Does Genetics Play a Role in Acute Liver Injury After Amoxicillin Exposure?

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<ABSTRACT>
Amoxicillin-clavulanate has long been associated with drug-induced liver injury (DILI) and although approximately 4 times less common, amoxicillin has also been implicated. Many studies have associated possible genetic factors with susceptibility to DILI, but there is currently no literature with evidence of instances of DILI within the same family. Two sisters presented with similar symptoms and signs of liver injury including jaundice, scleral icterus, abdominal pain, and anorexia with transaminitis and abnormal coagulation studies. Both sisters were started on amoxicillin approximately 2–3 weeks before presentation. They both had progression of the liver injury, and on biopsies, they had similar findings indicative of DILI as well.

<INTRODUCTION>
Drug-induced liver injury (DILI) only accounts for 10% of acute hepatitis and although it is very rare, it is even rarer in the pediatric population.¹ There are over a 1,000 drugs that have been implicated in DILI with the most commonly associated drugs in the United States being acetaminophen followed by antibiotics.² Although amoxicillin is the most prescribed medication in the United States, with over 50 million prescriptions yearly, amoxicillin-clavulanate tends to be the antibiotic most commonly associated with DILI.³ Drugs associated with DILI can cause damage in a dose-dependent manner or it could be idiosyncratic. Multiple studies have investigated the genetic factor influence on DILI and at this point, HLA-DRB1*15:01 has been associated with amoxicillin-clavulanate, but there is no known factor associated with amoxicillin specifically.⁴,⁵

<CASE REPORT>
Patient 1: A previously healthy 3-year-old girl presented with worsening abdominal pain associated with emesis and decreased oral intake. On her admission, she was found to have significant transaminitis and cholestasis with abnormal coagulation studies. Test results were aspartate aminotransferase (AST) of 4911 U/L, alanine transaminase (ALT) of 4343 U/L, gamma-glutamyl transferase of 151 U/L, total bilirubin of 6.4 mg/dL, direct bilirubin of 5.4 mg/dL, prothrombin time (PT) of 15.3 seconds, partial thromboplastin time of 26.8 seconds, and international normalized ratio (INR) of 1.4. She was previously seen 1 month before admission where her complete blood count, comprehensive metabolic panel (CMP), and liver function tests were within the normal limits. Two weeks before admission, she was started on a 10-day course of amoxicillin. One day before admission, the patient’s mother noticed yellowing of the eyes and face. Her parents deny recent travel, and the child is up to date with vaccinations. Her family history is significant for a father with a fatty liver disease and a mother who was told recently that she has an “inflamed liver from a medication.” The child’s workup included hepatitis A, B, and C, alpha-1 antitrypsin, ceruloplasmin, Epstein-Barr virus, cytomegalovirus, adenovirus, urine toxicityology, celiac panel, and autoimmune hepatitis laboratory test results (antinuclear antibody, anti-liver-kidney microsomal antibody, antisMOOTH muscle antibody, and antisoluble liver antigen) were all negative. An abdominal ultrasound revealed hepatomegaly with no mass or lesions. There was also diffuse gallbladder wall thickening with trace pericholecystic fluid, no ductal dilatation, and no evidence of cholelithiasis.
While admitted, the patient remained afebrile with stable vital signs. She was started on ursodiol 140 mg every 8 hours, omeprazole 10 mg twice daily, and vitamin K 2.5 mg orally daily. Laboratory test results were repeated on day 1 of admission, which were significant for AST 3826 U/L, ALT 3840 U/L, gamma-glutamyl transferase 135 U/L, total bilirubin 7.5 mg/dL, direct bilirubin 6.6 mg/dL, PT 15.3 seconds, partial thromboplastin time 31.6 seconds, and INR 1.7. Complete blood count and CMP were unremarkable, including creatinine of 0.22 mg/dL and platelet count of 227 × 10^9/L. With the increasing INR, she was switched to 5 mg IV vitamin K daily. With vitamin K, her INR continued to climb to 1.9 at which time the case was discussed with a regional liver transplant center and it was determined that the patient would benefit from liver biopsy and prompt pathology reading for the possible start of treatment. On transfer, liver biopsy was performed, and the findings showed “features of acute and chronic hepatitis” (Figure 1). The pathologist further noted “plasma cells were conspicuous, a non-specific finding, and can be seen in a variety of acute and chronic hepatitis including drug injury, infection, and autoimmune hepatitis.” She was continued on ursodiol and started on prednisone. She improved and was discharged within a few days.

