CLINICAL CHALLENG

Hepatitis C Infection with Persistently Normal ALT levels

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Clinical Scenario

A 46 year old navy personnel was referred to our department since he was found to be positive for HCV antibody (HCV Ab) in annual screening. On his past history, he had blood transfusion in 1982 when he had a femur fracture in Pakistan. He denied any unsafe or high risk sexual contact and used to drink alcoholic beverages. Markers of HBV and HIV, and serum levels of iron, copper, ferritin and ceruloplasmin were normal. Abdominal ultrasonography revealed no abnormality. Complete blood count including platelet count, protrombin time and partial thromboplastin time were also in normal limits. Upon 12 months serum ALT and AST were constantly less than 35 IU/L. He underwent liver biopsy with automatic needle and the histology activity index was 5 (grade 4 and stage 1 based on Modified Knodell scoring system). The HCV viral load reported 160 IU/ml and the genotype was 1a. A counselling session was performed at this point.

Epidemiology

Up to 60% of HCV-infected first-time blood donors and intravenous drug abusers have been reported to have normal ALT. It has been estimated that approximately one-third of patients with chronic hepatitis C have persistently normal aminotransferase.

Normal ALT

The limits that are presented as normal limits in routine clinical laboratory reports are mostly taken from statistical extraction of distribution indices like 95 percentile, 2 standard deviations and similar indicators within population studies including health surveys, health screening registries and reference labs pooled data. These “reference values” may face error because they are not real pathophysiologic cut-off of normal versus diseased cases. They are just based on the assumption that most of non-healthy individuals are above these values, although many normals may be higher and many ill cases may be lower. So, the definition of normal ALT is population-based, but not case-based. Suppose a case with frequent ALT reading of 10 whose its level increased to 35; is it normal or not? The reference

values should be checked locally and controlled frequently in each laboratory, too.In conclusion, the values are race-based, gender-dependent, age-variant and changeableby body mass index, so the results should be judged cautionally for each patient. The accepted cut-off point in most reports is 35-40; which may be 53-60, considering 1.5 folds upper normal limit. It means that you may face numbers that could not be easily classified to normal or healthy. Up to now, it is well known that the limits should be lower for females and children.

Persistently Normal ALT

Persistently normal ALT in HCV patient is defined by presenting all of the following criteria:

1. Presence HCV infection detected by using HCV Ab and confirmatory tests ie. HCV RNA by RT-PCR. It may be noted that presence of HCV Ab dose not mean HCV infection in all occasions and especially in low risk patients, HCV Ab has a low pre-test likelihood for the infection. The studies that reported HCV Ab cases as infected are now facing selection bias by the above mentioned definition.
2. Persistent normal ALT level defined by less than 1.5 folds of normal upper limit during at least 6 months in at least three separate readings (two out of three exams should be filled to the definition of normal). The level of ALT like the level of viremia is of fluctuating nature in HCV infection. So, several measurements on different occasions should be performed. One month lag between the exams is logical. The compliance of the patients at this point is very important. So, doctors should inform patients of the schedule and the reason behind it.
3. Absence of prominent stigma of cirrhosis or end-stage liver disease.It is obvious that ALT may be normal in many cirrhotic cases. Although compensated (child A) cirrhosis may be encountered like chronic hepatitis,any stigma of decompensation exclude the patient from the definition ofPNALT.

Natural History and Histology

Most of patients with chronic HCV infection and normal serum ALT are asymptomatic. Frequently, patients are discovered incidentally when anti-HCV antibodies are detected after blood donation.

Because some hepatologists do not routinely do liver biopsy in HCV RNA positive patients with normal ALT, the course of HCV infection with PNALT remains poorly defined. It was shown that one-fourth to one-fifth of PNALT cases end up in ALT elevation during follow up visits. Up to 80% of patients with PNALT have some stigmata for liver damage on liver biopsy. Recent studies showed abnormal histology in nearly all such patients. However, there was significant histology activity score (for inflammation and / or fibrosis) in 16% of patients with PNALT and 77% were found to have some degree of fibrosis on liver, although it was a significant score only in 8 percent.

