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CASE REPORT

Hepatology

Extrahepatic biliary atresia and normal-range serum gamma-glutamyltranspeptidase activity: A case report

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Abstract

An infant with biliary atresia had normal-range ('low') serum gamma-glutamyltranspeptidase (GGT) activity, exceptional because GGT generally is elevated in biliary atresia. Mechanisms underlying low-GGT cholestasis in biliary atresia are not defined, but the phenomenon is associated with worse clinical outcome. Testing in our patient revealed no variants in genes mutated in several disorders also associated with poor prognosis and with low-GGT cholestasis; indeed, at age 14 months she has stable disease with unremarkable biomarker values. Nonetheless, we recommend extended investigations in such patients, including genetic testing, to detect coexistent disorders and to expand understanding of GGT in biliary atresia.

KEYWORDS

gamma-glutamyl transferase, low GGT, normal GGT

1 | INTRODUCTION

Biliary atresia is a rare disease of early infancy. It obliterates extrahepatic bile ducts with fatal outcome if untreated. Patients present with cholestasis and elevated values for biomarkers of hepatobiliary injury, generally including serum gamma-glutamyltranspeptidase (GGT) activity.[1] GGT is an ectoenzyme expressed in the liver principally along biliary-tract luminal margins, whence bile acids leach it into bile that then leaks between damaged hepatocytes into plasma.[2] However, infants with biliary atresia and low or normal GGT are described, in association with a relatively adverse prognosis.[3,4] In nonobstructive cholestasis of infancy, normal-range GGT has long been associated with unfavourable outcome,[5] traced in recent years to several disorders characterised by normal-range GGT despite conjugated hyperbilirubinaemia. These include types of progressive familial intrahepatic cholestasis, with lesions in *ATP8B1*,[6,7] *ABCB11*[6,7] and *TJP2*[8]; disorders of bile-acid synthesis and conjugation[9,10] and severe liver disease of intrauterine onset (infection, 'neonatal haemochromatosis/gestational alloimmune liver disease).[11]

Here, we report an infant with clinical, imaging-study and, at liver biopsy, histopathologic features consonant with nonsyndromic biliary atresia who presented with a clinical-biochemistry anomaly: none-levated GGT values. No reason exists a priori for coexistence of biliary atresia with other forms of neonatal liver disease (alloimmune, infectious or heritable) to be impossible. This report describes our attempt to identify evidence in our patient for a disorder other than

biliary atresia that might underlie failure of GGT to rise despite conjugated hyperbilirubinaemia.

2 | CASE

A 6-week-old female infant, the first-born child of unrelated parents after an uncomplicated full-term pregnancy, was referred for evaluation of conjugated hyperbilirubinemia with brownish urine. The girl was well-grown, without dysmorphism, but deeply jaundiced—reportedly since birth. Although stools were described as 'always yellowish', the diaper contained acholic faeces. Serum direct bilirubin concentrations were elevated, while GGT was not (Figure 1). Serum bile-acid concentrations and transaminase activities also were elevated. Liver synthetic function was normal. Sonography at Day 44 showed an enlarged and blunt-edged liver, with an orthotopic but rudimentary gallbladder (Figure 2A). Intrahepatic bile ducts were thickened but not dilated. No extrahepatic bile ducts were seen. Biliary atresia was provisionally diagnosed. Light microscopy of a percutaneous liver-biopsy specimen (Day 47) found bile thrombi in lumina of intraportal bile ducts, as expected in biliary atresia (Figure 2B), with portal-tract oedema and mild fibrosis; intralobular cholestasis also was present, with moderate lobular disarray interpreted as nonspecific. At laparotomy (Day 56), the liver was slightly firm but not manifestly cirrhotic. Only remnants of the gallbladder and common bile duct were seen (Figure 2C). They could not be cannulated for cholangiography. A Kasai portoenterostomy was performed. On microscopy, the hypoplastic lumina of excised gallbladder and other extrahepatic biliary-tract structures were focally effaced by fibrosis and chronic inflammation, again as expected in biliary atresia. Bile-duct lumina at the porta hepatis were patent.

Given the adverse implications of normal-range GGT in biliary atresia, and bearing in mind that various disorders other than biliary atresia can manifest conjugated hyperbilirubinaemia with normal-range GGT,

What is Known

- Serum gamma-glutamyltranspeptidase (GGT) activity is typically elevated in biliary atresia.
- In approximately 12%–25% of cases, GGT is normal or low.
- Normal or low GGT in patients with biliary atresia is associated with a worse prognosis, but the reasons are unknown.

