Daan Van Wessel[1], Prof. Richard J. Thompson[2], Tassos Grammatikopoulos[2], Agustina Kadaristiana[2], Irena Jankowska[3], Patryk Lipiński[3], Dr. Piotr Czubkowski[3], Emmanuel M. Gonzales[4], Emmanuel Jacquemin[4], Anne Spraul[4], Prof. Etienne M. Sokal[5], Mohammad Shagrani[6], Dieter Broering[6], Talal Algoufi[6], Nejat Mazhar[6], Emanuele Nicastro[7], Deirdre A. Kelly[8], Gabriela Nebbia[9], Henrik Arnell[10], Björn Fischler[10], Jan Hulscher[11], Daniele Serranti[12], Prof. Cigdem Arikan[13], Esra Polat[14], Dominique Debray[15], Florence Lacaille[15], Cristina Goncalves[16], Loreto Hierro[17], Gema Muñoz Bartolo[17], Yael Mozer-Glassberg[18], Amer Azaz[19], Jernej Brecelj[20], Antal Dezsőfi[21], Pier Luigi Calvo[22], Enke Grabhorn[23], Ekkehard Sturm[24], Wendy Van Der Woerd[25], Dr. Bettina E. Hansen[26], Prof. Henkjan J. Verkade[1] and NAPPED (NAtural course and Prognosis of PFIC and Effect of biliary Diversion), (1)Pediatric Gastroenterology and Hepatology, University Medical Center Groningen, (2)King's College London, (3)Gastroenterology, Hepatology, Nutritional Disorders and Pediatrics, The Children's Memorial Health Institute, (4)Service D'hépatologie Et De Transplantation Hépatique Pédiatriques, Bicêtre Hôspital, (5)Université Catholique De Louvain, Cliniques St Luc, Brussels, Belgium, (6)Liver & SB Transplant & Hepatobiliary-Pancreatic Surgery, King Faisal Specialist Hospital & Research Center, (7)Pediatric Hepatology, Gastroenterology and Transplantation, Spedale Papa Giovanni XXIII, (8)Liver Unit, Birmingham Women's and Children's Hospital, (9)Servizio Di Epatologia e Nutrizione Pediatrica, Fondazione Irccs Ca' Granda Ospedale Maggiore Policlinico, (10)Pediatric Digestive Diseases, Astrid Lindgren Children's Hospital, Karolinska University Hospital, (11)Pediatric Surgery, University Medical Center Groningen, (12)Department of Health Sciences, University of Florence, (13)Department of Pediatric Gastroenterology, Hepatology and Nutrition, Organ Transplantation Center, Memorial Atasehir Hospital, Istanbul, Turkey, (14)Pediatric Gastroenterology, Hepatology and Nutrition, Kent Hospital, (15)Unité D'hépatologie Pédiatrique Et Transplantation, Hôpital Necker, (16)Coimbra University Hospital Center, (17)Pediatric Liver Service, La Paz University Hospital, (18)Nstitute of Gastroenterology, Nutrition and Liver Diseases, Schneider Children's Medical Center of Israel, (19)Sheikh Khalifa Medical City, (20)Pediatric Gastroenterology, Hepatology and Nutrition, University Medical Center Ljubljana, (21)1st Department of Pediatrics, Semmelweis University, (22)Department of Pediatrics, Azienda Ospedaliera Città Della Salute e Della Scienza Di Torino, (23)Klinik Für Kinder- Und Jugendmedizin, Universitätsklinikum Hamburg Eppendorf, (24)University Children’s Hospital Tübingen, (25)Wilhelmina Children's Hospital, University Medical Center Utrecht, (26)Toronto Centre for Liver Disease, University Health Network

Abstract Text:

Background:
Severe deficiency of FIC1 (FIC1-def) is due to mutations in the *ATP8B1*gene,

and is responsible for progressive familial intrahepatic cholestasis type 1. The *ATP8B1*encodes the FIC1-protein, which functions as an aminophospholipid translocase. Because of secondary impaired biliary bile salt secretion, patients typically present with pruritus and low gamma-GT cholestasis in early childhood. FIC1 is also expressed in other tissues, such as pancreas and intestine, and extrahepatic manifestations may occur in FIC1-def patients. Ursodeoxycholic acid or surgical biliary diversion (SBD) techniques might be beneficial for some patients, yet many patients require liver transplantation (LTx) at some stage. We aim to better understand the natural course of FIC1-def and the efficacy of interventions. Therefore, we have set up an extensive international consortium, “NAPPED” (NAtural course and Prognosis of PFIC and Effect of biliary Diversion).

