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Elevated plasma bile acids in hypergalactosaemic neonates: a diagnostic clue to portosystemic shunts

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Abstract To determine whether plasma levels of total bile acids may provide a useful index for hypergalactosaemia due to porto-systemic shunts, these levels were determined in hypergalactosaemic neonates. Increased levels were found in all cases with portohepatic venous or portocaval shunts. The levels of both total bile acids and galactose were normalized when the shunts disappeared on the echograms. Both bile acids and galactose are almost completely absorbed by the liver via the first portal blood passage. Portosystemic shunts contribute to elevated levels of bile acids and galactose.

Conclusion Increased plasma levels of total bile acids serve as a diagnostic clue to the presence of portosystemic shunts in neonates with hypergalactosaemia.

Key words Galactoasemia · Portosystemic shunt · Total bile acids

Abbreviations *PC* portocaval · *PV* porto-hepatic venous · *TBA* total bile acids

Introduction

Mass screening programmes have detected deficiencies of galactose-metabolizing enzymes in many neonates with hypergalactosaemia. However, in some cases, the cause of hypergalactosaemia is unknown.

Recent evidence has shown that porto-hepatic venous (PV) shunts cause hypergalactosaemia [2, 4]. In these reported cases, the diagnosis was suspected by the persistence of hypergalactosaemia, despite normal enzyme activities and was confirmed by ultrasonography, computed tomography or angiography.

In the present study we investigated nine hypergalactosaemic patients with portocaval (PC) or PV shunts. All cases exhibited increased levels of plasma total bile acids (TBA) increased levels of which serve as a diagnostic index for the differential diagnosis of hypergalactosaemia.

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Subjects and methods

A total of 318 hypergalactosaemic neonates were screened between 1986 and 1996 and referred to our institution (age; 12 days–30 days). The diagnosis was confirmed by assays of RBC galactose-metabolizing enzymes. Galactokinase activity was assayed by HPLC [5], galactose-1-phosphate uridyltransferase according to Hansen and Mayes [3] and UDP-galactose epimerase by the method of Gitzelmann and Steinmann [1]. Patients without enzyme deficiencies were examined by ultrasonography, computed tomography or angiography.

Blood galactose levels were determined by the Paigen method. Galactose challenge tests were performed by feeding the neonates lactose-containing milk instead of a galactose-restricted diet. One hour after the meal, blood galactose was checked. Plasma TBA levels were estimated using commercial kit method (First Chemical Inc., Kyoto, Japan).

Results

Nine hypergalactosaemic neonates with portosystemic shunts (seven cases with intrahepatic and two with extrahepatic shunts) were detected in our screening programme (Table 1). Haemangiomas were treated with prednisolone and the hypergalactosaemia reduced by dietary control. Two patients presented with hepatic portal hypoplasia with extrahepatic PC shunt through the anomalous vein caused by hepatic portal vein hypoplasia (Table 2). All nine patients showed increased levels of TBA and normal enzyme activities (Tables 1, 2). Serum concentrations of transaminases, lactate dehy-

Table 1 Hypergalactosaemic neonates with intrahepatic portosystemic shunts (*AV* arteriovenous)

Cases	Diagnosis	Age	TBA (μmol/l)	Galactose (mmol/l)(mg/dl)
1	PV and AV shunt with haemangiomas	18 days		1.11 (20)
	PV shunts; haemangiomas disappeared	5 years	110	0.33 (6)[a]
	PV shunts	6 years	98	0.44 (8)[a]
2	PV shunts with haemangiomas	14 days	30	0.44 (8)
		30 days	130	
	PV shunts; haemangiomas disappeared	2 years	38	0.33 (6)[a]
3	PV shunts with haemangiomas	30 days	98	0.44 (8)
	PV shunts disappeared	9 months	11	< 0.11 (< 2)[a]
4	PV and AV shunts with haemangiomas	12 days	97	> 1.11 (> 20)
	PV and AV shunts disappeared	1 year	13	< 0.11 (< 2)[a]
5	PV shunts with haemangiomas	15 days	91	0.89 (16)
		10 months	34	
6	PV shunts with haemangioma	22 days	100	0.89 (16)
	PV shunts disappeared	2 months	6	< 0.11 (< 2)[a]
7	PV shunts	19 days	138	0.44 (8)
	PV shunts disappeared	3 months	17	< 0.11 (< 2)[a]
	Normal ranges		< 50 (< 1 month)	< 0.44 (< 8 < 1 month)
			< 20 (> 1 month)	< 0.11 (< 2 > 1 month)

