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CASE STUDY

Markedly Elevated Gamma-glutamyltransferase

Marta Kushnir

Abstract: Gamma-glutamyltransferase (GGT) is a highly sensitive but poorly specific liver enzyme commonly used to detect hepatobiliary disease and possible alcohol abuse. Isolated elevations of this enzyme may be due to biochemical anomalies rather than the presence of pathology.

Address: The Franklin Life Insurance Company, 1 Franklin Square, Springfield, IL62713-0001: e-mail: Marta.Kushnir@worldnet.att.net

Correspondence: Marta Kushnir, M.D. Vice President and Medical Director, The Franklin Life Insurance Company

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Case Presentation

The applicant is a 27-year-old male applying for $150,000 of 10-Year Level Term. He is married and a chemical lab technician by profession. He states on his application that he was declined for life insurance in 1994 because of elevated liver function tests. Alcohol use is reported as 1-2 beers per week. There is no other remarkable social or medical history. His parents (both age 52) and one brother (age 30) are reported to be alive and in good health.

Documents submitted include an APS with routine office visits since April 4, 1994. According to his physician, the applicant never had laboratory studies done until 1994 when he applied for life insurance. Physical examination, inspection and laboratory tests were unremarkable except for an isolated GGT elevation of >999u/l (normal for males 4-52u/l). He was declined for insurance at this time. The physician repeated a blood profile and all results were normal except for a GGT of 2000u/l. A recheck one-year later found the GGT to be 4584u/l. Other laboratory tests including a CBC and lipid profile were within normal limits, hepatitis B serology and hepatitis C serology were negative. The patient told his physician that some years ago, his father was found to have a GGT of 1500u/l. He further stated that his father was referred to a "liver specialist" but a diagnosis was not determined nor was follow-up recommended. No data was available on his sibling.

The attending physician referred the applicant to the hepatology division at a major university medical center. All blood studies including CBC with differential, lipid panel, protein, albumin, bilirubins, total iron, iron binding capacity, iron saturation percent, prothrombin time, alpha-1-antitrypsin, alpha-fetoprotein, cholyglycine and ceruloplasmin were within normal limits. Again, the only abnormality was a GGT of 5045 u/l.

A liver biopsy was not performed nor was any further testing recommended. No diagnosis

was made but the hepatologist stated that the applicant's future risk of liver disease was equal to that of any normal, healthy person.

Case Discussion

Szewzuk and Orlowski first reported serum GGT in 1960 as a clinical diagnostic procedure in the diagnosis of hepatic diseases using the synthetic substrate alpha-(N-gamma-DL-glutamyl)-amininitrile.[1]

In subsequent years other synthetic substrates were utilized. The human body contains GGT distributed in various organs. The kidneys contain the greatest concentration — almost three times that of the liver. Other organs that contain appreciable amounts of GGT are the pancreas, small intestine and the brain. However, the biological significance of this enzyme still remains to be clarified. For example, there is still no explanation as to why no rise in serum GGT is observed in renal disease. Isoenzyme analyses have been performed in an attempt to improve the diagnostic specificity of the serum GGT assay. Tissue-specific patterns have not been described, and disease specific patterns cannot be reproduced with confidence. The following facts are also of note: erythrocytes contain no GGT, thus hemolysis does not affect the result; GGT is a rather stable enzyme, at 24C stable for 2 days, at 38Cstable for one day; no diurnal change nor change by exercise or food intake has been observed; normal GGT levels differ by age and sex.[2,3]

Fischer and Rambach examined 1,756 liver biopsies performed in the years 1987-1991. In 139 cases the patients exhibited both a nearly normal liver histology and elevated GGT values. After excluding patients with known causes for an elevated GGT, they followed 15 patients who over the course of at least one-year, were documented as having at least three elevated GGT measurements. Biopsy and repeat blood work did not exhibit laboratory-chemical or histological signs of progression or regression tendencies and were thus interpreted as a "functional" liver disorder with parallels to Gilbert's syndrome.[4]

Another comparable chemical idiosyncrasy is chronic hyperamylasemia. This is a well-described entity of a benign nature in which macroenzymes are the cause of elevated serum amylases. It is important to recognize macroamylasemia as to avoid misdiagnosis of pancreatic disease. Several methods, such as electrophoresis, exist for confirmation of this condition. However, it may be sufficient to determine that serum lipase or urine amylase is normal in this context.[5,6]

In this case, the initial presentation in 1994 of the isolated grossly elevated GGT in the absence of any other lab abnormality certainly warranted further evaluation. It is well known that GGT is markedly increased in lesions, which cause intrahepatic or extrahepatic obstruction of bile ducts, including parenchymatous liver diseases with a major cholestatic component. In cases with isolated elevation of GGT without accompanying increase of alkaline phosphatase, an alcoholic drinking pattern or the intake of medicines, which would induce enzyme release, should be considered. There was no evidence of excess alcohol intake or any medication history in this applicant. In addition, the extreme persistence of the enzyme elevation without effect on other laboratory tests and the absence of any physical changes over a three year period make clinical significance doubtful and suggest a benign biochemical etiology such as seen in Gilbert's syndrome and hyperamylasemia.

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