Predisposing Factors for Spontaneous Closure of Congenital Portosystemic Shunts

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In a review of 382 cases of congenital portosystemic shunt, we found that presentation with neonatal cholestasis strongly predicts spontaneous closure of intrahepatic shunts (OR 8.3, 95% CI 3.4-20.2). Spontaneous closure before the 24th month of age is more likely for distal or multiple shunts, but rare for patent ductus venosus. *(J Pediatr 2015;167:931-5).*

Congenital portosystemic shunts (CPSSs) are rare malformations (1:25 000/1:30 000 at birth) associated with hepatic encephalopathy, pulmonary complications, and liver tumors in older children, adolescents, and adults.[1,2] Most complications of CPSS rarely develop before the third year of life.[1] Spontaneous closure of the CPSS is a rare event, being observed by the age of 18-24 months in 14% of intrahepatic shunts and 1% of extrahepatic shunts.[2,3] Available data do not allow predicting which patient will undergo spontaneous shunt closure in the first 24 months of life.

Patients' Description

Clinical Presentation

We retrospectively reviewed the medical charts of all consecutive patients with history of neonatal cholestasis and diagnosis of intrahepatic CPSS referred to 3 tertiary centers for pediatric hepatology from December 2009-September 2014. The study was conducted in accordance with the Helsinki Declaration and approved by the local institutional review boards. Eleven consecutive patients (4 females) were identified. They all presented with jaundice within the first month of life (Table I). Stool discoloration and dark urine were reported in 3 patients, but none had acholic stools. As shown in Table I, total and conjugated bilirubin levels were elevated in all patients (179 ± 115 and 113 ± 110 μmol/L, respectively). Alanine aminotransferase levels were elevated in 6 of the 11 patients (median alanine aminotransferase levels 2.5 ± 2.3 × upper limit of normal), whereas gamma-glutamyl transpeptidase levels were normal in 7 out of 8 patients who had it tested. All but patient 11 had normal coagulation status at presentation. One showed thrombocytopenia. Four babies (36.4%) presented persisting fasting hypoglycemia (overall mean 3.95 ± 1.14 mmol/L). Two patients required enteral feeding to maintain normal glucose levels. Three presented as failure to thrive. Four of the 5 patients who had blood ammonia levels tested presented hyperammonemia (63 ± 26 μmol/L). Two children had mild hypoxemia (patients 6 and 8). Among the 4 patients who were screened for galactosemia at birth, only 1 had a positive result. Preterm birth was registered in 3 patients, intrauterine growth restriction in 2, and oligohydramnios in 2 (Table I).

CPSS	Congenital portosystemic shunt

Diagnostic Evaluation

Congenital portosystemic shunt was identified at Doppler ultrasonography requested as part of neonatal cholestasis investigation in 11 patients (Table II). All other causes of neonatal cholestasis were excluded. The median age at diagnosis was 1 month (range 0.2-2.9). The shunt originated either from the portal vein bifurcation (2 patients, patent ductus venosus), left portal branch (7 patients), or the right portal branch (2) in all other children, terminating in the inferior vena cava (1) or the median (4), left (3), right (1), or left and median (2) hepatic veins. All but 1 patient had a single communication. The portal vein was patent in all. Hepatomegaly and splenomegaly were found in 2 and 3 patients, respectively (Table I). None had polysplenia. All children with splenomegaly had liver calcifications evident at ultrasound. No patient had ascites or presented liver tumors. Three patients had associated cardiac malformations. Two patients had multiple cutaneous hemangiomas (Table II). No associated chromosomic syndromes were found. Brain magnetic resonance and head ultrasound showed no anomalies in the 9 patients tested.

Follow-Up and Outcome

Patients were followed for 17.4 ± 17.4 months (Table III; available at www.jpeds.com). Median age at last follow-up was 18.5 months (range 1.8-60). One child developed pulmonary hypertension and died at 2 months of age for cardiac complications during percutaneous shunt closure. Cholestasis resolved spontaneously in all other patients at a

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Table I. New patients with CPSS and neonatal cholestasis: clinical and laboratory features of patients at presentation

