

Invited Commentary

Serum Gamma Glutamyltransferase Levels in Cholestasis of Infancy

K TSE

Abstract Serum gamma glutamyltransferase (GGT) level in cholestasis of infancy is a complex issue. Experience and caution are required in its interpretation. The common differential lists mentioned in the literatures, including different types of Progressive Familial Intrahepatic Cholestasis and bile acid synthetic disorders, are discussed. Other causes of cholestasis of infancy with normal serum GGT, such as, Smith-Lemli-Opitz Syndrome, Arthrogryposis multiplex congenita, Renal dysfunction and Cholestasis (ARC) Syndrome are also mentioned.

Key words Bile acid synthetic disorders; Cholestasis; Gamma glutamyltransferase; Infant; Progressive Familial Intrahepatic Cholestasis

Serum gamma glutamyltransferase (GGT) level in cholestasis of infancy is a complex issue. GGT is usually not included in the common liver function test (LFT) of the local public hospitals. It is done on request even though extra blood is usually not necessary. The serum concentration will change with the infant's age. The normal reference ranges can be up to five to eight times the upper limit of adult serum levels in the first few days of life, and even higher in premature infants. The serum GGT levels decline rapidly and reach adult levels by six to nine months of age.¹ Reference ranges provided with the laboratory reports vary with the methodology. In the local public hospitals, when cumulative results are printed on the report, the reference range will be provided according to the patient's age when the last blood test was done, i.e., the

earlier results could be misinterpreted easily. Please consult your laboratory colleagues for further detail.

There are many causes for cholestasis of infancy. Idiopathic neonatal hepatitis (INH) is a diagnosis by exclusion. Most infants with INH will recover completely, but a small proportion of them may have poor outcome. Serum GGT at low levels, or within normal reference ranges, were found to be associated with poor prognosis in many liver diseases in children.^{2,3} The list of differential diagnosis included: Progressive Familial Intrahepatic Cholestasis (PFIC), Benign Recurrent Intrahepatic Cholestasis (BRIC), bile acid synthetic disorders, portal vein obstruction, and congenital hepatic fibrosis.^{2,3} Patients with PFIC and bile acid synthetic disorders are sometimes misdiagnosed as idiopathic neonatal hepatitis because of diagnostic availability. PFIC-1 is Byler's disease, due to mutation of *FIC1* gene. PFIC-2 is due to the mutation of the ATP-dependent bile salt export pump gene (*ABCB11*). They are very similar clinically. The serum primary bile acid concentrations are high. Histologically, there are subtle differences between PFIC-1 and PFIC-2, e.g., retention of coarsely granular bile, Byler's bile, in canalicular spaces of the liver biopsy specimens from patients with PFIC-1.⁴ The DNA studies for the mutations of both PFIC-1 and -2 are

Department of Paediatrics & Adolescent Medicine, Tuen Mun Hospital, Tsing Chung Koon Road, Tuen Mun, N.T., Hong Kong, China

K TSE (謝江) FRCP (Edin), FHKCPaed, FHKAM (Paed)

Correspondence to: Dr K TSE

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available locally. PFIC is a progressive disease and will progress to cirrhosis and death. There were some reported success with ursodeoxycholic acid and surgical diversion of bile salts from the enterohepatic recirculation. Otherwise, liver transplantation will be necessary.⁴ PFIC types 1 and 2 share the same gene loci of Benign Recurrent Intrahepatic Cholestasis (BRIC) types 1 and 2.^{1,5} Patients with BRIC types 1 or 2 will have better prognosis, i.e., not all the infants with cholestasis and serum GGT at low levels will have bad prognosis.¹ The serum GGT levels in patients with PFIC-3, Multidrug Resistance Gene 3 (MDR3)-deficient disease, are high.¹ Children suffering from PFIC-1 would have raised GGT levels when there were extensive portal fibrosis and bile duct proliferation on liver biopsy,³ i.e., high serum GGT levels do not exclude PFIC.

Bile acid synthetic disorders are very complex. There are many enzyme defects reported with cholestasis in infancy.^{6,7} Some defects are associated with serum GGT at low levels, while high serum levels were reported with the other enzyme defects.^{6,7} The most common defect is 3 β -hydroxy-C27-steroid oxidoreductase (dehydrogenase / isomerase) deficiency (3 β HSD), accounting for 90% of the cases in the disorders. The serum GGT level is low in 3 β HSD. But the serum GGT level was reported to be high in the second common bile acid synthetic disorder, Δ^4 -3-oxo-steroid 5 β -reductase (5 β RD) deficiency, and some other bile acid synthetic disorders, i.e., high serum GGT level does not exclude all the bile acid synthetic disorders. These bile acid synthetic disorders are clinically indistinguishable from PFIC, but the serum primary bile acid levels are low. Please consult your chemical pathologist on the interpretation of serum primary bile acid levels. The diagnosis of bile acid synthetic disorders is by fast atom bombardment-mass spectrometry (FAB-MS) analysis and gas chromatography-mass spectrometry (GC-MS) analysis of urine.^{6,7} The tests are not available locally. Cholic acid replacement can revert the disease progression in these two bile acid synthetic disorders. Unfortunately, it is not available in the market as a drug but in special center where the diagnostic test is available. Without specific replacement or liver transplantation, most of these patients will die prematurely. Some of the patients with the other bile acid synthetic disorders would have their jaundice subsided, e.g., Cerebrotendinous Xanthomatosis (CTX). CTX may rarely present as cholestasis of infancy with serum GGT at low levels. Some patients may have the jaundice resolved spontaneously while the others may die early.^{8,9} The

survivors will have slowly progressive chronic disease characterised by dementia and peritendinous xanthomata in adulthood. Early replacement therapy by chenodeoxycholic acid is very helpful. The drug is available locally. Please consult the literatures for further details of bile acid synthetic disorders.^{6,7}

