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REVIEW / DERLEME

Liver function tests in chronic viral hepatitis cases

Kronik viral hepatit olgularında karaciğer fonksiyon testleri

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ABSTRACT

The liver has many vital functions and biochemical tests are used for the assessment. For the diagnosis of chronic hepatitis: (1) persistence of increased alanine aminotransferase (ALT) for 6 months after an episode of acute hepatitis; or (2) increased ALT (without another explanation) on more than one occasion over a period of 6 months are needed. The time period may be shorter for the patients with risk factors. Although the clinical picture of HBV and HCV in chronic cases is similar, aminotransferase activities are different. In HBV, ALT activity is generally constant, except increases are evident at seroconversion times. On the other hand, two-third of HCV cases experience fluctuation. In the evaluation of a patient with a new diagnosis of chronic viral hepatitis, a comprehensive medical history should be taken, followed by full physical examination. Laboratory workup should start with a comprehensive metabolic panel with liver function tests including assessment of synthetic function with prothrombin time and serum albumin level measurement. Screening for the chronic hepatic injury is not cost-effective and should be limited to high-risk individuals. ALT should be the preferred biochemistry parameter besides viral serology and increased activity should be confirmed before further evaluation. For treatment, patients with increased ALT are more likely to respond than those with initially normal ALT activity.

Keywords: Chronic viral hepatitis, Hepatitis B virus, Hepatitis C virus, Alanine aminotransferase, Aspartate aminotransferase

ÖZ

Karaciğerin pek çok hayati fonksiyonu vardır ve bu fonksiyonlar biyokimya testleri ile değerlendirilir. Kronik viral hepatit tanısı için: (1) akut hepatit atağından sonra 6 ay boyunca yüksek seyreden alanin aminotransferaz (ALT) aktivitesi; veya herhangi bir neden olmaksızın 6 ay içinde bir kereden fazla ALT yüksekliği gereklidir. Risk gruplarında süre kısaltılabilir. Kronik olgularda HBV ve HCV benzer klinik tablolar sergileseler de, aminotransferaz aktiviteleri farklıdır. HBV olgularında ALT aktivitesi genelde sabitken, serokonversiyon dönemlerinde artışlar izlenir. HCV olgularının üçte ikisinde ise dalgalanmalar olur. Yeni tanı almış kronik viral hepatit olgularında ayrıntılı tıbbi öykü alınmalı ve ayrıntılı fizik muayene yapılmalıdır. Laboratuvar incelemeleri karaciğer fonksiyon testleri ve protrombin zamanı ile serum albümin düzeyi ölçümleri gibi karaciğerin sentez fonksiyonlarını da değerlendiren testleri de içeren ayrıntılı bir metabolik panel ile başlamalıdır. Kronik viral hepatit taraması maliyet-etkin değildir ve sadece yüksek risk taşıyanlar ile sınırlı olmalıdır. Viral serolojinin yanı sıra biyokimya testi olarak ALT tercih edilmeli, artmış aktivite ileri incelemeden önce mutlaka teyid edilmelidir. Tedavi izleminde artmış ALT aktivitesi olan olgular başlangıçta normal olanlara göre daha iyi cevap verirler.

Anahtar kelimeler: Kronik viral hepatit, Hepatit B virüsü, Hepatit C virüsü, Alanin aminotransferaz, Aspartat aminotransferaz

Introduction

The liver has many vital biochemical functions including excretion, synthesis, metabolism, and storage. Endogenous and exogenous organic anions are extracted, biotransformed, and excreted into the bile, while the measurement of endogenously produced compounds like bilirubin and bile acids are used for the assessment of excretory function. Hepatic synthetic function not only involves glucose synthesis via gluconeogenesis, but also protein, triglyceride, fatty acid, cholesterol, and bile acid synthesis as well. Activation and detoxification of drugs, and the disposal of exogenous and endogenous substances, such as galactose and ammonia are included in hepatic metabolic functions.

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Liver is the major site for glycogen storage besides some minerals and vitamins. Liver function tests are useful in (1) detecting, (2) diagnosing, (3) evaluating severity, (4) monitoring therapy, and (5) assessing the prognosis of liver disease and dysfunction. Different tests are utilized to assess different functions of the liver (Table I) [1].

Table I. Main liver function tests and their usage

Test	Usage
Bilirubin, total	Diagnosing jaundice, modest correlation with severity
Alkaline phosphatase (ALP)	Diagnosing disorders of metabolism in children, cholestatic disorders in adults
Bilirubin, direct and indirect	Diagnosing cholestasis and space-occupying lesions
Aspartate aminotransferase (AST)	Sensitive test of hepatobiliary disease; AST>ALT in alcoholic disease
Alanine aminotransferase (ALT)	Sensitive and more specific test of hepatobiliary disease
Albumin	Indicator of chronicity and severity
Prothrombin time (PT)	Derangement of synthetic functions in acute cases, indicator of severity of cholestasis

Chronic hepatitis is defined as a chronic inflammation of the liver that persist for at least 6 months, or signs and symptoms of chronic liver disease in the presence of elevated cytosolic enzymes [2]. The clinical presentations of chronic hepatitis cases are highly variable. Most patients are diagnosed because of unexplained abnormalities of aminotransferases or positive results on screening tests for cause of chronic hepatitis. Moderate elevations of aminotransferase activities (twofold to fivefold) are characteristic, whereas results of most other tests are normal. Normal aminotransferase activities do not rule out pathological evidence of chronic hepatitis, especially in the presence of chronic viral hepatitis or nonalcoholic steatohepatitis [3,4].