[a] Indicates galactose levels after challenge tests

Table 2 Hypergalactosaemic neonates with extrahepatic portosystemic shunts

Cases	Diagnosis	Age	TBA (μmol/l)	Galactose (mmol/l)(mg/dl)
1	Portal hypoplasia	13 days		> 1.11 (> 20)
		4 years	297	> 1.11 (> 20)[a]
		6 years	138	> 1.11 (> 20)[a]
2	Portal hypoplasia	14 days		> 1.11 (> 20)
		3 years	171	
		5 years	121	0.89 (16)[a]
	Normal ranges		< 50 (< 1month)	< 0.44 (< 8 < 1 month)
			< 20 (> 1month)	< 0.11 (< 2 > 1 month)

[a] Indicates galactose levels after challenge tests

drogenase, γ-glutamyltranspeptidase and α-fetoprotein were not significantly elevated.

Hypergalactosaemia (0.44 mmol/l) and increased levels of TBA (124 μmol/l) were also found in the patient with biliary tract atresia. Two patients with hepatitis had hypergalactosaemia (1.67 and 0.89 mmol/l) but normal levels of TBA. However, none of 12 galactosaemic patients with enzyme deficiencies (1 patient with galactose-1-phosphate uridyltransferase deficiency; 3 patients with UDP-galactose epimerase deficiency; 3 heterozygous patients for uridyltransferase deficiency; 5 heterozygous patients for epimerase deficiency) had increased levels of TBA.

TBA returned to the normal range after PV shunts disappeared on the echograms, and no increases in galactose levels were seen on challenge tests in four cases (Table 1). TBA levels remained elevated in five cases with persisting PV or PC shunts (Tables 1, 2).

Discussion

Increased plasma levels of TBA are attributable to the presence of PV or PC shunts. Bile acids are excreted into the intestinal tract, reabsorbed, and transported through the portal vein to be metabolized in the liver (first-pass effect) [8]. PC shunts lead to an increase in the plasma levels of TBA.

Similarly, galactose is effectively extracted from the portal blood by the liver [4, 7], and portosytemic shunts induce hypergalactosaemia [2, 4].

Plasma TBA and galactose levels decreased to normal values after the PV shunts had disappeared on the echograms, and remained elevated with persistent PV or PC shunts.

A causal relationship between galactose and TBA metabolism is improbable in view of our observation that plasma TBA levels were not increased in hypergalactosaemic patients with enzyme deficiencies. There were no signs of hepatic damage to explain the increased levels of plasma TBA.

In one patient with hepatitis, galactose was elevated but TBA levels were normal. The patient with biliary tract atresia showed both hypergalactosaemia and increased plasma levels of TBA, but the latter was caused mainly by a defect in the excretion of bile acids. The hypergalactosaemia in this case was caused by severe hepatic damage. Mild to moderate damage to hepatic

cells will produce hypergalactosaemia, but does not contribute to the elevation of plasma levels of TBA.

Severe hepatic cell damage that progresses to cirrhosis can induce an elevation of plasma levels of TBA [6], accompanied by hypergalactosaemia [8]. Liver cirrhosis with portal hypertension may lead to portosystemic shunting, followed by elevated galactose and TBA levels. However, in the absence of signs of liver cell damage, the co-existence of increased plasma TBA levels and increased galactose levels may suggest the presence of portosystemic shunts.

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