50	0.0008

*Unpaired t test.

†According to Child-Pugh's classification.

To evaluate whether thrombosis was related to low concentrations of coagulation inhibitors we measured antithrombin III, protein C, and protein S³ concentrations in the patients with thrombosis (four men, five women; age 40-72) and in nine patients without (four men, five women; 45-70). In each group seven patients had moderate and two severe liver failure.

Data were analysed with the unpaired t test, Mann-Whitney U test, χ^2 test with continuity correction, or (if n $\leq$ 5) Fisher's test and the two tailed test.

The patients' age and sex and the cause of cirrhosis did not significantly distinguish patients with and without splanchnic venous thrombosis. The proportion of patients with moderate or severe liver failure was greater in those with thrombosis than in those without, although the difference was not significant (table). Thrombosis was significantly associated with the presence of lupus anticoagulant (odds ratio 18.7 (95% confidence interval 2.8 to 143.5); P=0.0008) and anticardiolipin antibodies (6.7 (1.3 to 37.9); P=0.015) (table). Seven of the nine patients with lupus anticoagulant had markers of hepatitis C virus infection. Concentrations of antithrombin III, protein C, bound protein S, and free protein S did not differ between the patients with cirrhosis who had thrombosis and those who did not.

Comment

This study shows that 12% (95% confidence interval 5.8% to 22.1%) of patients with cirrhosis of the liver may have splanchnic venous thrombosis. Thrombosis is rare in compensated cirrhosis, which suggests that liver failure is an important factor. The pathogenesis of thrombosis in patients with cirrhosis is not known. Lupus anticoagulant has been reported in such patients² but has not previously been evaluated as a risk factor for thrombosis.

Our finding that over half of the patients with thrombosis were positive for lupus anticoagulant or anticardiolipin antibodies indicates that antiphospholipid antibodies may be a risk factor. A previous study showed that antiphospholipid antibodies may promote hepatic veno-occlusive disease or splanchnic venous thrombosis.⁴ Plasma concentrations of antithrombin III, protein C, and protein S, which may be low in patients with cirrhosis, may also promote thrombosis, but no differences were found between patients with and without thrombosis. Although the origin of antiphospholipid antibodies in cirrhosis is unknown, lupus anticoagulant has often been observed in viral infections, particularly hepatitis C virus infection⁵; in our study three quarters of patients positive for lupus anticoagulant had markers of hepatitis C virus infection. In conclusion, this study shows a significant relation between splanchnic venous thrombosis and lupus anticoagulant, indicating that lupus anticoagulant may be an important risk factor for thrombosis in patients with cirrhosis.

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Value of Kleihauer testing after administration of anti-D immunoglobulin

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The standard dose of 500 IU of anti-D immunoglobulin given in Britain to RhD negative mothers postnatally is lower than that used in Europe, the United States, and Canada, where 1000-1500 IU is the routine dose. In Britain a Kleihauer test is performed after the 500 IU dose is given.¹ The results of this test should indicate the volume of fetomaternal haemorrhage that has occurred and whether a further dose of anti-D immunoglobulin is required. Kleihauer testing is not performed routinely in Europe, the United States, or Canada as the higher dose of anti-D immunoglobulin used prevents Rh sensitisation in all but 0.3% of cases.

Use of the Kleihauer test in RhD negative mothers who have been given anti-D immunoglobulin is intrinsically incorrect as the test measures fetal haemoglobin and not RhD positive cells. Up to a quarter of women have an increased proportion of fetal haemoglobin during pregnancy, and increased proportions of fetal haemoglobin can also occur in women with haemoglobinopathies. The Kleihauer test can be performed and reported in several ways but has poor reproducibility.² In Britain no quality assurance scheme exists for assessing Kleihauer testing.

These factors detract from the test's reliability in assessing accurately the size of a fetomaternal haemorrhage. We undertook a survey of the laboratories responsible for Kleihauer testing for a single transfusion centre in Britain to assess how effective Kleihauer testing is in monitoring the outcome of doses of anti-D immunoglobulin.

Subjects, methods, and results

We surveyed all hospital transfusion laboratories served by the Mersey and North Wales Blood Transfusion Service. Using a questionnaire, we requested information on the techniques used for Kleihauer testing, the methods of reporting, and situations in which increased doses of anti-D immunoglobulin and further Kleihauer testing were recommended. We also asked about antenatal Kleihauer testing after potentially sensitising episodes to see whether the British recommendations for antenatal use of anti-D immunoglobulin and Kleihauer testing were being followed.³

We contacted 23 hospital transfusion laboratories, all of which returned a completed questionnaire. Eleven hospitals did not perform Kleihauer testing since they were not responsible for an obstetric unit. The remaining 12 hospitals performed Kleihauer testing for all RhD negative mothers delivered of an RhD positive baby. No uniformity existed, however, with regard to the technique or counting procedure used or the reporting of the test (table).

Most of the hospitals reported the number of fetal cells per low power field. None indicated whether the

Variations in Kleihauer testing in 23 hospital transfusion laboratories served by Mersey and North Wales Blood Transfusion Service

	No of hospitals
<i>Postnatal testing</i>	
No of tests a year:	
100-500	6
>500	6
Reagents used:	
In house	3
Commercial kits*	9
No of microscopic fields examined†:	
3	3
5	1
10	3
20	1
50	4
<i>Antenatal testing</i>	
Done in cases of:	
Amniocentesis	7
Haemorrhage	10
Ectopic pregnancy	1
Maternal trauma	1

*Kits from four manufacturers were used.

†One hospital scanned high power fields, 11 low power fields.

result represented a large fetomaternal haemorrhage, requiring a further dose of anti-D immunoglobulin. Ten hospitals indicated that they would give advice on further doses of anti-D immunoglobulin if asked. One hospital would not recommend repeat Kleihauer testing after a large transplacental haemorrhage for which an increased dose of anti-D immunoglobulin had been given.

Antenatal Kleihauer testing also showed wide variations in practice (table). Only one hospital complied with all the current recommendations.³

Comment

If the hospitals we contacted are representative the results of our survey are worrying. European recommendations state that the postpartum dose of anti-D immunoglobulin should be 1000-1500 IU⁴; routine Kleihauer testing is not recommended. The failure rate of anti-D prophylaxis in Britain, though low at 1.5%, is considerably higher than that in some other European countries—for example, in the Netherlands it is 0.65%.

Because of this failure rate, the known variability and poor reproducibility of Kleihauer testing, and the results of our survey we believe that the adequacy of the dose of anti-D immunoglobulin given to RhD negative mothers should be assessed with a more reliable and accurate technique. The technique should measure RhD positive cells rather than fetal haemoglobin. Furthermore, because of the reported failure rate in Britain the recommended dose of 500 IU anti-D immunoglobulin should be reviewed.

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See editorial by Letsky and De Silva