Although significant fibrosis could be explained by missed flares in ALT, it should be stressed that fibrosis is often taken as the best predictor of those at risk of progressive liver damage from HCV infection. On the other hand, liver fibrosis tends to be worse in persons with elevated aminotransferases than those with normal ALT level and necroinflammatory scores are significantly lower in patients with normal ALT. Interface hepatitis was found to be the most significant risk factor .There were not biochemical, viral or demographic factors to predict significant histologic damage in patient with PNALT. The relationship between age, HCV genotype, viral load and severity of liver disease in HCV infected patient with PNALT has not been yet established. In one study, histologic grade was significantly higher in men than in women. Liver histology and outcome of patients with PNALT were not influenced by baseline ALT level (low normal vs. high normal). Thus, histologic examination of hepatic tissue is the best way to identify liver injury and prognosis of patients with PNALT.

Hepatocellular damage results in the leakage of cytoplasmic enzyme ALT into the circulation. For this reason, elevated ALT has been frequently used as a sole biochemical marker for liver inflammation in chronic hepatitis C.

Liver cell death in hepatitis C occurs via apoptosis and necrosis, and those dying by apoptosis synthesize less ALT. This might explain the poor correlation that exists between elevation of ALT and hepatic injury detected by liver biopsy. Female sex, young age and long duration of infection are more strongly associated with persistence of normal ALT. Host immunogenetic factors such as the presence of HLA DRB are the other explanation for this biochemical condition. The majority of PNALT cases are reported to be females. It has been shown that ALT decrease during normal pregnancy in patient with chronic hepatitis C. Also, estrogen therapy leads to marked decrease in ALT levels in women with chronic hepatitis of various etiologies. It has been suggested that estrogens could modulate some immune-mediated mechanisms.

Treatment

At the 1997 National Institutes of Health Consensus Conference on “Management of Chronic Hepatitis C” it was concluded that treatment of HCV infected patients with normal ALT levels was not beneficial, and alfa interferon therapy might worsen the course of disease. This conclusion led to exclusion of these patients from routine therapy. After 1997 combination therapy with interferon plus ribavirin was approved by FDA. Five studies of combination therapy have been runned in patients with normal or minimally elevated ALT (up to 1.5 ULN), to evaluate the efficacy and safety of this regimen. The investigators suggested that combination therapy with interferon plus ribavirin for chronic hepatitis C with PNALT is associated with sustained virologic response rate comparable to those with elevated ALT. After treatment, transient ALT elevation in minority of patients has been reported. Within non-responders of PNALT cases, in comparison with high ALT patients, persistent elevation of ALT in about 10 percent of patients developed at the end of follow up. This is attributed mostly to natural course of HCV infection.

Facts

- ALT is not a sensitive or specific marker ofhistologically active disease in HCV patients.
- PNALT may be seen in active hepatitis, histologically minimal disease or liver disease.
- The best modality to establish the disease activity is biopsy. The stage of fibrosis>= 3 or histology activity index>= 5 may point severity.
- Treatment of HCV infection in PNALT cases is of compatible therapeutic responses with high ALT level cases.
- Genotype 2 or 3 responds better to the treatment regardless of being PNALT or not.

Recommendation

A) All HCV patients, regardless of ALT level, should be considered for biopsy if no contraindication presents and the patient is not frankly compatible with the diagnosis of decompensated cirrhosis.

B) HCV treatment should be individualized based on histology activity and fibrosis on liver biopsy, regardless of genotype, gender and intravenous drug use. Ishak-Knodell histology activity>= 5 or fibrosis stage>= 3 may be the good cut-off level for initiating treatment. In the absence of contraindications, combination therapy should be the first choice. In presence of cirrhosis on histology, dose adjustments should be considered.

Options in future

Patients with genotype 2 or 3 may be treated initially without liver biopsy this conclusion may be formed in future since they are easy-to-treat with high treatment response rate, and the focus aim of treatment would be shifted from histology to the virus itself.

Selected Articles

A) Natural Histology

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B) Treatment

1. Tassopoulos N. Treatment of patients with chronic hepatitis C and normal ALT levels. J Hepatol 1999 (suppl1): 193-6.
2. Hui CK, Monto A, Belaye T, Wright TL. Outcomes of interferon alfa and ribavirin treatment for chronic hepatitis C in patients with normal serum aminotransferases Gut 2003; 52: 1644-8.
3. Van Thiel D, Caraceni P, Molloy P, Hassanein T, Kania R, Guarakar A. Chronic hepatitis C in patients with normal or near normal alanine aminotransferase levels. J Hepatol 1995; 23: 503-8.
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