**Patient 2:** A 12-month-old previously healthy girl presented with 2 days of scleral icterus and increased lethargy. On admission, laboratory test results were remarkable for ALT of 2667 U/L, AST of 3030 U/L, alkaline phosphatase of 578 IU/L, total bilirubin of 6.7 mg/dL, and direct bilirubin of 5.6 mg/dL. CMP was unremarkable, but platelets were 134 × 10^9/L. Coagulation studies were also elevated (PT 16.3 seconds, partial thromboplastin time 33.7 seconds, INR 1.4). Workup included hepatitis A, B, and C, alpha-1 antitrypsin, ceruloplasmin, Epstein-Barr virus, cytomegalovirus, urine toxicology, celiac panel, and autoimmune hepatitis laboratory test results (antinuclear antibody, anti-liver-kidney microsomal antibody antibody, antismooth muscle antibody, and soluble liver antigen)—all of which were negative. Abdominal ultrasound was unremarkable. Of note, her sister (patient 1) was admitted 3 days earlier for a similar clinical picture. The patient also received 10 days of amoxicillin 160 mg twice daily approximately 2 weeks before presentation at the hospital. She denied pruritus, easy bruising, travel, fever, chills, dyspnea, and emesis.

A liver biopsy was performed, and she was started on ursodiol along with 2.5 mg of IV vitamin K twice daily. Liver biopsy showed “moderate to severe acute portal and lobular hepatitis, most compatible with the clinical concern for drug-induced liver injury” (Figure 2). Her INR remained stable at 1.3–1.5 for 3 days with improving liver function tests and cholestasis. Before discharge, INR was 1.0 with ALT 1184 U/L, AST 759 U/L, alkaline phosphatase 563 IU/L, total bilirubin 3.2 mg/dL and direct bilirubin 2.4 mg/dL.

**DISCUSSION**

This case series highlights the probability of genetic factors having a role in the pathogenesis of DILI. Augmentin may be the single most common causal agent of idiosyncratic DILI, responsible for 10%–13% of DILI-related hospitalizations, with the thinking that the injury is from the clavulanate in the Augmentin, but amoxicillin may have a role as well. Amoxicillin, on its own, is responsible for DILI in 0.3 per 10,000 prescriptions. Although much work has been done in the past to show the HLA genetic association between Augmentin and DILI, there is still not enough evidence to decisively establish that these genetic factors are truly causative of DILI. This case series exemplifies the importance of further studies to understand the role of genetic predisposition to DILI. Autoimmune hepatitis certainly may be triggered by medications, but the liver biopsies were not indicative of autoimmune hepatitis, and the obtained blood work for autoimmune hepatitis was also negative. Although viral hepatitis remains a consideration, workup was negative and the biopsies were more consistent with drug-induced injury. In addition, the jaundice did not occur in conjunction with upper respiratory symptoms, but 2 weeks later and in both cases after amoxicillin exposure.

**Figure 1.** Liver biopsy showing lymphoplasmacytic portal interface hepatitis (arrow) with prominent eosinophils (arrow heads) (hematoxylin and eosin stain, 40× magnification).

**Figure 2.** Liver biopsy showing lymphoplasmacytic portal interface hepatitis with less prominent eosinophils (hematoxylin and eosin stain, 40× magnification).
DISCLOSURES

Author contributions: A. Schosheim wrote the manuscript, revised the manuscript for intellectual content, and is the article guarantor. D. Mockler and A. Chawla edited the manuscript and revised it for intellectual content.

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