HISTOPATHOLOGIC AND BIOCHEMICAL LIVER TEST ABNORMALITIES IN CHRONIC ASYMPTOMATIC OR OLIGOSYMPTOMATIC ALCOHOLICS: A REVIEW

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PURPOSE: To review the medical literature regarding the histopathologic and biochemical liver test abnormalities in chronic asymptomatic or oligosymptomatic alcoholics.

METHODS: Review of articles in the MEDLINE and LILACS databases regarding serum levels and prevalence of alterations in aspartate-aminotransferase, alanine-aminotransferase, alkaline phosphatase, and total bilirubin, in relation to liver histopathology, with or without discrimination of types of histopathologic alteration.

RESULTS: Global mean prevalence rates of aspartate-aminotransferase and alanine-aminotransferase alterations were 86.3% and 51.1%; in cases with steatosis they were 79.1% and 38.5%; and in cases of hepatitis, 90.1% and 58%. In all studies, prevalence rates of aspartate-aminotransferase alterations were significantly higher with lower variability than those of alanine-aminotransferase. Mean aspartate-aminotransferase levels were higher than 2N (N is the upper normal limit of the method employed) in all cases with hepatitis histopathology, while those of alanine-aminotransferase were 1.48N, in the same cases.

Prevalence of alkaline phosphatase and total bilirubin abnormalities were 74.5% and 74.9% globally; in cases of steatosis, they were 70.9% and 67.9%; and in cases of hepatitis, 75.9% and 77.7%. Mean alkaline phosphatase levels were above the upper normal limit in all cases, but those of total bilirubin were above normal in 4 of 7 hepatitis studies.

CONCLUSIONS: Prevalence of aspartate-aminotransferase alteration was consistently related to presence of histopathologic abnormalities; an enzyme level higher than 2N suggests the diagnosis of alcoholic hepatitis.

DESCRIPTORS: Chronic alcoholism. Asymptomatic or oligosymptomatic alcoholics. Liver tests. Liver enzymes and bilirubin. Histopathology.

Various drugs, including alcohol, produce metabolic alterations and may lead to hepatocellular damage through complex interactive mechanisms. Hepatocytes submitted to noxious stimuli may be functionally or structurally damaged, transitorily or permanently, depending on the strength and duration of the stimuli. Nonetheless, even structurally damaged liver cells may be at least partially functional. Because of this ambiguity, possible confusion arises regarding structural damage with functional alteration, especially when functional tests are altered, which are taken to indicate structural damage. Non-invasive presumptive diagnosis of structural damage usually becomes dependent on quantitative and associated functional evaluations. In almost all stages, the various drug-induced alterations of hepatocytic membranes and organelles can be accompanied by enzyme alterations and can be observed histologically[1]. The liver being the main organ responsible for drug biotransformation[2] may be or not functionally[3,4,5] or structurally[6,7,8] altered in chronic alcoholics, and such alterations may be or not followed by clinical manifestations or laboratory abnormalities[7].

Asymptomatic or oligosymptomatic alcoholic patients are usually not receptive to undergoing liver biopsy, and performance of this procedure in them is not easily acceptable from the ethical perspective. Furthermore, in clinical practice, utilization of liver biopsies suffers from various limitations, including the following: biopsies not visually guided

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produce an average of 24% false negatives[9]; no evidence of necrosis or fibrosis was obtained in 40% to 50% of chronic alcoholics[10]; biopsies are associated with significant morbidity and with 0.015% to 0.03% mortality rates[11]; and other negative factors include the unnecessary upsetting of patients and the hospitalization costs. Consequently, it is difficult to accept and follow the norm established by the International Consensus[12] of classifying the liver lesions that may occur in these patients according to the histologic findings.

Liver histologic abnormalities including steatosis, hepatitis, and cirrhosis that are caused by alcohol are not mutually exclusive. On the contrary, each one may be present in the same case with variable intensity[13], representing a disease continuum[14]; clinical[15,16] and biochemical[8,15] alterations may overlap in the 3 types of histopathologic lesions.

