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DECREASED HEPATIC LXR AND ABCG5/8 GENE EXPRESSION ASSOCIATE WITH PARENTERAL NUTRITION, SERUM PLANT STEROLS AND LIVER INJURY IN INTESTINAL FAILURE

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Aim of the study. Parenteral nutrition (PN) associated cholestatic liver injury is a serious complication of pediatric intestinal failure (IF). In animal models, it is characterized by parenteral plant sterol induced suppression of nuclear receptor LXR and its target genes ABCG5 and ABCG8, encoding canalicular sterol transporters. We studied LXR, ABCG/8 expression in relation to liver injury, PN and serum plant sterols in children with IF.

Methods. After ethical approval, RNA (qRT-PCR) expression of LXR and ABCG5/8 were analyzed from liver biopsies in 40 IF patients and 6 donor livers (controls). Gene expression was quantified using ΔΔCt method and expressed relative to controls. Serum plant sterols were measured with gas liquid chromatography.

Main Results. Fourteen patients remained on PN after 31 (7.1-74) months and 26 patients had weaned off after 5.2 (2.3-13) months on PN. Gene expression of LXR and ABCG5/8 was up-regulated in IF patients compared to controls (**table**). Up-regulation of LXR expression was significantly suppressed in patients receiving PN or having portal inflammation, and expression of ABCG5/8 in patients with cholestasis and/or portal inflammation (**table**). Portal inflammation grade inversely associated with LXR and ABCG5/8 gene expression (r=-0.497- -0.602, P<0.05 for all), and cholestasis grade inversely with ABCG5 (r=-0.404, P=0.010) and ABCG8 (r=-0.404, P=0.010) gene expression. During PN delivery, ABCG8 gene expression was inversely associated with increased serum concentration of plant sterols, campesterol (r=-0.600, P=0.023) and avenasterol (r=-0.537, P=0.048).

Conclusions. PN delivery, cholestasis and portal inflammation were coupled with failure of up-regulation of hepatic gene expression of LXR and sterol transporters ABCG5/8, possibly interfering physiological biliary secretion of plant sterols contributing to liver injury in IF.

Table. Gene expression of LXR, ABCG5 and ABCG8.

	Nutrition		Controls	Cholestasis		Portal inflammation	
	PN	Weaned off		Yes	No	Yes	No
Patients (n)	14	26	6	8	32	7	33
LXR	1.4±0.2[a]	1.7±0.1	1.0±0.2[c]	1.3±0.2	1.6±0.1	1.2±0.1[a]	1.6±0.1
ABCG5	2.8±0.4	3.0±0.2	1.1±0.2[b,c]	2.3±0.4[a]	3.1±0.2	2.0±0.2[a]	3.1±0.2
ABCG8	1.9±0.3	1.9±0.1	1.1±0.2[c]	1.5±0.3[a]	2.0±0.1	1.2±0.1[a]	2.0±0.1

Fold changes are mean ± SEM. [a]P<0.05 between groups; [b]P<0.05 patients on PN vs controls; [c] P<0.05 patients weaned off PN vs controls.