'National Academy of Clinical Biochemistry Guidelines on Use of Laboratory Tests in the Diagnosis and Monitoring of Hepatic Injury' states that in the absence of liver biopsy showing evidence of chronic hepatitis, one of the following laboratory results should be used for the diagnosis of chronic hepatitis: (1) persistence of increased alanine aminotransferase (ALT; EC 2.6.1.2) for 6 months after an episode of acute hepatitis; or (2) increased ALT (without another explanation) on more than one occasion over a period of 6 months. In patients with risk factors for chronic viral hepatitis, genetic causes of hepatic injury, autoimmune liver injury, or in the presence of clinical signs or symptoms of liver disease the time period may be shorter (evidence IIB) [2].

Although the clinical picture of HBV and HCV in chronic cases is similar, aminotransferase activities are different. In HBV, ALT activity is generally constant, except increases are evident at seroconversion times. On the other hand, two-third of HCV cases experience fluctuation [5-7]. Serum ALT activities of chronic hepatitis C cases range between one to four times the upper reference limit, reaching maximum less than seven times. On the other hand, 15-50% of cases with chronic hepatitis C have normal ALT activities [6,8,9], but this rates decreases with increasing number of measurements [8]. From 43% of cases experiencing fluctuation between normal and abnormal, 16% of those with normal ALT on their first two visits and 11% of those with normal ALT on their first three visits subsequently develop increased ALT [8]. Chronic hepatitis C cases with persistantly normal ALT activities experience lower rates of progression to cirrhosis [7,10]. ALT activity is consistently higher than aspartate aminotransferase (AST; EC 2.6.1.1) with all causes of chronic hepatic injury except for alcoholic hepatitis [11-14]. Additionally, ALT may be normal in cirrhotic cases but AST activity increased [15,16]. Total bilirubin, direct bilirubin, and alkaline phosphatase (ALP; EC 3.1.3.1) are generally normal in chronic viral hepatitis cases [17,18].

In the evaluation of a patient with a new diagnosis of chronic viral hepatitis, a comprehensive medical history should be taken, followed by full physical examination. Laboratory workup should start with a comprehensive metabolic panel with liver function tests including assessment of synthetic function with prothrombin time and serum albumin level measurements. Although ALT reflects liver inflammation, its correlation with necroinflammation is not satisfactory and even poorer for fibrosis [19,20]. Thrombocytopenia (count<150000/μL) is often a sign of portal hypertension and liver cirrhosis, but its sensitivity and specificity is limited for the diagnosis of cirrhosis (68% and 76 %, respectively) [21]. AST/ALT ratio>1 is another laboratory marker suggestive of cirrhosis, which is also seen in alcoholism. Combined tests like AST/platelet ratio index (APRI) and Forn index show good correlation with liver fibrosis [22,23]. Measurement of 25-hydroxy-vitamin D3 level will be beneficial, as its deficiency has been found to be correlated with reduced antiviral activity of peg-interferon plus ribavirin treatment [24-26]. Chronic viral hepatitis cases

with cirrhosis should be monitored in every 3-6 months with clinical examinations and laboratory tests (comprehensive metabolic panel, coagulation profile, complete blood count) with the calculation of the Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) score to determine the prognosis of patient [27,28].

According to 'European Association for the Study of the Liver Disease (EASL 2012)', ALT is considered as a classification criteria for the phases of chronic hepatitis B (CHB): (1) immune tolerant phase with HBeAg positive, HBeAb negative, Viral DNA>20000 IU/mL and normal ALT level, (2) HBeAg-positive CHB (immune reactive) phase with HBeAg positive, HBeAb negative, Viral DNA >2000 IU/mL and elevated ALT level, (3) low replicative phase with HBeAg negative, HBeAb positive, Viral DNA <2000 IU/mL and normal ALT level, and (4) HBeAg-negative CHB phase with HBeAg negative, HBeAb positive, viral DNA >2000 IU/ml and elevated ALT level [29-31].

Screening for the chronic hepatic injury is not cost-effective and should be limited to high-risk individuals like anyone who has ever injected illicit drugs, recipients of blood transfusions or solid organ transplants before July 1992, or clotting factor concentrates before 1987, patients who have ever received long-term hemodialysis treatment, persons with known exposure to hepatitis C, persons infected with HIV, children born to HCV-positive mothers, persons with persistently elevated levels of alanine aminotransferase, and anyone born from 1945 through 1965 according to "Centers for Disease Control and Prevention Hepatitis C Virus Testing Recommendations", August 2012 [32-34]. ALT should be the preferred biochemistry parameter besides viral serology and increased activity should be confirmed before further evaluation [17,18]. An increase of one to two times the upper reference limit should not be attributed to disease state [17,18,35]. Especially in young individuals creatine kinase (CK; EC 2.7.3.2) measurement should be considered to rule out skeletal muscle as the origin besides history of exercise [36]. Generally, chronic HBV carriers have normal ALT activity like many cases of chronic HCV cases but repeated testing increase the chance of revealing increased values [37]. Anti-HCV-positive chronic cases should be confirmed with HCV RNA tests and negative results in the presence of increased ALT activities should be repeated (evidence IIB).

For treatment, patients with increased ALT are more likely to respond than those with initially normal ALT activity [38,39]. For HCV treatment HCV RNA levels and ALT activity should be measured after 12 weeks of treatment to determine nonresponders (evidence IIB).

Key Points

- Liver function tests are useful in detecting, diagnosing, evaluating severity, monitoring therapy of chronic liver diseases.
- Persistence of increased alanine aminotransferase for 6 months after an episode of acute hepatitis indicates chronicity.
- In the treatment of Chronic hepatitis patients with increased ALT are more likely to respond than those with initially normal levels.

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