Brief report

The hemostatic status of pediatric recipients of adult liver grafts suggests that plasma levels of hemostatic proteins are not regulated by the liver

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Plasma levels of coagulation factors differ profoundly between adults and children, but are remarkably stable throughout adulthood. It is unknown which factors determine plasma levels of coagulation factors in a given individual. We hypothesized that the liver, which synthesizes coagulation factors, also controls plasma levels. We measured a panel of coagulation factors in samples taken from either adults or young children who underwent a liver transplantation with adult donor livers. Samples were taken 1-3 months after transplantation, when the patients were clinically stable with adequate graft function. After liver transplantation, the hemostatic profile of the pediatric group was remarkably different from that of the adult group, and resembled the hemostatic profile of normal children. Thus, children transplanted with an adult liver graft maintain a pediatric hemostatic profile after transplantation despite receiving an adult liver graft. These findings suggest that plasma levels of hemostatic proteins are not controlled by the liver. (*Blood*. 2011;117(6):2070-2072)

Introduction

The liver plays a central role in hemostasis because it synthesizes many of the plasma proteins involved in coagulation and fibrinolysis.[1] Although plasma levels of the various proteins vary between individuals, levels of these proteins within an individual are remarkably stable throughout adulthood,[2] although subtle elevations in coagulation factors are observed with increasing age.[3] In young children, the hemostatic system is still in development, and plasma levels of various hemostatic proteins in young children are profoundly different from that of adults.[4-8] Although levels of many coagulation factors increase toward values found in adults in the first year of life, striking differences between infants and adults are still present in children at 6 months of age.[6] More subtle differences between children and adults are still observed between the ages of 1 and 16 years.[4] It is not known which factors control the levels of coagulation factors in a given individual, but it appears plausible that the liver may be involved.

Children with end-stage liver disease may undergo liver transplantation. These children will frequently obtain a split-liver graft from an adult donor. In these children undergoing transplantation, a unique situation occurs in which liver mass is not significantly different from children who do not, but liver tissue is of adult origin. Here we investigated whether transplantation of an adult (split) liver graft into very young children would convert the pediatric hemostatic status to a hemostatic profile similar to that of adults.

Methods

Patients

Eleven children who underwent a primary (n = 10) or second (n = 1) liver transplantation for biliary atresia (n = 10) or metabolic disease (n = 1) with a mean of age 8.5 months (range, 4.2-11.7 months) and 9 adults with a mean age of 56 years (range, 46-65 years) who underwent transplantation for cirrhosis of various etiology (primary sclerosing cholangitis, 2 [one of which was a retransplantation]; viral hepatitis, 2; cryptogenic, 1; alcoholic cirrhosis, 2; alpha-1 antitrypsin deficiency, 1; and nonalcoholic steatohepatitis and alcohol abuse, 1) were included in this study. The children all received split-liver grafts from adolescent or adult donors (mean 38 years, range 18-64 years). Eight adults received a full-sized graft from adult donors (≥ 18 years of age), whereas one adult received a split-liver graft from an adult donor.

Plasma and serum samples were drawn when the patients were clinically stable and had adequate liver function. In the children, blood samples were drawn at the day before discharge from the hospital, whereas all adults had their blood drawn in the outpatient clinic. Blood samples were taken at 38 days (range, 20-68 days) after transplant in the children, and 49 days (range, 27-84 days) after transplantation in the adults, and the time between transplantation and blood draw was not significantly time between children and adults ($P = .21$). Additional methods are published as a supplement, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article.

Results and discussion

Table 1 shows liver function parameters in adults and children taken 1-3 months after liver transplantation. Albumin and bilirubin levels were consistent with adequate liver function, and values were comparable between adults and children. Transaminases and γ-glutamyl transpeptidase were slightly greater in the pediatric group, although the differences were not statistically significant.

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Table 1. Liver function parameters in the study population

Parameter	Value in children (n = 11), mean (range)	Value in adults (n = 9), mean (range)	*P*
AST, U/L	43 (16-88)	31 (14-116)	.36
ALT, U/L	55 (13-126)	27 (13-75)	.06
Total bilirubin, mg/dL	0.6 (0.3-1.0)	0.8 (0.3-1.3)	.07
Direct bilirubin, mg/dL	0.4 (0.2-0.8)	0.2 (0-0.4)	.10
Albumin, g/dL	3.7 (2.7-4.6)	4.1 (3.3-4.5)	.15
γ-GT, U/L	172 (69-507)	92 (47-227)	.13

ALT indicates alanine transaminase; AST, aspartate aminotransferase; and γ-GT, γ-glutamyl transpeptidase.