What is New

- We report an infant with biliary atresia and normal GGT, extensively investigated but without identification of an underlying disease conducing to low GGT.
- We recommend further investigations in such patients to expand understanding of GGT in biliary atresia.

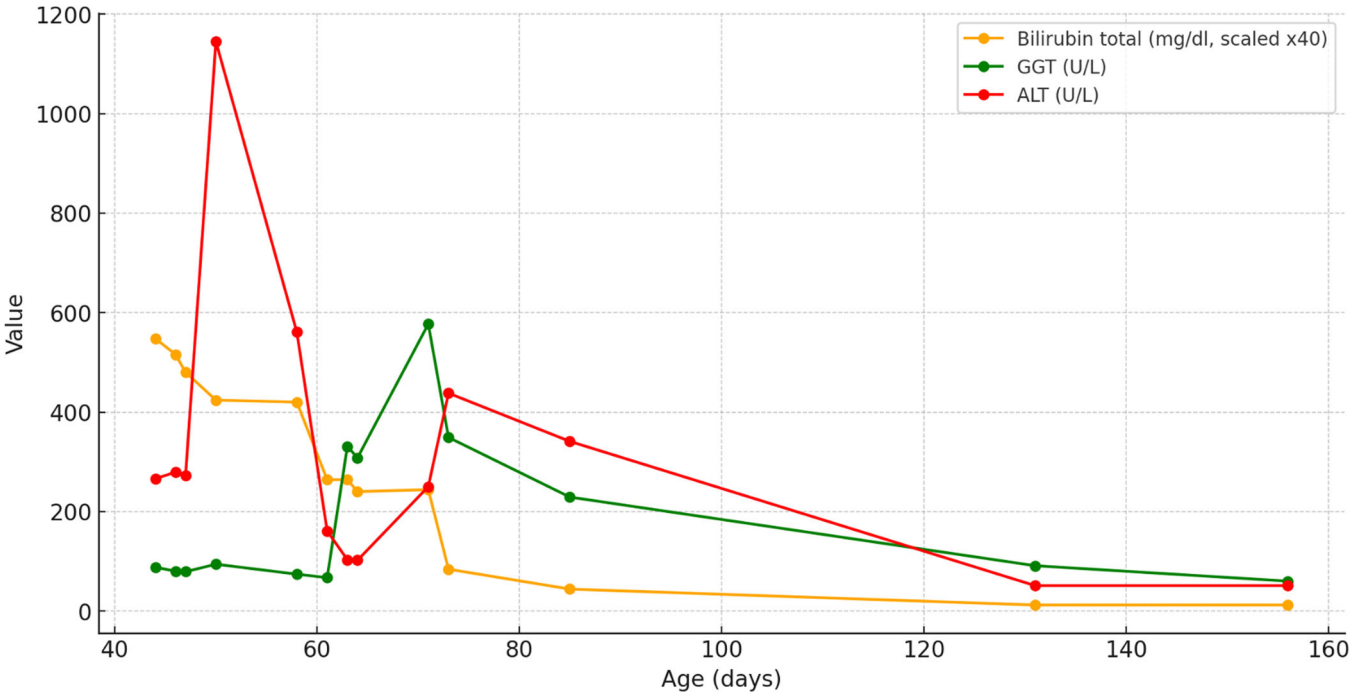

FIGURE 1 Line diagram showing the evolution of values for serum total bilirubin (mg/dL, scaled ×20), GGT (U/L), and ALT (U/L). ALT, alanine aminotransferase; GGT, gamma-glutamyltranspeptidase.

