OPEN

Liver Transplantation and Development of Diabetes in an Adolescent Male With HNF1B Disease

*Jody A. Weckwerth, PA-C, †Amanda R. Dahl, MD, †Siobhan T. Pittock, MD, †Seema Kumar, MD, ‡Charles B. Rosen, MD, *Rayna M. Grothe, MD, and §Katryn N. Furuya, MD

Abstract: Mutations in the hepatocyte nuclear factor-1-beta (*HNF1B*) gene cause a variety of diseases in different organ systems. Mutations have been described as causing neonatal cholestasis, maturity-onset diabetes of the young (type 5), cortical renal cysts, urogenital abnormalities, liver dysfunction, and atrophy of the pancreas. We describe a male patient who presented with cholestatic liver disease in infancy which progressed by age 14 to end-stage liver disease due to HNF1B disease. He subsequently underwent liver transplantation at age 15 and then developed diabetes requiring insulin which did not resolve after cessation of corticosteroids. To our knowledge, this is the first case reported of liver transplantation for decompensated cirrhosis secondary to HNF1B disease.

Key Words: liver transplantation, HNF1B, MODY type 5, cholestatic liver disease, HNF-1-beta

Mutations of the transcription factor gene hepatocyte nuclear factor-1-beta (*HNF1B*) on chromosome 17q were originally associated with maturity-onset diabetes of the young type 5 (MODY type 5) and with pancreas hypoplasia. Hepatic and biliary associations in HNF1B disease have also been described. The patient discussed herein presented with cholestatic liver disease in infancy and ultimately underwent liver transplantation at age 15 followed by post-transplant development of diabetes requiring insulin.

Received September 3, 2020; accepted March 13, 2021.

From the *Division of Pediatric Gastroenterology and Hepatology, Department of Pediatrics, Mayo Clinic, Rochester, MN; †Division of Pediatric Endocrinology, Department of Pediatrics, Mayo Clinic, Rochester, MN; ‡Department of Surgery, William J. von Liebig Center for Transplantation, Mayo Clinic, Rochester, MN; and §Division of Pediatric Gastroenterology and Hepatology, Department of Pediatrics, University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI.

The authors report no conflicts of interest.

J.W. contributed to the conception and design of this work; collected and interpreted data; and drafted the initial article and approved the final version submitted. A.D. contributed to the conception and design of this work; collected and interpreted data; and drafted portions of the initial article, revised the article, and approved the final version submitted. S.P. helped collect and interpret data; reviewed and revised the article, approved the final version submitted. S.K. helped collect and interpret data; reviewed and revised the article, approved the final version submitted. C.R. contributed to design of this work; reviewed article, approved the final version submitted. K.F. contributed to the conception and design of this work; collected, analyzed and interpreted data; reviewed and revised the article, approved the final version submitted.

Correspondence: Jody A. Weckwerth, PA-C, Division of Pediatric Gastroenterology and Hepatology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, 200 1st St. SW, Rochester, MN 55905. E-mail: weckwerth.jody@mayo.edu

JPGN Reports (2021) 2:3(e085)
ISSN: 2691-171X
DOI: 10.1097/PG9.0000000000000085

CASE REPORT

The patient presented to an outside facility with jaundice at 4 weeks of age. At 6 weeks of age, liver biopsy showed a paucity of interlobular bile ducts and zone 3 canalicular cholestasis with no significant portal fibrosis. A presumptive diagnosis of Alagille syndrome was established at a second facility based on clinical criteria. There were neither butterfly vertebrae nor cardiac anomalies; however, posterior embryotoxon was reportedly present on ophthalmologic examination. Genetic testing for *JAG1* mutation was performed and was negative. During childhood, his cholestasis persisted. Bilateral simple renal cysts were identified. From age 1 to 5 years, he developed multiple long bone fractures from severe metabolic bone disease attributed to vitamin D deficiency and cholestasis, despite treatment with calcitriol and both oral and intramuscular ergocalciferol.

