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DIFFERENTIAL PROGRESSION OF LIVER FIBROSIS IN SYNDROMIC AND ISOLATED BILIARY ATRESIA

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Aim of the study: Most biliary atresia (BA) patients require liver transplantation after portoenterostomy (PE) due to liver fibrosis, which progresses for unclear reasons. We addressed predictors, histology and molecular characteristics of liver fibrosis after PE.

Methods: After ethical approval, 28 BA patients with liver biopsies obtained during and after successful PE were included (Table). Biopsies were scored for fibrosis (Metavir F0-F4) and cholestasis (0-3). Expression of collagen 1 (COL1A2) and α-SMA (ACTA2), a marker of collagen producing myofibroblasts, were determined by immunohistochemistry and qRT-PCR. 29 pediatric donor livers and subjects undergoing cholecystectomy were used as controls.

Main results: Median serum bilirubin was 159±68 at PE and 10±19 μmol/L at follow-up, while histological cholestasis diminished from 2.0±0.9 to 0.0±0.3 ($p<0.001$ for both). Despite effective resolution of cholestasis fibrosis persisted (Metavir 2.0±0.7 to 2.0±1.2, $p=0.170$). Compared to controls, BA patients had markedly higher expression of collagen (area fraction, 17±5.5% and 16±11% vs 3.5±1.8%, $p<0.001$) and α-SMA (17±6.7% and 14±7.8% vs 7.1±4.2%, $p<0.001$) similarly both at PE and at follow-up, respectively. Collagen encoding COL1A2 correlated positively with collagen and α-SMA protein expression ($r=0.475$, $p=0.019$ and $r=0.512$, $p=0.013$, respectively). Absence of associated anomalies was the only factor found to predict progression of fibrosis. Patients with associated anomalies (n=11) displayed significantly lower Metavir fibrosis stage, expression of α-SMA and collagen at follow-up than isolated BA patients, although PE and follow-up age and Metavir stage (2.5±0.5 vs 2.0±0.7, $p=0.138$), expression of collagen (18±5.3% vs 17±5.8%, $p=0.688$) and α-SMA (17±5.6% vs 16±7.1%, $p=0.385$) at PE were comparable between syndromic and isolated patients, respectively (Table).

Conclusion: Despite resolution of cholestasis after successful PE, liver fibrosis and expression of collagen 1 and α-SMA remain markedly up-regulated. This up-regulation was lower in syndromic than isolated BA supporting different pathogenesis in these subgroups.

	All (n=28)	Isolated (n=17)	Syndromic (n=11)
PE age (d)	60.5 ± 35.6	64.0 ± 33.6	50.0 ± 39.8
Follow up age (y)	3.04 ± 4.29	2.81 ± 4.44	4.20 ± 4.06
Metavir stage (0-4)	2.0 ± 1.2	3.0 ± 1.1	2.0 ± 1.1*
α-SMA area fraction (%)	13.9 ± 7.79	15.5 ± 7.22	11.1 ± 8.15*
Collagen 1 area fraction (%)	15.6 ± 11.3	19.4 ± 9.98	10.0 ± 12.8*
Collagen 1 grade (0-4)	2.0 ± 1.2	2.0 ± 0.9	1.0 ± 1.2*
COL1A2 gene (fold change)	2.72 ± 2.37	3.02 ± 2.50	2.06 ± 2.20

Table. Characteristics of native liver fibrosis median three years after portoenterostomy
Data are median ± SD. *Mann Whitney U-test vs isolated patients, P≤0.05.