Methods: We present retrospective follow up data on individual patients from 22 centers in Europe, North-America, Asia and Australia. All patients were either compound heterozygous or homozygous for disease associated mutations in the *ATP8B1*gene. We used time-dependent Cox regression for native liver survival (NLS), adjusted for gender and birth year, in patients that had undergone SBD (SBD+ve) or not (SBD-ve). Continuous variables are expressed as median [range].

Results: We included 46 FIC1-def patients (predominately males, 76%; P<0.001). Age at first visit was 0.5 [0-16.8] years. Use of ursodeoxycholic acid prior to first visit was 39%. Age at last follow up was 5.4 [0.25-27.8] years. Overall SBD rates at five/ten years of age were 37/43%, for males (36/45%) and females (50/50%, respectively; p=0.15). SBD rates in compound heterozygous and homozygous patients were 34/34% and 37/45%, respectively (p=0.29). Overall five/ten-year NLS was 74/46%. Five/ten-year NLS in males and females was 71/49% and 88/58%, respectively (p=0.87). NLS in compound heterozygous and homozygous patients was 78/33% and 72/52%, respectively (p=0.61). NLS did not differ significantly between SBD+ve patients and SBD-ve patients [HR=1.16; 95%CI(0.33-4.01); p=.82]. HCC was not encountered in any patient during follow-up, in contrast to observations in other cholestatic diseases. Mortality prior to LTx was 2%. The observed NLS at 18 years of age was 46%.

Conclusion: Our large global cohort of this extremely rare condition allows to address genotype - phenotype relationships in FIC-1 deficiency and to study the natural course of diseases. Our data indicate that mortality is relatively low and that the vast majority of patients reaches adulthood, with native or transplanted liver, and thus becomes an important, relatively new patient entity for adult hepatology practice.

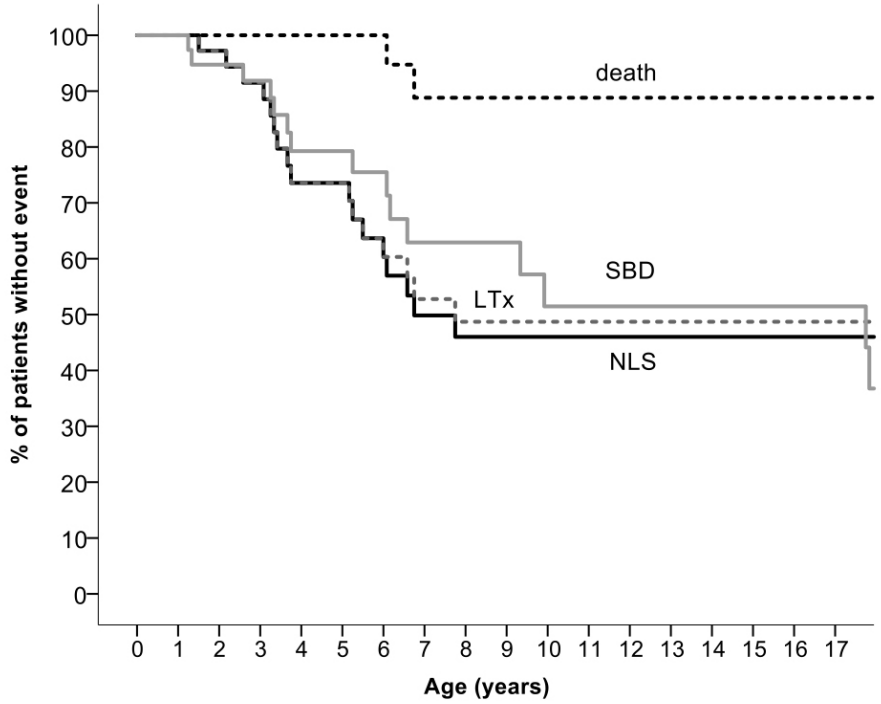

Figure. Native liver survival (NLS), liver transplantation (LTx), surgical bile diversion (SBD) and death in patients with FIC1 deficiency between age 0-18 years (n=46).

Title:
The Natural Course of FIC1 Deficiency: Results from the Napped-Consortium
Submitter's E-mail Address:
d.b.e.van.wessel@umcg.nl
Presentation Type:
Oral or Poster
Sponsorship:
We received partial sponsoring by an unrestricted grant from Albireo AB.
Religious Observation Days:
Not Applicable
Category:
Pediatric Hepatology
Description:
SO4 Metabolic and Genetic Diseases