

## **Mild Transaminitis in asymptomatic aircrew- a clinical dilemma**

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**A** 42years old commercial aircrew reported for his renewal medical examination. The individual was asymptomatic and denied any medical complaints. The general and systemic examination was unremarkable and there were no cutaneous markers for acute or chronic liver dysfunction. All the investigations including hematological and biochemical parameters were normal except for mild elevation of aminotransferases (AST/ALT: 52/60 IU/L). On further inquiry there was no history of consumption of alcohol or hepatotoxic drugs or past history of jaundice. The ultrasound of the abdomen was normal and the viral markers for hepatitis B and C were negative. This is a common clinical problem faced by majority of aeromedical examiners. More importantly, there are dilemmas of aero medical decision making (ADM) in such cases especially for authorised medical attendants (AMA) in military and civil aviation set ups. This paper answers the relevant questions pertaining to mild transaminitis in aircrew.

### **How significant is the problem?**

Mildly elevated aminotransferases in an asymptomatic aircrew is a commonly encountered problem. According to American Gastroenterological Association (AGA), 1 to 4 percent of the asymptomatic population may have elevated serum chemistries [1]. Although one study of 19,877 asymptomatic young air force trainee found that only 0.5% had elevated ALT levels [2], physicians who have more patients with obesity, diabetes, and hyperlipidemia will have to address this issues more often. The dilemma being faced in

such cases is whether to investigate further or not, and if to investigate how to proceed. It is seen that these abnormalities are not always investigated appropriately, and opportunities to intervene in treatable causes are some times missed [3].

### **What are aminotransferases and its clinical significance?**

Aminotransferases include Aspartate transaminase (AST) and Alanine transaminase (ALT). AST is a mitochondrial enzyme, which is present in liver, cardiac muscles, skeletal muscles, kidneys, brain, pancreas, lungs, leucocytes and erythrocytes in decreasing order of concentration. ALT is a cytosolic enzyme and is more specific for liver. AST is also referred to as serum glutamic oxaloacetic transaminase (SGOT) and ALT as serum glutamic pyruvic transaminase (SGPT). The aminotransferases are normally present in serum at low levels. Damage to liver cell membrane causes release of increased levels of these enzymes in to the blood stream. ALT and AST are thus two reliable markers of hepatocellular injury or necrosis. Although levels of AST and ALT can be extremely elevated (>2000 u/L in hepatocyte injury and necrosis), elevation less than five times the upper limit of normal are much more common. The range of possible etiologies at this level is broader (table 1). There is, however, a poor correlation between degree of liver damage and the levels of transaminases. The absolute elevation of aminotransferases is thus of no prognostic significance in acute hepatocellular disorder.

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The ratio of AST to ALT at times gives a clue to the likely cause. In many acute and chronic liver disease or steatosis the ratio is less than or equal to 1. An AST: ALT ratio greater than 2 is suggestive of alcoholic hepatitis. Wilson's disease related hepatitis could cause the AST: ALT ratio to exceed 4 [4]. In a study of 140 patients with nonalcoholic steatohepatitis (NASH) and alcoholic liver disease, the mean AST: ALT ratio was 0.9 for NASH and 2.6 in patients with alcoholic liver disease [5]. With in the population studied, 87 percent of patients with an AST: ALT ratio of 1.3 or less had NASH (87% sensitivity, 84% specificity). As the severity of NASH increased, so did the AST: ALT ratio.

Liver function tests have their own shortcomings. They can be normal in patients with serious liver disease and abnormal in patients with diseases that do not affect the liver. The normal range for transaminases for any laboratory is the mean value in a group of healthy people  $\pm$  2SD. Thus 5% of the results of normal individual will fall outside the defined normal range. There is also a significant positive correlation between ALT and body mass index; ALT is also significantly lower in women than in men suggesting that the normal range for ALT be adjusted for gender [6]. The aim of evaluation in such cases is thus to differentiate physiological from pathological rise of transaminases.

### **How to approach such a case?**

The first step in evaluation of asymptomatic rise of aminotransferases is to confirm the laboratory result by doing a repeat test on the same day or the next day. If the repeat enzyme levels are normal, no further investigations are warranted. If the result is again abnormal, the individual is subjected to tests directed towards finding the aetiology.