Studies of chronic asymptomatic or oligosymptomatic alcoholics[7,17,18] have revealed enzyme and bilirubin alterations that are sometimes so minor that it is difficult to interpret their real meaning with regard to whether they indicate the presence of liver damage, whether they indicate an abnormal liver test, or whether they indicate a mere biochemical alteration that is not abnormal. Such ambiguity has led to arguments and even divergent positions among researchers and specialists[19].

A review of the bibliography was conducted, selecting reports on chronic oligosymptomatic or asymptomatic alcoholics containing liver biochemical and histopathologic evaluations, with the purpose of exploring conceptual aspects and the criteria for interpretation of biochemical tests. On these bases, we intended to establish criteria for such interpretations of enzymes and bilirubin abnormalities for patients with mild or sub-clinical symptoms.

MATERIALS AND METHODS

A systematic search in the MEDLINE and LILACS databases was conducted from 1982 to 2000, in English and neo-Latin languages, employing the following terms singly or associated: alcoholism or alcoholic, oligosymptomatic or asymptomatic or subclinical, liver disease.

Publications included in this study referred to asymptomatic patients and those presenting mild and non-specific clinical manifestations or sub-clinical liver disease (oligosymptomatic), and contained data on prevalence and types of histopathologic liver alterations and prevalence and levels of liver enzymes and bilirubin. Excluded were publications not containing data on liver histopathology and/or liver enzymes and bilirubin as well as those not relating the 2 types of abnormalities. Other comments on such criteria are indicated in specific cases below.

A total of 14 studies were selected comprising 1540 patients (1412 males, 128 females) presenting, singly or associated, data on prevalence of liver tests alterations, average plasma levels of liver enzymes and bilirubin, and correlation between prevalence and degrees of liver test alterations with liver histopathology, with or without discrimination of the type of histopathologic alteration. Four of these did not include data on histopathology[4,17,18,20], 5 related the prevalence of liver test abnormalities to histopathologic alterations but did not specify the types of the latter[6,7, 21-23]; and 5 related the average serum levels of liver enzymes and bilirubin to the specific types of histopathologic alterations[3,24-27]. One of the studies with liver histopathology[21] was excluded because the biochemical alterations were not correlated with the histopathology classes.

Seven studies[3,6,22-26] of a total of 847 patients (796 males, 51 females) were analyzed for evaluation of prevalence of liver test alterations according to anatomopathologic lesions. Five studies[3,24-27] of a total of 277 patients (267 males, 10 females) were reviewed for correlated elevated serum levels of biochemical tests and types, specific or not, with anatomopathologic lesions. Three reports[6,22,23] did not detail the serum levels of liver enzymes. From 2 articles[24,26], data expressed as the average and its standard error were transformed into the average and the standard deviation.

Statistical comparisons were conducted on qualitative variables, through the chi-square test, or where indicated, two-tailed Fisher's exact tests. Correlation between variables was established with Pearson's coefficient and significance test. From some studies, data were displayed as 2 x 2 matrixes and coded, relating the biochemical tests and histopathologic alterations as true positive (a), false positive (b), false negative (c) or true negative (d). Sensitivity [(a/a+c)100], specificity [(d/b+d)100], positive [(a/a+b)100] and negative [(d/c+d)100] predictive values, all expressed as %, plus prevalence and proportion of probabilities (odds; posPP/negPP) were calculated. The probability of finding individuals with enzymes and bilirubin higher than twice the upper limit of normality was calculated based on the normal probability curve [(z~N (0;1)], with the purpose of comparison with the Consensus criteria. The 5% significance level was adopted.

RESULTS

The prevalence of abnormalities and the average values of liver enzymes and bilirubin, with the respective reference values, are presented in tables 1 and 2.

