Radiology Case Reports

Volume 8, Issue 1, 2013

Disodium gadoxetate uptake in progressive familial intrahepatic cholestasis type I: Enhancing our understanding of the cholestatic disease

Mikin V. Patel, MD; Shlomo Leibowich, MD; Jesse L. Courtier, MD; Sue Rhee, MD: and John D MacKenzie, MD

Hepatocyte-specific magnetic resonance imaging (MRI) contrast agents are commonly used to depict anatomic hepatobiliary lesions and are also useful in characterizing the kinetics of hepatocyte uptake and excretion. We report a case of a 13-year old female with progressive familial intrahepatic cholestasis (PFIC) type 1 who demonstrated decreased uptake and excretion of gadoxetate disodium contrast material. This case illustrates the challenge of imaging children with cholestasis using hepatobiliary-specific contrast agents; we propose an alternative explanation for the delayed excretion that may be related to the underlying genetic defect of this child.

Introduction

MRI offers distinct advantages for the evaluation of liver disease in children, including superior tissue contrast and lack of ionizing radiation. Several contrast agents targeted to the hepatobiliary system are also available for MRI and provide valuable information for characterizing liver lesions and the structure of bile ducts (1, 2). These hepatobiliary specific contrast agents also give functional information. Liver disease may alter the imaging kinetics of these agents —due in part to alterations in transport through the hepatocyte —which may in turn suggest complex hepatobiliary pathology, including liver dysfunction and cirrhosis (3, 4). However, one area that remains to be explored is the potential role for these contrast agents in the management of various familial disorders of bile formation and cholestasis. In this report, we present an example of the potential imaging features and challenges for evaluating this patient population with hepatobiliary-specific MRI contrast agents.

Case report

A 13-year-old female with a history of PFIC type 1 (status post cholejejunostomy at age 8 months) presented with increasing jaundice and pruritis, and decreasing ostomy output. Her medical history was otherwise unremarkable, and her symptoms had been previously well managed with ursodiol, cholestyramine, and surgical biliary diversion. She was found to have elevated total and direct bilirubin levels in the blood and was referred for MRI evaluation of the abdomen and biliary system after a liver Doppler ultrasound study showed no abnormality.

The MRI included routine abdominal imaging sequences at 3 Tesla and magnetic resonance cholangiopancreatography (MRCP) imaging before and after the dynamic intravenous injection of gadoxetate disodium (EOVIST, Bayer Healthcare, Wayne, NY). The liver parenchyma appeared normal in contour and in T1- and T2-weighted signal characteristics. The nongadolinium portion of the MRCP depicted the cholejejunostomy with no stricture or obstruction, which was later confirmed by cholangiography performed by the retrograde injection of iodinated contrast material into the cholejejunosomy. Postcon-

Citation: Patel MV, Leibowich S, Courtier JL, Rhee S, MacKenzie JD. Disodium gadoxetate uptake in progressive familial intrahepatic cholestatis type I: Enhancing our understanding of the cholestatic disease. *Radiology Case Reports.* (Online) 2013;8:661.

Drs. Patel, Leibowich, Courtier, and MacKenzie are in the Depatment of Radiology and Biomedical Imaging, and Dr. Rhee is in the Department of Pediatrics, all at UCSF Benioff Children's Hospital, San Francisco CA. Contact Dr. MacKenzie at john.mackenzie@ucsf.edu.

Competing Interests: The authors have declared that no competing interests exist.