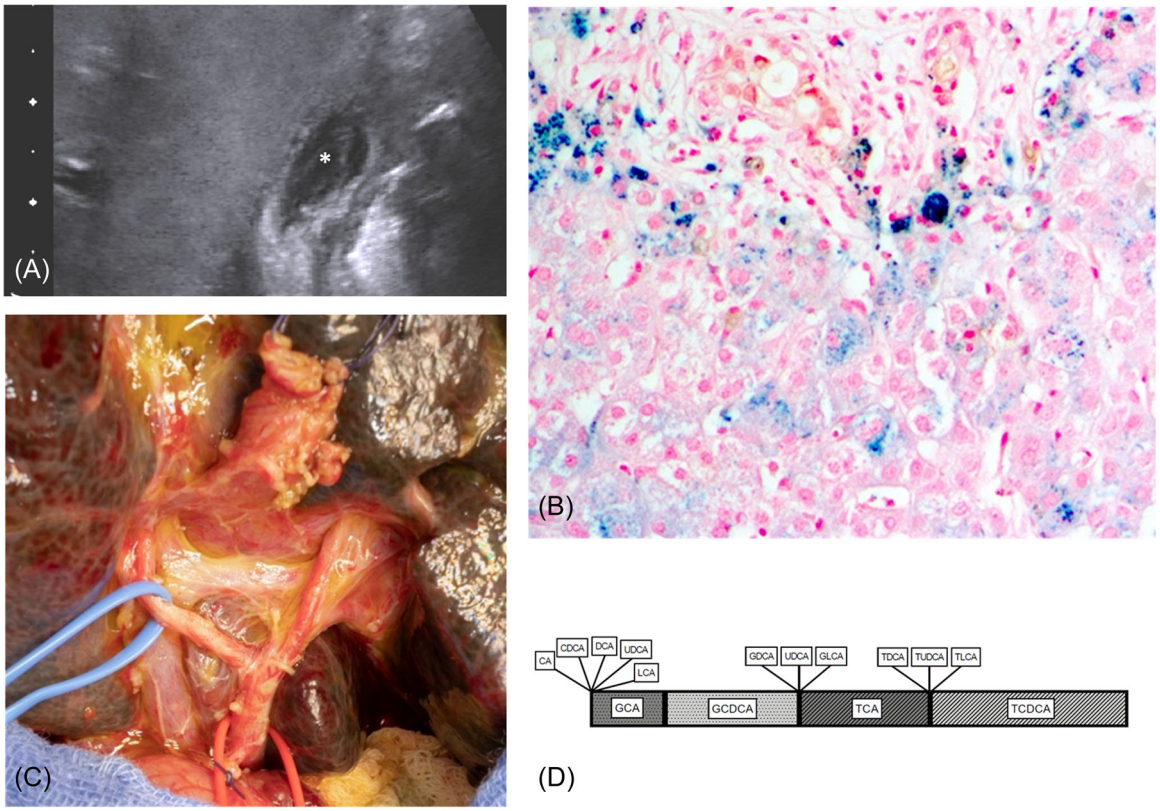

FIGURE 2 (A) Sonogram showing a longitudinal view of the right upper quadrant of the abdomen. The gallbladder (*) appears small (<2 cm), consistent with biliary atresia. The small size and abnormal shape are indicative of underdevelopment due to bile duct obstruction. The liver parenchyma shows increased echogenicity, suggesting fibrosis. (B) Liver at percutaneous biopsy. Moderate portal-tract fibrosis, with oedema, is apparent. A bile plug 'ghost' lies in a principal bile duct (11:00, near margin), with distortion of cholangiocytes. Siderosis of hepatocytes is physiologic; siderosis of histiocytes reflects uptake of iron released from damaged hepatocytes. Perls' iron stain ('Prussian blue') with nuclear fast red counterstain; original magnification ×400. (C) Intraoperative visualisation during Kasai portoenterostomy. The blue vessel loop encircles the right branch of the hepatic artery. The red vessel loop encircles the hepatic artery at the level of the porta hepatis. The upper part of the picture shows the fibrous remnant of the extrahepatic bile ducts. (D) Relative contribution of each measured bile acid to the total serum bile acid pool. The profile shows substantial deviations from the normal distribution seen in healthy age-matched infants. The absence of secondary and unconjugated bile acids reflects impaired enterohepatic circulation caused by biliary atresia. *Unconjugated bile acids*: CA, CDCA, DCA, UDCA and LCA. *Conjugated bile acids*: GCA, GDCA, TCA, TDCA, TCDCA, GCDCA, GLCA, TLCA and TUDCA. CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; GCA, glycocholic acid; GCDCA, glycochenodeoxycholic acid; GDCA, glycodeoxycholic acid; GLCA, glycolithocholic acid; LCA, lithocholic acid; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid; TDCA, taurodeoxycholic acid; TLCA, taurolithocholic acid; TUDCA, tauroursodeoxycholic acid; UDCA, ursodeoxycholic acid.

additional investigations were conducted. Intrauterine severe liver disease, with synthetic insufficiency, and overwhelming acute hepatitis were not considerations. GGT was immunohistochemically demonstrable at bile-canaliculus margins and cholangiocyte apices, a normal finding, and thus available for bile-acid elution into bile and reflux into plasma to serve as the biomarker GGT.[12] Bile salt export pump, multidrug resistance-associated protein 2, tight junction protein 2, CD13 and several species involved in bile-acid synthesis and conjugation (encoded by *AKR1D1*, *AMACR, BACL*, *BAAT* and *CYP27A1*) were unremarkably expressed.

Urinary and serum bile-acid profiles were assessed (File S1). Total bile acids were substantially elevated predominantly consisting of primary conjugated bile acids, without indications of a bile acid synthesis disorder (Figure 2D). Whole-exome sequencing revealed no pathogenic or likely pathogenic variant in genes associated with normal GGT despite conjugated hyperbilirubinaemia (File S1).

