

Filtering Out Doubt in Abnormal LFTs

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As presented at Memorial University's Wednesday At Noon series, St. John's, Newfoundland (March 2006)

Liver function tests (LFTs), which determine the potential cause of hepatic inflammation or damage, are commonly ordered, even when liver disease is unsuspected. This is a result of automated chemistry in many medical laboratories. Therefore, it is prudent to have a systematic approach to the interpretation and subsequent follow-up of these chemical tests.¹

A reasonable approach would include an assessment of the magnitude of the abnormality, with other parameters considered, if they are known (*i.e.*, duration). For instance, the cause of transaminases less than twice the upper limit of the normal level for more than six months is likely different than the cause of an isolated alkaline phosphatase that is five times the normal level. The pattern of liver function abnormality helps to define possible etiologies and guide subsequent investigations.

Hepatocellular pattern of injury is reflected in abnormal chemistry that manifests as elevation of the transaminases. A cholestatic pattern is defined as a predominant elevation of the alkaline phosphatase (ALP) and it is in this pattern that an obstructing lesion of the biliary tree should be considered—though infiltrative or inflammatory conditions of the biliary tree will also give such a pattern. A mixture of both, where transaminases and ALP are significantly elevated is also commonly seen. True assessment of liver function requires an evaluation of synthetic function, as measured by parameters of:

- coagulation (international normalized ratio [INR]),
- conjugation and secretion (bilirubin) and
- protein synthesis (albumin).

If there is evidence of hepatic dysfunction, then a

Gary's case:

- Gary, 25, seeks your help for a complaint of intermittent jaundice
- His blood work reveals normal levels of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase (ALP). The bilirubin is 62 $\mu\text{mol/L}$ and when fractionated, is predominately unconjugated
- This pattern suggests a defect in conjugation or increased production of bilirubin, such as that which occurs in hemolysis
- Screening for hemolysis is negative; therefore, this pattern is typical of a benign condition known as Gilbert's syndrome

Yolande's case:

- Yolande, 60, is seen and found to have an isolated elevation of ALP
- It is now three times the upper limit of normal and you note that four years ago, when the value was last checked, it was only slightly above normal
- Asymptomatic, minimal elevation of ALP is not an uncommon occurrence and consideration of primary biliary cirrhosis is reasonable in this case. This can be further evaluated by an ultrasound, which will help to rule out an obstructive or infiltrative lesion
- Determination of the serum IgM level and testing for the presence of the antimitochondrial antibody (AMA) will help to confirm this diagnosis

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clinical assessment that includes an evaluation for possible encephalopathy and other manifestations of chronic liver disease seems prudent and is easily performed in the clinical setting.

Pattern evaluation will help illustrate these concepts and offer examples of common causes of each.

One must always consider the possibility that drugs may contribute to any abnormal LFT. Drug induced hepatitis, while significant in its own right, should be distinguished from drug induced hepatocellular jaundice, which has a significant mortality associated with it. Drug induced hepatotoxicity may manifest as either:

- hepatocellular,
- cholestatic or
- hypersensitivity injury patterns, which may occur via several possible mechanisms.²

Drugs that commonly produce a hepatocellular pattern of injury include:

- non-steroidal anti-inflammatory drugs,
- statins and
- acetaminophen.

A cholestatic pattern is seen with chlorpromazine, erythromycins and amoxicillin-clavulanic acid as representative examples. A mixed pattern may also be encountered.

Hepatitis C

It is estimated that there are approximately 250,000 Canadians infected with the hepatitis C virus (HCV) and up to one-third are unaware that they are infected. Approximately 70% to 80% of recent infections are due to intravenous drug use, while the risk of HCV infection from blood transfusion in Canada is estimated to be < 1 in 3,000,000 units transfused.³ Most people do not have a clinically recognizable illness at the time of acute infection. Unfortunately, the infection enters a chronic phase in up to 85%. Even though the rate of progression to cirrhosis is slow and occurs over decades, HCV has become the commonest reason for liver transplantation in North America due to



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Walter's case:

- Walter, 47, has just moved to your town and requests that you take over his care. He has not seen his previous FP for almost three years and would like to see you for a full history and physical
- He tells you that he was advised to lose 11 kg (25 lbs.) and to begin regular exercise because he was a borderline diabetic. He has a high-stress office job and likes to relax in the evenings with a scotch or two. He does not take any prescription medications, but does use an OTC non-steroidal anti-inflammatory drug (NSAID) two to three times per week for tension headaches
- There is no other history of note obtained on the initial office visit. His physical exam is normal, except his BMI is 32. Initial bloodwork reveals elevated liver function tests and an abnormal lipid profile. Further evaluation determines that he is anti-hepatitis C virus (HCV) positive
- Walter will need to lose weight and address the manifestations of his metabolic syndrome. You suggest that he stop using NSAIDs to manage his headaches and try alternative approaches, such as acetaminophen and relaxation exercises. He must significantly limit his use of alcohol to address both his underlying HCV infection and metabolic syndrome
- You elect to try him on a statin to appropriately manage his hyperlipidemia and careful monitoring demonstrates that he does not develop statin-associated hepatitis⁴
- There is evidence, in the literature, that patients with mild elevation of transaminases on the basis of steatohepatitis are not at an increased risk of developing statin-associated hepatitis. At some point you will need to address whether he is an appropriate candidate for pegylated interferon and ribavirin therapy for his HCV infection

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the large number of infected individuals. Therefore, it is advisable to have an approach to the investigation and management of this group of patients.

It is appropriate to inquire as to the possibility of risk factors associated with the acquisition of HCV infection. Individuals found to have HCV infection should be encouraged to lose weight if appropriate and to avoid alcohol, as moderate alcohol use and

Lorraine's case:

- Lorraine, 45, presents with transaminase levels approximately 2.5 times the normal level
- On review of her chart, you discern that these tests were normal six months ago, but they were less than twice the upper limit of the normal level two years ago. Her ALP, bilirubin and international normalized ratio are normal
- This is an example of a hepatocellular process. The duration is possibly as long as two years and given this scenario, it is unlikely that this represents an acute illness. Common causes of hepatocellular injury include:
 - viral infections (acute or chronic),
 - steatohepatitis,
 - autoimmune disorders,
 - drug exposure or
 - disorders of metabolism, such as seen with iron, in hemochromatosis or with copper in Wilson's disease
- Given the chronicity of the abnormality, you decide to evaluate her for possible causes of chronic hepatitis. The results of testing for hepatitis B and C are negative, as are copper and iron studies, alpha-1 antitrypsin levels and autoimmune markers such as the anti-smooth muscle antibody and the IgG level
- You suspect that she has non-alcoholic steatohepatitis and arrange an ultrasound exam, which is reported to show changes consistent with this diagnosis
- It is important to recognize that the ultrasound is neither specific nor particularly sensitive for this diagnosis

obesity are lifestyle issues that have been shown to increase the rate of progression to cirrhosis. The current version of anti-HCV antibody test is very sensitive and specific, but it is advisable to obtain polymerase chain reaction-based qualitative RNA testing prior to initiation of therapy, because a reduction in the viral load is used to assess response to therapy.

The current standard of care for the treatment of hepatitis C is combination therapy, with weekly subcutaneous pegylated interferon and daily oral ribavirin. Genotyping should also be done if therapy is being considered. A sustained virologic response of up to


50% can be expected in Genotype 1, which is the commonest form of HCV in North America. Genotypes 2 or 3 have a higher likelihood of response, up to 75% to 85%. A 2 log (100-fold) drop in the viral titre, at week 12, in Genotype 1 is predictive of a good response to a standard 48-week course of treatment. Viral load determination may not be necessary in Genotypes 2 or 3, which may only require a 24-week course of therapy.

Careful monitoring for adverse responses to treatment is necessary. Interferons produce a predictable decrease in the neutrophil and platelet counts. Flu-like symptoms and symptoms of depression are common and should be managed appropriately. Occasionally, retinopathy and congestive heart failure may result from treatment. Ribavirin will induce a hemolytic anemia and is teratogenic. Appropriate birth control therapy is necessary for both male and females during their treatment. Contraindications to therapy include:

- decompensated liver disease,
- certain autoimmune diseases and
- uncontrolled depression.

Physicians considering therapy for their patients should obviously be comfortable with the management surrounding all of these issues, or arrange for referral to a colleague who is able to assist them.

Final thoughts:

Abnormal LFTs are common. A well thought-out approach to this problem will simplify the clinical approach and result in improved patient care. 

References

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