A comprehensive medical history and physical examination directed towards the common aetiology,

i.e., alcohol and medication related hepatotoxicity, along with other relatively common conditions are performed (Table 1). The presence of other significant health condition that can cause or augment liver transaminase elevation should also be noted, particularly diabetes mellitus, heart disease, thyroid disease, muscle disease and cancer. Has an algorithmic approach for such cases. AGA approach however follows step wise, time consuming methodology which is not possible to follow in case of an aircrew due to the time constraint. Keeping the time constrain in mind along with the safety issues, it is suggested, to follow a revised accelerated screening protocol. Unless an obvious cause for the raised aminotransferase is present, a full battery of screening test (Table 2) can be performed on day one. Additional tests for liver function assessment like prothrombin time and albumin is also done. If all the tests are negative and the aircrew does not have features of chronic liver disease or its complication, they can safely be re-flighted with or without restrictions. A close clinical follow up and serial liver chemistry testing is however essential. Notwithstanding the above, it should however be noted that if markedly elevated and/or persistent ALT and AST levels are noted, or if significant symptom or evidence of chronic or decompensated liver disease are present, a more expeditious and complete initial diagnostic evaluation is warranted. Similarly chronic AST or ALT elevation (more than 6 months) usually warrants additional comprehensive serologic and radiologic evaluation and potentially a liver biopsy.

The cause of rise in aminotransferase is often obscure. In a study involving 19,877 United States (US) Air Force basic trainees, 99 (0.5%) had elevated ALT levels, however, cause was found in only 12 of the 99 [2]. According to AGA, the decision to perform a liver biopsy needs to be based on individual basis, taking into consideration

**Table 1. Causes of persistent elevation of aminotransferases**

<u>Hepatic cause</u>	<u>Nonhepatic causes</u>
a. Alcohol abuse	a. Muscle disorders- inherited and acquired
b. Medication	b. Strenuous exercise
c. Chronic hepatitis	c. Celiac spruce
d. Steatosis and non alcoholic steatohepatitis	
e. Autoimmune hepatitis	
f. Hemochromatosis	
g. Wilson’s disease	

**Table 2. Laboratory investigations to identify the cause of persistently elevated aminotransferase in an asymptomatic aircrew.**

<b>Test</b>	<b>Interpretation</b>
Hepatitis-C antibody serology	Indicative of chronic hepatitis C
HBsAg	Indicative of chronic hepatitis B
Serum iron and total iron binding capacity(Iron) (Normal Values 60-150 µg/dl(TIBC) (Normal Values 250-400 µg/dl)	Iron over load suggests hemochromatosis
Serum ceruloplasmin (Normal Values 23-50 mg/dl)	Decreased levels is suggestive of Wilson’s disease
Serum protein electrophoresis & ANA	Increase in polyclonal immunoglobulin suggests autoimmune hepatitis while marked decrease in a-globulin band suggests a1-antitrypsin deficiency

individual’s age, lifestyle, liver chemistry abnormality, desire for prognostic information and associated co morbid conditions.

**What are the common causes of elevated aminotransferases in an asymptomatic aircrew?**

Alcohol. Alcohol hepatitis typically has an AST: ALT ratio of at least 2:1. This decrease in ALT is a consequence of alcohol related deficiency of pyridoxal 5-phosphate. Serum AST level rarely exceeds 300 IU/L. Serum gamma glutamyl transpeptidase (GGT) rises due to enzyme induction and serum alkaline phosphatase may be increased, especially, with those with cholestasis.

Medication. Almost any medication can cause

an elevation of aminotransferases Common drugs causing this is listed in table -3. To prove or disprove medication as a cause of elevated transaminase, the suspected drug needs to be discontinued and normalization of transaminases sought, this is however not always feasible.

Chronic hepatitis. Hepatitis B and C can cause chronic hepatitis. A history of blood transfusion, intravenous drug abuse or surgery gives a clue to the likely presence of chronic hepatitis, which can then be confirmed using laboratory investigations.