Case	Sex	Gestational age (wk)	IUGR	Age at jaundice (d)	Conjugated bilirubin (μmol/L)	ALT (IU/L)	GGT (IU/L)	PLT (×1000)	PT (%)	Ammonium (mg/dL)	Persistent hypoglycemia	Hepatomegaly	Liver tumor	Splenomegaly	Failure to thrive	Dyspnea	Hypoxemia	Hepatic encephalopathy
1	M	39	N	3	14*	15*	83*	81*	84*	53*	Y	N	N	Y	N	N	N	N
2	F	37	N	30	198.36	264	38	426	91	NA	N	N	N	N	N	N	N	N
3	M	NA	NA	1	215.46	166	596	470	88	106	N	N	N	N	N	NA	NA	N
4	M	36	NA	27	25.65	32	15	NA	88	NA	N	N	N	N	N	NA	NA	N
5	M	36	Y	15	268.47	166	NA	NA	100	NA	Y	N	N	N	Y	N	Y	N
6	M	39	N	19	301	51	19	NA	NA	NA	N	N	N	N	N	NA	NA	N
7	M	41	N	7	54.38	108	NA	NA	96	NA	N	Y	N	N	Y	Y	Y	N
8	M	37	N	20	64.13	37	NA	NA	95	NA	Y	Y	N	Y	N	Y	N	N
9	F	31	N	15	24*	8*	60*	485*	NA	66*	N	N	N	N	N	N	N	N
10	F	40	N	7	15*	69*	60*	208*	100*	56*	N	N	N	N	N	N	N	N
11	F	39	N	18	63	38	204	127	67	35	N	N	N	N	Y	Y	Y	N

ALT, alanine aminotransferase; *F*, female; *GGT*, gamma-glutamyl transpeptidase; *IUGR*, intrauterine growth restriction; *M*, male; *N*, absent; *NA*, not available; *PLT*, platelets; *PT*, prothrombin time; *Y*, present.
*Values at diagnosis, values at presentation not available.

median age of 3 months (range 0.3-5) after 2.4 ± 1.4 months from presentation (Table II). Spontaneous closure of the congenital portosystemic shunt was observed in 6 patients at 8.4 ± 8.9 months of age. In 4 children the shunt is still patent at 30.7 ± 21.5 months of age (Table III). Three are completely asymptomatic and present normal liver function tests, no clinical sign of hepatic encephalopathy or chronic liver disease, and no signs of pulmonary hypertension or hepatopulmonary syndrome. The older patient with an open shunt (patient 9, 5 years old at last follow-up visit) presents mild hepatic encephalopathy.

Predictors of Spontaneous Shunt Closure

The high frequency of spontaneous shunt closure in our series raised the question of whether it could be more frequent in children presenting with neonatal cholestasis. All articles about intrahepatic and extrahepatic CPSS (in adult and pediatric patients) published in the English literature from 1964 to October 2014 were reviewed (PubMed search terms: "congenital portosystemic shunt," "congenital absence of the portal vein," "patent ductus venosus," "Abernethy malformation"). The minimum information required for patients to be included in the study was: type of shunt, mention of previous medical history, outcome (presence or absence of spontaneous shunt closure), and age at spontaneous shunt closure. Articles providing insufficient data were excluded. Selected articles are listed in Table IV (available at www.jpeds.com). Data were sought for the following variables: sex, type of shunt (intrahepatic vs extrahepatic), origin and end of shunt, single vs multiple communication, presentation with neonatal cholestasis (as defined by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines), spontaneous shunt closure, age at spontaneous shunt closure, shunt closure procedure (percutaneous, surgical, or liver transplantation), reason for shunt closure, age at closure procedure, outcome (dead, alive with closed shunt, alive with a still open shunt), age at last follow-up. Data are presented as mean ± SD or median and range. All statistical analyses were performed using SPSS 21.0 for Mac OS X (IBM Corp, Armonk, New York). Categorical variables were compared using the Pearson $\chi 2$ test. The Kaplan–Meier method was applied for calculation of the cumulative rate of spontaneous shunt closure using the log rank test. Graphs were obtained with GraphPad Prism 5 for Mac OS X (GraphPad, San Diego, California). A P value <.05 was considered statistically significant.

The patients were classified according to the type of shunt (intrahepatic vs extrahepatic) and the presence or absence of neonatal cholestasis. A total of 392 patients from 209 articles were reviewed (Table IV). Twenty-one patients were excluded because the information provided was incomplete. Of the 382 patients selected for the analysis (371 from the literature and 11 from the series described above; 214 males, 161 females, 7 not specified), 194 had an extrahepatic shunt and 188 had an intrahepatic shunt.