At age 12, genetic testing for Alagille syndrome (*JAG1* and *NOTCH2*) was again negative. He was subsequently found to have a c.884G>A (p.R295H) mutation in the *HNF1B* gene. At that time, he had neither endocrine nor exocrine pancreatic insufficiency but did have renal cysts. Renal function was normal.

At age 14, he developed decompensated cirrhosis with jaundice and coagulopathy, peripheral edema, hepatic encephalopathy, and refractory hypovitaminosis D. He was noted on imaging to have an atrophic appearing pancreas yet had normal hemoglobin A1c and serum glucose levels. He was treated for symptoms of the end-stage liver disease up until transplant. He underwent a deceased donor whole organ liver transplant at age 15 with initial immunosuppression of prednisone, tacrolimus, and mycophenolate mofetil as per our standard protocol. The goal level of tacrolimus was set at 8–10 ng/mL rather than our standard of 10–12 ng/mL in hopes of avoiding nephrotoxicity. The liver explant (see Fig. 1) histology was negative for hepatocellular carcinoma (HCC) and showed chronic biliary-type disease with loss of intrahepatic bile ducts in approximately 90% of the portal tracts.

Two weeks post-transplant, the patient was noted to have serum glucose of 658 mg/dL, HbA1c of 4.1%, random insulin of 29.9 mcIU/mL (reference range 2.6–24.9 mcIU/mL) while bicarbonate was 15 mmol/L (reference range 21–29 mmol/L), and beta-hydroxybutyrate was 0.1 mmol/L. He was receiving 15 mg prednisone daily (equivalent to 86 mg/m^2/day using BSA of 1.85 m^2), mycophenolate mofetil 750 mg every 12 h, and tacrolimus 7.5 mg every 12 h. Tacrolimus level was slightly above the goal range of 8–10 ng/mL at the time and dosing was adjusted accordingly. He was started on insulin aspart at mealtimes and insulin glargine daily. At the time of discharge, he was on a total insulin dose of 0.88 units/kg/day.

Type 1 diabetes mellitus associated auto-antibodies [insulinoma-associated protein 2 (IA-2), glutamic acid decarboxylase 65 (GAD65), insulin antibodies, and zinc transporter ZnT8 (ZnT8)] were negative. Steroids and mycophenolate mofetil were discontinued by 4 months and 6 months, respectively, after transplant while he continued on tacrolimus. At 12 months post-transplant, the patient continues to be insulin-dependent though insulin requirements have decreased to the equivalent of 0.3 units/kg/day. Insulin was discontinued for 2 weeks at one time but was resumed due to rising blood

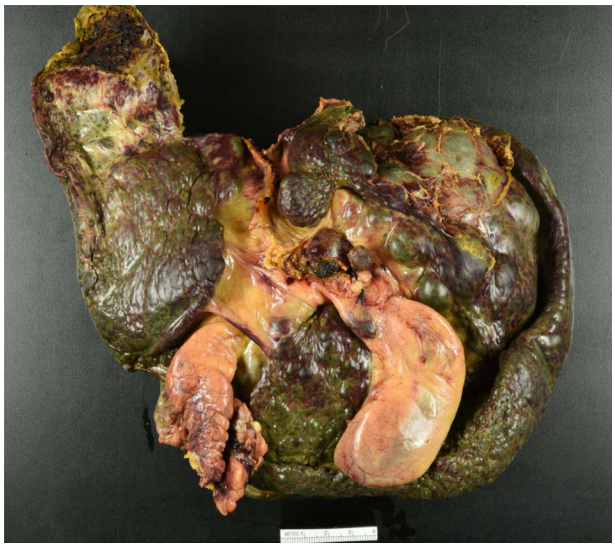

FIGURE 1. Liver explant photograph.

glucose following an increase in the dose of tacrolimus. The transplanted liver is functioning well.

