HEPATOLOGY - General Hepatology

H-O-019

Native liver survival in patients with FIC1 deficiency: Impact of genotype, serum bile acid concentrations and surgical biliary diversion

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Objectives and Study: Mutations in ATP8B1 can lead to persistent cholestatic disease, also known as familial intrahepatic cholestasis protein type 1 (FIC1) deficiency or PFIC1. Apart from cholestasis and end-stage liver disease, patients may develop diarrhea, hearing loss, pancreatitis and allograft steatohepatitis. We analyzed factors associated with its prognosis, including the presence of predicted protein truncating mutations (PPTMs), serum bile acid concentrations (sBA) and surgical biliary diversion (SBD), using the largest genetically defined cohort of FIC1 disease to date.

Methods: Our multicenter, retrospective cohort study included 130 patients with compound heterozygous or homozygous predicted pathological mutations in ATP8B1. Patients were categorized according to the number of PPTMs (defined as splice site, frameshift due to deletion or insertion, nonsense, duplication); FIC1-A (n=63, no PPTM), FIC1-B (n=30, one PPTM) or FIC1-C (n=37, two PPTMs). Cut-offs for sBA were based on ROC analyses.

Results: Overall, serum bile acids concentration (sBA) at first presentation (below age 1y) was negatively associated with NLS during follow-up (%NLS at 10y: sBA< 194 µmol/L, 57% vs. sBA≥194 µmol/L, 31%; P=0.03, left figure). The proportion of patients with sBA at presentation < 194µmol/L was 45%, 60% and 68% in FIC1-A, FIC1-B and FIC1-C patients, respectively (P=0.09). Survival analysis showed that at age 18y, 44% of all patients were alive with native liver. Native liver survival (NLS) was comparable between the three groups (%NLS at 10y: FIC1-A, 67%; FIC1-B, 43%; and FIC1-C 58%, P=0.15). A lower fraction of FIC1-C patients underwent SBD (%SBD at 10y: FIC1-A, 66%; FIC1-B, 60%; and FIC1-C, 43%; P=0.02). Overall, undergoing SBD was associated with a decrease in sBA (pre-SBD 230µmol/L, post-SBD 74µmol/L; P=0.005). SBD tended to be associated with prolonged NLS (HR 0.53, 95%CI 0.28-1.01, P=0.05), as with a post-SBD sBA concentration < 65µmol/L (P=0.05, right figure). The proportion of patients achieving a post-SBD sBA concentration < 65µmol/L was comparable among FIC1-A, FIC1-B and FIC1-B patients (50; 40; and 63%, resp.; P=0.63), as was NLS at 10 years post-SBD (69; 45, 66%; resp. P=0.31).

Conclusion: Patients with one or two predicted protein-truncating ATP8B1 mutations do not differ in natural history from patients with other ATP8B1 mutations. Irrespective of the type of ATP8B1 mutations, serum bile acid concentration at initial presentation and surgical biliary diversion are associated with native liver survival in patients with FIC1 deficiency.

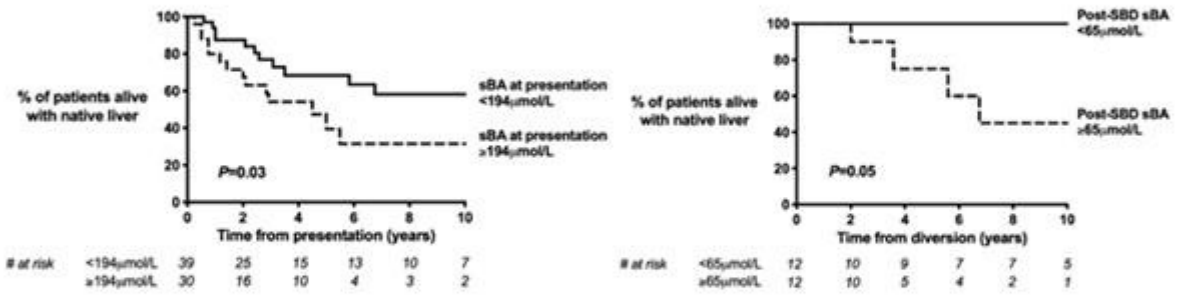

Figure. Proportion of patients with FIC1 deficiency that is alive with native liver, with a serum bile acid concentration at presentation <194μmol/L or ≥194μmol/L (left figure); and, with a post-surgical serum bile acid concentration <65μmol/L or ≥65μmol/L(right figure). Log-rank test.

[Figure]

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