A few dysmorphic syndromes may also present with cholestasis in infancy and serum GGT at low levels. Smith-Lemli-Opitz Syndrome (SLOS) is due to the deficiency of 7-dehydrocholesterol Δ^7 reductase (7-DHC) which is responsible for the last step for cholesterol synthesis.¹⁰ Cholesterol is the building block of many substances, including hormones and bile salts. The patients with SLOS will have characteristic faces (microcephaly, ptosis, anteverted nares, micrognathia), growth and mental retardation, 2,3 toe syndactyly, and other abnormalities. The diagnostic test is blood for 7-dehydroxy-cholesterol which is absent in normal subjects but high in the patients. The test is available locally. Early cholesterol supplement may improve the growth and behaviour, but cholesterol does not cross the blood brain barrier. Some other cholesterol synthetic disorders may also present with cholestasis in infancy but the serum GGT levels were usually not reported.¹⁰

Arthrogyriposis multiplex congenita, Renal dysfunction and Cholestasis (ARC) Syndrome was also reported as cholestasis in infancy with serum GGT at low levels.⁴ The prognosis is poor.

Family history is important and the above-mentioned diseases are generally autosomal recessive in inheritance. Some of them may have dysmorphic features. It is advisable to check serum GGT levels in patients with cholestasis. There is an article in this issue of journal on the dynamic of serum GGT in cholestasis of infancy.¹¹ Please be aware that the reference ranges used may vary with methodology. The dynamic of serum GGT in cholestasis may have prognostic implication. Prompt diagnosis and specific treatment are necessary for PFIC and bile acid synthetic disorders.

From time to time, there are patients with serum GGT levels fluctuating around the normal reference ranges. Other infants may have short lasting cholestasis, and high serum liver enzymes but serum GGT levels within normal reference ranges. Patients should receive holistic care. Diagnosis and prognosis are not solely dependent on single laboratory result. Please consult the experts in the field for further details. There are still lots of mysteries in Medicine.

References

1. Arthuro Batres L, Maller ES. Laboratory assessment of liver function and injury in children. In: Suchy FJ, Sokol RJ, Balistreri WF, eds. *Liver disease in children*. 2nd Ed. Lippincott Williams & Wilkins, 2001;158-60.
2. Maggiore G, Bernard O, Riely CA, Hadchouel M, Lemonnier A, Alagille D. Normal serum gamma-glutamyl-transpeptidase activity identifies groups of infants with idiopathic cholestasis with poor prognosis. *J Pediatr* 1987;111:251-2.
3. Maggiore G, Bernard O, Hadchouel M, Lemonnier A, Alagille D. Diagnostic value of serum gamma-glutamyl transpeptidase activity in liver diseases in children. *J Pediatr Gastroenterol Nutr* 1991;12:21-6.
4. Whittington PF, Emerick K McBride, Suchy FJ. Familial hepatocellular cholestasis. In: Suchy FJ, Sokol RJ, Balistreri WF, eds. *Liver disease in children*. 2nd Ed. Lippincott Williams & Wilkins, 2001;315-34.
5. Lam CW, Cheung KM, Tsui MS, Yan MS, Lee CY, Tong SF. A patient with novel ABCB11 gene mutations with phenotypic transition between BRIC2 and PFIC2. *J Hepatol* 2006;44: 240-2.
6. Bove KE, Heubi JE, Balistreri WF, Setchell KD. Bile acid synthetic defects and liver disease: a comprehensive review. *Pediatr Dev Pathol* 2004;7:315-34.
7. Setchell KDR, O'Connell NC. Bile acid synthesis and metabolism. In: Walker WA, Goulet O, Kleinman RE, Sherman PM, Shneider BL, Sanderson IR, eds. *Pediatric Gastrointestinal Disease, Pathophysiology, Diagnosis, Management*. 4th ed. BC Decker, 2004;1308-43.
8. Clayton PT, Verrips A, Sistemans E, Mann A, Mieli-Vergani G, Wevers R. Mutations in the sterol 27-hydroxylase gene (CYP27A) cause hepatitis of infancy as well as cerebrotendinous xanthomatosis. *J Inherit Metab Dis* 2002;25:501-13.
9. Clayton PT, Verrips A, Sistemans E, Mann A, Mieli-Vergani G, Wevers R. Mutation in the Sterol 27-Hydroxylase Gene associated with fetal cholestasis in infancy. *J Inherit Metab Dis* 2002;25:501-13.
10. Porter FD. Human malformation syndromes due to inborn errors of cholesterol synthesis. *Curr Opin Pediatr* 2003;15:607-13.
11. Wang JS, Wang ZL, Wang XH, Zhu QR, Zheng S. The Prognostic Value of Serum Gamma Glutamyltransferase Activity in Chinese Infants with Previously Diagnosed Idiopathic Neonatal Hepatitis. *HK J Paediatric (new series)* 2008;13:39-45.