Steatohepatitis and non-alcoholic steatohepatitis. A mild elevation in aminotransferase may be the only clue to presence of steatohepatitis. The enzyme levels are usually less than four times the normal values [7]. They usually have an AST:

Medication	Herbal supplements and vitamins
<b>Antibiotics</b>	Chaparial leaf
Synthetic penicillins	Ephedra
Ciprofloxacin	Gentian
Isoniazide	Germander
Rifampicin	Jin bu huan
Nitrofurantoin	Kava
Fluconazole	Senna
	Shark cartilage
<b>Antiepileptic drugs</b>	Vitamin A
henytoin	
Carbamazepine	
Non steroidal anti-inflammatory drug	
Sulfonamide Glipizide	
<b>HMG co-A inhibitors</b>	
Simvastatin	
Lovastatin	
Pravastatin	

ALT ratio that is less than 1:1. A presumptive diagnosis is made in presence of elevated aminotransferases, radiological evidence of fatty liver, insignificant alcohol intake, negative viral markers, absence of hepatotoxic drug intake and exclusion of metabolic and autoimmune liver disease. Liver biopsy if done shows fatty infiltration (microsteatosis), fibrosis around central vein, minimal to moderate inflammation, liver cell necrosis and hyaline inclusions in hepatocytes.

Autoimmune hepatitis. Autoimmune hepatitis is a disease affecting predominantly young to middle aged women [8]. The ratio of female patients to male is 4:1 [9]. It is a chronic disorder characterized by continuing hepatocellular necrosis, and inflammation usually with fibrosis and tends to progress to cirrhosis and liver failure. Screening test employed is serum protein electrophoresis, which shows presence of hypergammaglobinemia in more than 80% of individuals. Additional diagnostic tests include antinuclear antibody (ANA), antibodies against smooth muscles (anti-sm) and liver-kidney microsomal antibodies (anti-LKM). The

natural history is often variable with spontaneous remissions and exacerbations.

Hemochromatosis. It is an uncommon disorder of iron storage with the clinical expression being 5 to 10 times more frequent in men than women [10]. The excess iron is deposited in parenchymal cells leading to tissue damage and impaired organ function. The organs involved commonly are the liver, pancreas, heart, joints and pituitary. Liver is usually the first organ to be affected and hepatomegaly is present in more than 95% of asymptomatic individuals. Screening test commonly employed is serum iron and total iron binding capacity. Serum ferritin being an acute phase reactant provides less specific information, although it can be used for follow up of a diagnosed case. If the screening tests are suggestive of iron overload, a liver biopsy should be performed to assess extent of hepatic iron overload and the severity of liver damage. All first-degree relatives of patients with hemochromatosis should be tested for C282Y and H63D mutations.

Wilson's disease. It is an inherited disorder of copper metabolism with two mutant ATP7B genes. The resultant toxic accumulation of copper predominantly affects the liver and brain. The worldwide prevalence of Wilson's disease is 1 in 30,000. The diagnosis is suspected when any young individual (< 40years) presents with unexplained disorder of central nervous system, sign or symptoms of hepatitis or unexplained persistent elevation of transaminases. The initial screening test for Wilson's disease is measurement of serum ceruloplasmin, which is low (< 20mg/dl) in approximately 85% of affected individuals. Kayser-Fleischer rings are usually seen in individuals with neurological or psychiatric disturbances.

Non hepatic causes. Elevated AST may be caused by disorders affecting non-hepatic tissues, especially, striated muscles. If striated muscles are the source of elevated AST, serum levels of creatine kinase and aldolases will also be elevated concomitantly. In a recent study, occult celiac spruce was the cause of chronically elevated serum aminotransferase levels in 13 of 140 asymptomatic patients who were referred for this reason to a liver clinic [11]. The diagnosis is made by measuring serum levels of antigliadin and anti endomysial antibodies. Hyperthyroidism has been found in several studies to increase serum levels of liver enzymes including AST and ALT [12]. Genetic influences on the levels of ALT are also possible [13]. The AGA technical review states that the serum ALT has a diurnal variation, may vary day to day and may be affected by exercise. It must also be noted that serum AST may be 15 percent higher in black men than white (1).

#### **What is the aeromedical disposal of such cases and how to you follow up?**

All aircrew need to be evaluated for any underlying cause for the elevation of aminotransferases. If despite exhaustive evaluation

no definite cause can be found, liver chemistry needs to be repeated at 6 monthly intervals (shorter interval if there is concern for evolving process). As isolated rise in level of liver enzymes does not pose risk of sudden incapacitation, no flying restriction needs to be placed other than regular review by AMA.

#### **Conclusion**

Hepatic aminotransferases are commonly found to be elevated in asymptomatic aircrew. This mild elevation may represent a serious underlying cause or a transient benign aetiology. All cases have to be investigated diligently so as to prevent missing opportunity for early intervention in cases of underlying liver pathology. Despite all investigations, no aetiology is apparent in a large number of individuals, yet they much to be followed up on regular basis. Liver biopsy is not advised as a routine but is performed on merit of each case.

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