Despite similar liver function parameters, the hemostatic profile of the pediatric recipients of an adult liver graft was remarkably different from that of adult liver transplant recipients (Table 2). The levels of the vitamin K-dependent coagulation factors II, IX, X, and protein C were substantially and significantly lower in children (all around 65%) compared with adults, in whom levels of these factors were around 100%. Plasma levels of all 4 factors have been previously reported to be much lower in very young children (< 6 months of age) compared with adults.[6] Even more, levels of these factors remain substantially decreased compared with adult levels until the age of 5.[4] Levels of factor VIII, protein S, and α1-antitrypsin have previously been reported to be decreased in children younger than the age of 6 months[6] but are comparable with levels found in adults in older children.[4] In our study, levels of factor VIII were high in children and adults. Persistently elevated factor VIII and von Willebrand factor levels are common after liver transplantation may be attributable to persistent low-grade endothelial activation for example caused by immunosuppressive drugs. Of importance, the site of synthesis of factor VIII in the liver is clearly distinct from the site of synthesis of the other coagulation factors,[9] and extrahepatic sites for FVIII synthesis exist as well.[10] Nevertheless, factor VIII levels in children who have undergone transplantation are significantly lower compared with values found in adults. Levels of protein S are lower in children than in adults, but levels of α1-antitrypsin were similar and normal in both children and adults. Fibrinogen levels, which have previously been reported not to be different between adults and young children, were also similar in our pediatric and adult group. Pediatric reference values for C4BP and protein C inhibitor have to our knowledge not yet been reported. Levels of C4BP were normal and similar in children and in adults, whereas levels of protein C inhibitor were normal in the adults, but decreased at around 70% in the children. Finally, levels of α2-macroglobulin in children up to the age of 16 years have been reported to be highly elevated compared with values found in adults.[4,6] In our population, α2-macroglobulin levels were similar in children and adults at around 100%.

Table 2. Levels of coagulation factors in children (n = 11) at 37 days after liver transplantation and in adults (n = 9) at 49 days after liver transplantation.

Parameter	Value in children, mean (range)	Value in adults, mean (range)	*P*
FII, %	67 (50-128)	89 (47-126)	.05*
FIX, %	63 (35-92)	113 (84-133)	< .0001*
FX, %	63 (46-96)	86 (60-131)	.02*
Protein C, %	64 (51-105)	111 (78-126)	< .0001*
Factor VIII, %	120 (53-161)	170 (108-247)	.01*
Protein S, %	73 (49-120)	97 (65-130)	.02*
α1-antitrypsin, %	127 (82-190)	121 (70-158)	.69
Fibrinogen, g/L	3.7 (1.5-8.1)	3.1 (2.1-5.0)	.34
C4BP, %	100 (49-154)	107 (64-211)	.60
PCI, %	68 (34-120)	126 (84–182)	< .0001*
α2-macroglobulin, %	97 (73-154)	105 (77–149)	.60

PCI indicates protein C inhibitor.
*Significance.

All data, except levels of α1-antitrypsin and α2-macroglobulin are consistent with the maintenance of a pediatric hemostatic status in children who have undergone liver transplantation. A decreased synthetic capacity of the liver would also explain the decreased levels of coagulation factors in the pediatric population. However, liver function as assessed by bilirubin and albumin levels is adequate and comparable between children and adults. Furthermore, several liver-derived coagulation factors are present in normal levels in both children and adults.

Collectively, our results may imply that plasma levels of hemostatic proteins are not controlled by the liver. The regulatory mechanisms behind maintenance of plasma levels of coagulation factors remain to be established but may involve hormonal systems such as thyroid- or sex hormones, which are known to influence plasma levels of coagulation factors.[11,12] Alternatively, maintenance of coagulation factor levels may be accomplished by an extrahepatic sensor of plasma coagulation factor levels that communicates signals for hepatic synthesis to the liver when coagulation factor levels decrease below a certain threshold. Such a sensory system has not yet been identified, but may, for example, be present in the vascular endothelium. A final hypothesis is that the clearance rate of certain coagulation factors is the key factor in maintaining constant plasma levels. In this scenario, clearance rate of many coagulation factors should be increased in children. Animal experiments have indicated increased clearance of fibrinogen but not of prothrombin in newborns, and observations in humans have shown increased clearance of recombinant factor VIIa and factor VIII but not of factor IX and activated protein C in children.[13-17] Collectively, these observations are not fully consistent with a role of clearance the altered coagulation profile of children. Moreover, because coagulation factors are mainly cleared by the liver, the regulation of clearance rate should determined by the results presented in this report be present outside of the liver. In conclusion, the regulatory mechanism for plasma levels of coagulation proteins remains to be elucidated, but data presented here suggest the liver is not involved.

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Authorship

Contribution: T.L. designed the study, analyzed and interpreted data, and wrote the paper; M.P., E.B.H., and M.C. included patients, collected and interpreted patient data, and revised the paper; J.C.M.M. supervised the laboratory analyses, analyzed and interpreted data, and revised the paper; R.J.P. designed the study, analyzed and interpreted data, and revised the paper.

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