DOI: 10.2484/rcr.v8i1.661

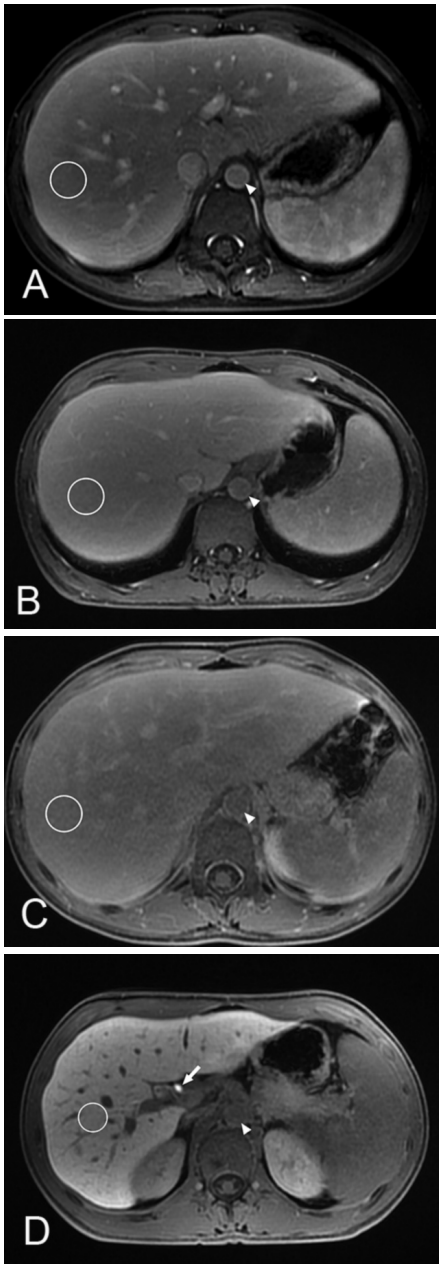

Figure 1. Comparison of relative amounts of hepatic delivery and bile excretion of gadoxetate disodium at 1.5 minutes (A and B) and 20 minutes (C and D) after the intravenous administration of the hepatobiliary-specific contrast agent in the child with PFIC type 1 (A and C) and a separate child with normal liver function (B and D). Signal intensities were measured by region-of-interest analysis at the aorta (arrowheads) and liver parenchyma (circles) away from any large vessels to calculate the liver-to-aorta ratio (L/R). The L/R ratio was lower in the patient with PFIC type 1 at both 1.5 and 20 minutes (L/R = 1.0 and 1.3, respectively) than the patient with normal liver function (L/R = 1.2 and 1.6, respectively). On delayed imaging, contrast excreted into the bile duct (arrow in D) in the normal patient, but not in the patient with PFIC type 1.

trast imaging was performed using a dynamic fast-spoiled gradient echo sequence with fat saturation.

The arterial and portal venous phases of the contrast-enhanced MRI showed normal vascular structures. However, relatively little contrast material was initially taken up by the liver. Instead, more contrast material was retained in the blood pool and drained into the hepatic veins (Fig. 1A) than is typically seen in normal patients who have received gadoxetate disodium (Fig. 1B). At 20 minutes after administration of gadoxetate disodium, the liver parenchyma showed relatively little enhancement and minimal excretion into the bile ducts (Fig. 1C), compared with normal hepatobiliary phase imaging (Fig. 1D). This lack of hepatobiliary uptake of gadoxetate disodium suggested intrinsic liver dysfunction, and the patient was referred for a liver biopsy. However, biopsy showed evidence of cholestasis, but normal interlobular bile ducts and no evidence of cirrhosis or steatohepatitis.

Discussion

An understanding of the molecular mechanisms of hepatic uptake and excretion of gadoxetate disodium (GD), coupled with knowledge of the molecular defect in PFIC type 1, may help explain the MR imaging findings in this patient. GD provides excellent visualization of hepatobiliary anatomy on MRI because it is readily taken up by hepatocytes, and approximately 50% is excreted into the biliary system (2). The cellular mechanism for hepatocyte uptake relies on the organic anion-transporting polypeptide (OATP) family of carriers, and subsequent biliary excretion occurs through the action of multidrug resistance protein 2 (MRP2) (1, 3, 4).

Patients with PFIC suffer from a disruption in bile transport causing cholestasis, and this ultimately leads to liver failure, cirrhosis, hepatocellular carcinoma, and extrahepatic manifestations. Three types of PFIC have been defined; the mechanisms responsible for dysfunction in bile transport are less well understood in PFIC type 1. PFIC type 1 is caused by a mutation in the ATP8B1 gene encoding the FIC1 protein, a P-type adenoside triphosphatase found mainly on the canalicular membrane of hepatocytes and in intrahepatic cholangiocytes (which are thought to mediate aminophospholipid translocation in the plasma membrane) (5, 6).

Although the precise mechanism for cholestasis has yet to be elucidated, it has been postulated that a FIC1 defect works indirectly to disturb the secretion of bile acids (5). Some investigators report that impaired FIC1 function results in downregulation of nuclear receptors, such as the farnesoid X receptor (FXR), and that this then causes subsequent downregulation of bile transporters such as OATP2 and the bile-salt export pump (BSEP) (6, 7).