DISCUSSION

Hepatic nuclear factor 1-beta (encoded by the *HNF1B* gene) is involved in the transcription and regulation of the liver, biliary system, kidneys, urogenital tract, and pancreas. HNF1B disease manifests in a variety of organ systems with onset varying from the neonatal period to adulthood. The term renal cysts and diabetes syndrome has been used to describe the syndrome associated with defects in HNF1B although manifestations in other organ systems are increasingly recognized. Neonatal cholestasis has been reported along with paucity of intrahepatic bile ducts, HCC, cortical renal cysts, and atrophy of the pancreas (1–3). Children can present with neurologic/behavioral symptoms (due to larger microdeletions in chromosome 17q), biliary system defects, or diabetes (4). Waller et al. describe a 14-year-old boy with HNF1B mutation who developed severe hyperglycemia after renal transplantation (5).

HNF1B variants manifest in a range of severity of phenotype. Before transplant, our patient had liver disease and renal cysts without other extrahepatic manifestations of HNF1B disease. Kidney function was normal. Imaging of the urogenital system showed only small cysts in the right kidney with otherwise normal kidneys and bladder. Despite his pancreas appearing atrophic on imaging pretransplant, he had no evidence of either endocrine or exocrine pancreatic insufficiency (normal fasting glucose and normal HbA1c). His pancreatic elastase was normal and he had excellent linear growth. Parathyroid hormone levels were normal for several years before transplant.

Insulin-dependent diabetes mellitus developed post-transplant while on prednisone, tacrolimus, and mycophenolate mofetil. The estimated incidence of diabetes after liver transplantation is 14%–44% and is likely due to dysfunction of the islets of Langerhans present in patients with cirrhosis as an effect of immunosuppressive agents, particularly calcineurin inhibitors like tacrolimus (6). Tacrolimus can decrease insulin secretion, cause pancreatic β-cell necrosis, and increase insulin resistance in a dose-dependent manner (7). We speculate that our patient's underlying predisposition to diabetes was exacerbated by tacrolimus.

To date, there is only one report of a pediatric patient undergoing liver transplant with HNF1B disease and that patient had HCC (8). Importantly, our patient is the first case report of a pediatric patient who underwent liver transplantation for decompensated cirrhosis due to HNF1B disease. In addition, he developed diabetes requiring insulin management after liver transplantation.

REFERENCES

1. Kotalova R, Dusatkova P, Cinek O, et al. Hepatic phenotypes of HNF1B gene mutations: a case of neonatal cholestasis requiring portoenterostomy and literature review. *World J Gastroenterol*. 2015;21:2550–2557.
2. Pinon M, Carboni M, Colavito D, et al. Not only Alagille syndrome. Syndromic paucity of interlobular bile ducts secondary to HNF1β deficiency: a case report and literature review. *Ital J Pediatr*. 2019;45:27.
3. Kitanaka S, Miki Y, Hayashi Y, et al. Promoter-specific repression of hepatocyte nuclear factor (HNF)-1 beta and HNF-1 alpha transcriptional activity by an HNF-1 beta missense mutant associated with type 5 maturity-onset diabetes of the young with hepatic and biliary manifestations. *J Clin Endocrinol Metab*. 2004;89:1369–1378.
4. Kettunen JLT, Parviainen H, Miettinen PJ, et al. Biliary anomalies in patients with HNF1B diabetes. *J Clin Endocrinol Metab*. 2017;102:2075–2082.
5. Waller SC, Rees L, Woolf AS, et al. Severe hyperglycemia after renal transplantation in a pediatric patient with a mutation of the hepatocyte nuclear factor-1beta gene. *Am J Kidney Dis*. 2002;40:1325–1330.
6. Ling Q, Xu X, Wang B, et al. The origin of new-onset diabetes after liver transplantation: liver, islets, or gut? *Transplantation*. 2016;100:808–813.
7. Regelmann MO, Goldis M, Arnon R. New-onset diabetes mellitus after pediatric liver transplantation. *Pediatr Transplant*. 2015;19:452–459.
8. de Leusse C, Maues De Paula A, Aschero A, et al. Hepatocarcinoma and cholestasis associated to germline hemizygous deletion of gene HNF1B. *J Pediatr Gastroenterol Nutr*. 2019;68:e85.