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Point of View

Features of Subtransaminasemia Interpretation

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Abstract

Alanine and aspartate aminotransferase levels often increase, without any accompanying clinical signs of liver disease. This biochemical phenomenon has increasingly begun to attract the attention of specialists because of the frequency of its occurrence, which is the reason for the rising recognition of the reality of this problem. In fact, determination of the increased level of transaminases at first suggests its relation to some liver disease, despite the absence of its clinical manifestations. Frequently, this is followed by a long process of looking for various liver diseases by both the doctor and patient. In principle, this approach is justified and undisputed. However, the question that arises is whether this tactic is always acceptable! If not, what alternative is to be sought for in such cases? These and other unresolved issues were the reasons that prompted this study, to take a fresh look at this rather old problem. IJBM 2011; 1(4):249-252.

Key words: *Alanine aminotransferase, aspartate aminotransferase, transaminasemia.*

Doctors often deal with cases of increased intracellular enzyme activity, in everyday practice. Alanine and aspartate aminotransferase (ALT, AST) levels often increase, without any accompanying clinical signs of liver disease [1, 15]. This biochemical phenomenon has increasingly begun to attract the attention of specialists because of the frequency of its occurrence, which is the reason for the rising recognition of the reality of this problem. The mounting interest in the problem of transaminasemia is largely due to its detection, thanks to the advancement of technology. With the reorientation currently being done in family medicine courses in the Republic, there is practically no primary care unit which does not possess this capability. Determination of ALT and AST levels in the blood serum has recently been included in the list of mandatory routine screening tests. Of course, as the frequency of identifying more cases with increased levels of ALT and AST increased, the problem of their competent interpretation remains more realistic.

In fact, determination of the increased level of transaminases at first suggests its relation to some liver disease, despite the absence of its clinical manifestations [5, 6]. Frequently, this is followed by a long process of looking for various liver diseases by both the doctor and patient. In principle, this approach is justified and undisputed. However, the question that arises is whether this tactic is always acceptable! If not, what alternative is to be sought for in such cases? These and other unresolved issues were the reasons that prompted this study, to take a fresh look at this rather old problem.

According to modern concepts, ALT and AST are regarded as biochemical indicators of liver cell damage and necrosis [4, 12-14]. In practice, the increased levels of serum transaminases are denoted by different, but similar value terms as follows: transaminasemia, hypertransaminasemia or hyperenzymemia hyper-ALT-emia and hyper-AST-emia. All of them are similar in meaning, and therefore, have equal chances for their use in any type of increase in the levels of transaminases. Notably, these terms not only have semantic closeness, they also pose a disadvantage, such as a limitation on the depth of information regarding the degree of the level of increase of the transaminases. Consequently, it becomes difficult to associate them with the severity of the cytolytic syndrome (CS). In our opinion, the existing phraseological

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limitation unreasonably underestimates the amount of information regarding the level of the transaminase indicators. To correct this difficulty, transaminasemia was distinguished into different levels, clearly indicating its range by grading. This approach, of course, increases the informative possibility of transaminasemia. Graded enzyme levels have proven useful in determining the CS expression, along with the functional capacity of the liver cells. This causes the diagnostic value of the transaminases levels to become more refined and thus more informative.

Today, the most attractive scale is the one employing three grades, with clearly defined bands between them. The number of grades is not as important as the fact that each grade should enable one to independently assess the severity of CS. Therefore, the most convenient scale will need to include all three levels of transaminasemia gradation: minimal (1.5-2 norms), moderate (5-6 norms) and maximal (10 and more norms). Undoubtedly, they are all based on the actual level of the transaminases. However, because these terms should always be appended to the term "transaminasemia", there is some added stylistic inconvenience. Now, it appears more convenient to replace them with terms that are already at the level of visual acquaintance, which will permit us to immediately identify the degree of the increase in the transaminases levels. Hence, we recommend our own original version of gradation of the transaminasemia levels (Table 1).

Table 1
Transaminasemia levels gradation

Parameter	Normal range	Subtransaminasemia	Transaminasemia	Hypertransaminasemia
ALT	<0.45	1,5-2 N	5-6 N	≥10 N
AST	<0.50	1,5-2 N	5-6 N	≥10 N

We consider it appropriate to term a minimal increase in the level of transaminases as subtransaminasemia (ST), moderate increase as transaminasemia and maximal increase as hypertransaminasemia. The fact that both transaminasemia and hypertransaminasemia are biochemical markers of CS needs no further interpretation. However, a completely different situation arises with ST, which in recent years has increasingly been identified not only in patients with liver diseases, but also in the pathologies of several other systems.

As part of this publication, we have elaborated on the characteristics of the frequency of the occurrence of ST and the possible causes of its development in various internal diseases. This issue is also important because the technical potential of ST recognition in the Republic, as noted earlier, has vastly increased due to a good supply of primary health care units with appropriate modern analyzers.

It should be remembered that not all individuals with ST have serious liver disease. Most often, general practitioners need to consider and interpret the increases in ALT and/or AST levels in patients with obesity, diabetes, lipid disorders, muscular dystrophy or even the complete absence of any disease symptoms [1, 11]. Iatrogenic ST, often associated with the doctor prescribing an unnecessary intake of antibiotics (cephalosporins), proton-pump inhibitors, ursodeoxycholic acid, nonsteroidal anti-inflammatory drugs (NSAIDs), etc. has, unfortunately, become quite common.