This potential effect of FIC1 on OATP2 and BSEP may provide the link between the autosomal recessive mutation in PFIC type 1 and the MRI kinetics of GD observed in our patient (Fig. 2). GD shares similar mechanisms for bile transport as it enters the hepatocyte through OATP1 and is pumped into the biliary canaliculi by MRP2 (1, 3, 4). We

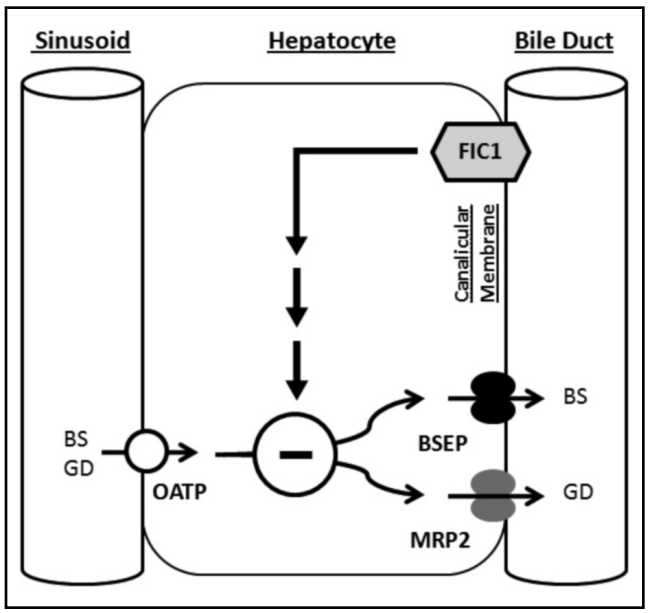

Figure 2: Proposed link between gadoxetate disodium transport in hepatocytes and the molecular defect in patients with PFIC type 1. Gadoxetate disodium (GD) and bile salts (BS) are taken up from the blood via the organic anion-transporting polypeptide (OATP) family of membrane proteins. GD and BS are subsequently excreted into the bile canaliculi via multidrug resistance proteins (MRP) and bile-salt export pump (BSEP) at the apical membrane. A defect in FIC1 protein in patients with PFIC type 1 may work upstream to eventually decrease the transport of GD and BS.

hypothesize that impaired FIC1 function may downregulate OATP1 and MRP2, which ultimately results in poor hepatocyte uptake of GD.

In conclusion, the pattern of hepatobiliary enhancement seen in our patient with PFIC type 1 may be linked to the molecular defect that gives rise to cholestasis in these patients. A defect in F1C1 protein may cause a decreased or delayed transport of gadoxetate disodium through the hepatocyte. Our case illustrates this attenuation of gadoxetate disodium kinetics as depicted on MRI. It is possible that hepatobiliary-targeted contrast agents such as gadoxetate disodium may help characterize and lend a better understanding to the molecular basis of PFIC type 1. Thus, the use of this imaging agent in this patient population warrants further investigation.

References

1. Fidler J, Hough D. Hepatocyte-specific magnetic resonance imaging contrast agents. *Hepatology*. 2011 Feb;53(2):678-82. [PubMed]
2. Seale MK, Catalano OA, Saini S, Hahn PF, Sahani DV. Hepatobiliary-specific MR contrast agents: Role in imaging the liver and biliary tree. *Radiographics*. 2009 Oct;29(6):1725-48. [PubMed]
3. Tsuda N, Matsui O. Cirrhotic rat liver: Reference to transporter activity and morphologic changes in bile canaliculi--gadoxetic acid-enhanced MR imaging. *Radiology*. 2010 Sep;256(3):767-73. [PubMed]
4. Tsuda N, Matsui O. Signal profile on gd-EOB-DTPA-enhanced MR imaging in non-alcoholic steatohepatitis and liver cirrhosis induced in rats: Correlation with transporter expression. *Eur Radiol*. 2011 Dec;21(12):2542-50. [PubMed]
5. Hori T, Nguyen JH, Uemoto S. Progressive familial intrahepatic cholestasis. *Hepatobiliary Pancreat Dis Int*. 2010 Dec;9(6):570-8. [PubMed]
6. Demeilliers C, Jacquemin E, Barbu V, Mergey M, Paye F, Fouassier L, Chignard N, Housset C, Lomri NE. Altered hepatobiliary gene expressions in PFIC1: ATP8B1 gene defect is associated with CFTR down-regulation. *Hepatology*. 2006 May;43(5):1125-34. [PubMed]
7. Pellicoro A, Faber KN. Review article: The function and regulation of proteins involved in bile salt biosynthesis and transport. *Aliment Pharmacol Ther*. 2007 Dec;26 Suppl 2:149-60. [PubMed]