The patient was discharged from hospital to her parents' care after 3 weeks. Her postoperative course, although uncomplicated, was of interest for a rapid rise in GGT; this then fell, as did values for other markers of hepatobiliary injury (Figure 1). At follow-up 3 months later and again aged 14 months, she was clinically well, without substantial abnormality in any biomarker value (Figure 1).

3 | DISCUSSION

GGT is of value as a marker of cholestasis particularly in pregnancy and childhood, when alkaline phosphatase in plasma can originate in the placenta or in

remodelling bone.[13] GGT enters plasma when bile acids elute it into bile that leaks across the bile-blood barrier formed by hepatocellular and cholangiocellular tight junctions. Mechanical or obstructive cholestasis, such as that in biliary atresia, is held to increase the concentration of bile acids in bile above the outflow block (facilitating elution of GGT from membranes in contact with bile), to slow the transit of bile through the liver (increasing exposure of GGT-containing membranes to bile acids) and to increase intraluminal biliary-tract pressure above the block (conducing to tight-junction disruption and thus to extravasation of bile into plasma).[2] In biliary atresia, GGT in serum most often rises.[14]

If GGT is not expressed at hepatocyte or cholangiocyte apices or if bile acids in a normal mix are not present in bile, GGT does not rise in serum. The disorders mentioned in the introduction have features like lack of GGT expression (PFIC1, involving *ATP8B1*) or lack of eluent bile acids resulting from various aetiologies. These include absence or dysfunction of the bile salt export pump, the principal hepatocellular transporter of bile acids into bile (PFIC2 and 4, with variants in *ABCB11* and *TJP2*, respectively), and absence or dysfunction of normal bile-acid synthesis and conjugation due to mutations in genes that encode enzymes involved in these processes or to generalised and severe hepatocellular synthetic insufficiency. Some of these disorders are heritable. The prognosis is adverse in all cases.

Two reports point out that biliary atresia patients with normal-range GGT fare worse than those in whom GGT rises pari passu with serum concentrations of conjugated bilirubin. Among 113 Australian children with biliary atresia, 12.3% had normal-range GGT. These children required liver transplantation at average age 14 months, the others at average 20 months.[3] Among 1998 Chinese children with biliary atresia, 24.8% had GGT values < 300 U/L. Their prognosis also was worse than that of the other children, with a slower fall in serum bilirubin values and shorter 2-year native-liver survival, at 52.5% versus 66.3%.[4] Both reports offered the speculation that lower GTT reflected more advanced liver disease.

In contrast to both reports, our patient's liver disease was not particularly advanced at intervention, and she is currently doing well with unremarkable liver synthesis and stable disease. The coming years are an open question, with worsening of liver function mostly seen in elder biliary atresia patients,[15] but so far, normal-range GGT at presentation has not presaged a relatively poorer outcome.

Biliary atresia is generally held to be sporadic rather than hereditary. As the causes of biliary atresia are unknown, they cannot be said to preclude coexistence with biliary atresia of heritable disorders; indeed, coexistence of biliary atresia and alpha-1-antitrypsin storage disorder is described.[6] As normal-range GGT in biliary atresia indicates a relatively unfavourable prognosis,[3,4] that some biliary atresia patients with normal-range GGT have a second disorder, one that impedes the usual response of GGT to biliary-tract obstruction, seems possible. In some instances, this second disorder may be heritable. Reports of patients with this anomaly have not addressed this possibility.[3,4] Instead, severe liver disease has been put forward as underlying failure of GGT to rise normally. Our patient with biliary atresia and normal-range GGT certainly did not have particularly severe liver disease. Nor does severe liver disease explain, we think, the seemingly paradoxical rise in GGT after Kasai portoenterostomy relieved biliary-tract obstruction, for which we can offer no explanation.

To our disappointment, our investigations did not find evidence of a second disorder in our patient. However, as far as we know, she is the first biliary atresia patient with normal-range GGT to have been thus investigated broadly for disorders known to uncouple the usual paired rise of GGT and serum conjugated-bilirubin values. We advocate similar studies in other such patients for two reasons. First, if a second disorder is identified mitigation can be undertaken early. Second, affected individuals who, like our patient, have no evidence of a disorder identifiable by criteria now applied represent a valuable cohort from which to gain insights into the physiology of access of hepatobiliary GGT to plasma in biliary atresia.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Patient information has been pseudonymised. Written informed consent for publication has been obtained from the parents.

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Note: Reference 16 is cited in supplementary information file.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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