Interestingly, patients with normal ALT and AST could have severe liver damage, accompanied by chronic hepatocyte damage (extensive necrosis, cirrhosis, hepatitis C), by significantly reducing the number of cells synthesizing transaminases [2, 3, 10]. The highest ALT activity is detected in the liver, with a lesser activity in the kidneys, pancreas, heart and skeletal muscle [10, 17]. ALT is an intracellular enzyme and its concentration in the blood serum of healthy individuals is low [18, 19]. The concentration depends on many demographic factors, particularly gender (females have a lower concentration than males), body mass (higher values in obese patients) and race. The Europeans have about a 15% lower ALT level than do the Asians and blacks [16, 18, 19].

In a special survey of the American Gastroenterological Association, dedicated to studying increased transaminases levels, the ALT levels were clearly observed to vary throughout the day during the week, depending on physical activity [13, 16].

Considering the inconsistency of the earlier published data concerning the frequency distribution of ST in the population and the possible causes of their origin, we decided to obtain our own results. Therefore, retrospective and prospective analyses of the results of ST of various origins were performed and documented in various medical records (ambulatory medical records, hospital records, etc.) of the Bukhara State Medical Institute Multidisciplinary Clinic. Medical records of patients treated in the hospital or those who had had ambulatory treatment in the last five years were subjected to retrospective analysis. Inclusion criterion was the presence of ST in two or more recent blood analysis, regardless of the type of pathology in general, and the liver in particular. Random sampling included 388 subjects with various diseases accompanied by ST. All the ST cases were divided into two large groups. The first group included subjects with ST clearly associated with various liver diseases. The second group included subjects with ST not hepatic in origin. Analyzed data were subjected to statistical analysis using the relative values formula. The results are presented in Table 2.

From the data presented in Table 2, in more than two-thirds of the patients, ST resulted from various liver diseases, including pathologies of viral and alcoholic origin. Also, a tangible part of ST was caused by nonalcoholic steatohepatitis and cholestatic liver disease, which together accounted for nearly one-third of all cases of ST of hepatic origin. In patients with the hepatic origin of ST, the increased transaminases levels were mainly due to ALT, the exception being cases of alcoholic liver

Table 1
Diseases and conditions accompanied by subtransaminasemia

Hepatic n=291 (67%)			Extrahepatic n=97 (33%)		
Cause	**Frequency (%)**		**Cause**	**Frequency (%)**	
	ALT (M±m)	**AST (M±m)**		**ALT (M±m)**	**AST (M±m)**
Nonalcohol steatohepatitis	47	42	Diabetes mellitus	15	16
	16.2±2.1	14.5±2.0		15.3±3.6	16.4±3.7
Chronic viral hepatitis	73	62	Drug induced liver damages	16	11
	25.2±2.5	21.3±2.4		16.7±3.7	11.6±3.2
Alcohol hepatitis	47	77	Thyrotoxicosis	6	5
	16.3±2.1	26.4±2.1		6.5±2.5	5.2±2.2
Cirrhosis (sub- and decompensated)	56	46	Myopathy	6	8
	19.4±2.3	15.7±2.1		6.1±2.4	8.4±2.8
Hemochromatosis induced hepatitis	19	17	Obesity	14	11
	6.4±1.4	5.7±1.3		14.6±3.5	11.2±3.2
Wilson disease	12	15	Heart diseases	73	12
	4.2±1.1	5.1±1.2		7.5±2.6	12.5±3.5
Chronic cholestatic hepatitis	36	33	Hemolytic anemia	7	8
	12.3±1.9	11.3±1.8		7.1±2.6	8.6±2.8
			Celiacia	6	7
				6.3±2.4	7.4±2.6
			Lipid disorders	15	14
				15.6±3.6	14.2±3.5
			Pregnancy	4	4
				4.3±2.0	4.5±2.1

disease and Wilson disease, in which the opposite was observed, namely, the prevalence of AST levels. The de Ritis coefficient which is normally 1.2±0.3 [7-9] was generally lower than 1 in patients having ST of hepatic origin. However, in those patients with alcoholic liver disease and Wilson disease, this coefficient varied a little, rising to more than 1. Nevertheless, this fact had no impact on the direction of the intensity of the de Ritis coefficient in patients with ST of hepatic origin.

The structure of the ST resulting from extrahepatic diseases was a little different. Surprisingly, in this group of patients, drug-induced ST was the most common. This fact, in our opinion, has been mainly due to the existing problems in drug implementation in the remote areas. A large part of the drugs, to date, are sold freely without a prescription. This practice has lead to an increase in the unauthorized use of drugs among patients, which is certainly unsafe in terms of ST development. However, the facts of polypharmacy, especially among general practitioners, cannot be ignored, as it sometimes also is the reason for drug-induced ST.

According to the data obtained in the majority of patients the source of drug-induced ST was due to cephalosporin antibiotics, NSAIDs etc. It is indeed a shame that medications which induce ST are often prescribed without substantial grounds, over a long time period.

Frequently, ST occurred in patients with diabetes, obesity and lipid disorders. If the transaminases level in patients with adipose- and drug-induced ST increased mainly because of ALT, in diabetic patients, however, on the contrary, for account of AST. Of course, such a scale in the level of enzyme fractions will definitely affect the severity of the de Ritis coefficient, which in most cases always exceeded 1, except however, for those rare cases in which it was equal to 1 or slightly lower.

Thus, based on the previous published results and our own results, the interpretation of ST in practice should always be undertaken with great care. In this case, the causes of ST should be noted to be due to diseases that are often completely unrelated to the hepatobiliary tract, and unfortunately, their number appears to be steadily increasing.

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