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CLINICAL VIGNETTE

One Cause of Chronic Transaminitis

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Introduction

The laboratory evaluation of the liver is typically divided by function and hepatocyte injury. AST (aspartate aminotransferase) and ALT (alanine aminotransferase) are enzymes involved in amino acid metabolism. While both enzymes are found in tissues throughout the body, ALT is typically in higher concentration within the liver than AST. Both are released into the blood stream in the setting of hepatocyte injury[1]. As such, they have become the standard laboratory screening tests for liver injury in outpatient clinics. Liver function is often evaluated by markers of the coagulation cascade (INR, PT) and metabolism byproducts (Bilirubin). The discovery of elevated liver enzymes and abnormal hepatic function tests in the primary care setting is common as these tests are included in screening panels[2]. The challenge is in the approach to the results.

Case Report

The patient is a 21-year-old Caucasian male with no major medical problems who presented for routine evaluation after being diagnosed with shingles. He had been seen in dermatology for a rash on his lower back later identified by viral culture as varicella zoster. He was asked to establish care in internal medicine clinic for a thorough health evaluation. His only medical conditions were chronic facial acne for which he had been treated with minocycline and occasional upper respiratory infections. It had been a few years since his last complete physical exam. He reported occasional alcohol consumption of about 4-7 drinks per week and no tobacco use. He denied any family history of liver disease.

The patient's exam was only significant for acne to his face and trunk. His abdomen was soft, without distension and his liver and spleen edges were not palpable. He had no stigmata of chronic liver disease including jaundice, palmar erythema, or spider angiomata.

Laboratory evaluation was significant for a total bilirubin of 1.8, AST of 80, ALT of 191, Alkaline phosphatase of 75, hemoglobin of 17.9, MCV 94, and negative HIV1/2, RPR, GC/Chlamydia. Three months later, patient returned for repeat liver tests which confirmed a chronic mild transaminitis and hyperbilirubinemia. Repeat hemoglobin was not resulted due to "increased yellowness due to icterus and/or other interfering substances." Subsequent workup to elucidate the cause of the elevated AST/ALT included a positive hepatitis A total antibody, hepatitis B surface antibody quant of 670, negative hepatitis B surface antigen, negative hepatitis C antibody screen, negative celiac antibody panel, normal TSH, total iron 270, iron percent saturation 91, and a ferritin of 4045.

The patient was referred for hematology consultation for evaluation of hemochromatosis. Autoimmune and inflammatory markers including ANA, rheumatoid factor and ESR were negative. Genetic analysis for hereditary hemochromatosis (HH) showed the patient to be homozygous for the HH mutation C282Y and confirmed the diagnosis. The two other analyzed HH mutations, H63D and S65C, were not found.

Discussion

Hemochromatosis is a clinical syndrome characterized by end organ damage from iron overload. The affected tissues include the liver, heart, pancreas and skin but are typically late stage findings. Most patients present with fatigue, skin discoloration and arthralgias. Classically it has been called "bronze diabetes" and is associated with a mutation of the HFE gene located on chromosome 6[3]. The C282Y mutation accounts for roughly 80% of all cases and is the most common genetic variant found in the classic phenotypic presentation[4]. It affects the HFE gene that codes the HFE protein which appears to interact with transferrin in iron regulation and absorption from the gut[5]. Furthermore, hepcidin is an amino acid polypeptide that is thought to play a critical role in iron regulation. The HFE mutation decreases the expression of hepcidin thereby increasing intestinal iron absorption[6]. The disregulation of iron leads to progressive saturation of serum transferrin with iron and eventual deposition in tissue.

The diagnosis is made by genetic testing for the C282Y or the less common H63D and S65C

mutations. Guidelines suggest that patients found to have transferrin saturation greater than 45% and/or an elevated ferritin should undergo genetic testing[6]. While ferritin is known to be an acute phase reactant, levels greater than 1000 are valuable in predicting the presence of cirrhosis in patients with hemochromatosis[7]. While liver biopsy was traditionally used for diagnostic purposes prior to the HFE genetic screen, it still has a role in prognosis by staging the level of hepatic fibrosis.[8]

Hereditary hemochromatosis is now known to be more prevalent than previously thought with an estimated frequency of homozygosity of 5 per 1000 individuals[9]. The argument in favor of screening is that early detection of asymptomatic disease has minimal associated morbidity and can lead to decreased complications of end organ damage[6]. Treated patients are more likely to live long healthy lives. Currently, the recommendation is that all first degree relatives of an affected person should be screened given the autosomal recessive inheritance pattern[8].

Treatment

After confirming the diagnosis of hereditary hemochromatosis, the patient was started on routine phlebotomy through his hematologist. Typical regimens include the removal of 500mL of whole blood once or twice weekly. He underwent MRI which showed findings of hemochromatosis and moderate splenomegaly. Subsequent liver biopsy showed siderosis and stage two fibrosis without cirrhosis.

According to guidelines, the goal ferritin is 50 to 100 µg/L[4]. The patient's ferritin levels have steadily decreased with the most recent value being 2372. When the goal ferritin is obtained, maintenance phlebotomy can continue at less frequent intervals.

Conclusion

While not every patient found to have transaminitis on routine clinical testing requires an extensive evaluation, clinical judgment should be used when deciding when and what tests are appropriate in individuals with chronic ALT/AST elevations. Hereditary hemochromatosis should always be on the list of differential diagnoses as the prevalence is high. Transaminitis and high serum transferrin saturation should lead to genetic testing for HFE gene mutations. Lastly, routine phlebotomy is a well tolerated treatment that can prevent long term complications of end organ damage.

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