Table 1 - Prevalence of alterations in liver enzymes in chronic asymptomatic or oligosymptomatic alcoholics according to the types of histopathologic lesions.

		Aspartate-aminotransferase		Alanine-aminotransferase		Alkaline phosphatase		Total bilirubin	
	n	n	%	n	%	n	%	n	%
- Liver steatosis									
Green[3]	5	3	60.0	-	-	-	-	1	20.0
Harinasuta et al.[24]	157	126	80.0	52	33.0	118	75.0	113	72.0
Nakamura et al. [3]	25	19	78.0	18	72.0	11	45.0	13	52.0
	Total	148	79.1	70	38.5	129	70.9	129	70.9
- Alcoholic hepatitis									
Green[3]	11	11	100.0	-	-	1	9.0		
Harinasuta et al.[24]	100	92	92.0	51	51.0	83	83.0	92	92.0
Helman et al.[25]	37	34	92.0	13	35.0	22	59.5	35	94.5
Lischner et al.[22]	135	-	-	90	67.4	92	59.0		
Mendenhall et al.[26]	184	161	87.5	118	64.1	150	81.5	142	77.2
Nakamura et al.[23]	12	12	100.0	11	88.0	10	84.0	10	84.0
	Total	310	90.1193	58.0355	75.9 372	77.7			
- Various lesions									
Bathal et al.[6]	100	38	38.0	-	-	-	-	28	28.0
Green[3]	29	9	31.0	-	-	-	-	2	6.9
Nakamura et al.[23]	52	30	57.0	22	43.0	20	39.0	-	-
	Total	77	42.5	52	43.0	20	38.5	30	23.9

Table 2 - Values of liver enzymes and total bilirubin in chronic asymptomatic or oligosymptomatic alcoholics according to the types of histopathologic lesions.

		Aspartate-aminotransferase	Alanine-aminotransferase	Alkaline phosphatase	Total bilirubin
1 - Liver steatosis					
- Green[3]	(n=5)	56.8 ± 37.0	-	-	0.62 ± 0.61
	RV	≤ 40 U/dL	-	-	≤ 1 mg/dL
2 - Alcoholic hepatitis					
- Green[3]	(n=11)	92.4 ± 30.2	-	-	0.61 ± 0.43
	RV	≤ 40 U/dL	-	-	≤ 1mg/dL
- Harinasuta et al.[24]	(n = 100)	144 ± 150	56 ± 80	8.6 ± 5	5.7 ± 6
	RV	≤ 40 U	≤ 38 U	≤ 4 B U	≤ 1.0 mg/dL
- Helman et al.[25]	(n = 12)	98	38	21.4	5.7
	RV	40 U/mL	35 U/mL	14 KA U	≤ 1.2 mg/dL
- Mendenhall et al.[26]	(n = 89)	84 ± 56.6	56 ± 56	165 ± 80.2	1.6 ± 0.94
	RV	10-40 mU/mL	10-30 mU/mL	40-120 U/mL	0.1-1 mg/dL
3 - Various lesions					
- Ryback et al.[27]	(n = 60)	64.0 ± 71.9	47.2 ± 48.7	84.1 ± 27.8	0.84 ± 0.41
	References values	10-40 mU/mL	10-30 mU/mL	40-120 IU/mL	0.1-1 mg/dL

RV = references values; B U = Bodansky units; KA U = King Armstrong units.

I. Aminotransferases

Mean prevalence rates of increases of aspartate-aminotransferase (AST) were 458/531 (86.3%) globally, with 148/187 (79.1%, range 60%-80%) in the steatosis cases and 310/344 (90.1%, range 87%-100%) in alcoholic hepatitis cases; the difference between these was not statistically significant. For alanine-aminotransferase (ALT), the prevalence rates of increases were 263/515 (51.1%) globally, 70/182 (38.5%, range 33%-72%) in the steatosis cases and 193/333 (58%, range 35%-88%) in alcoholic hepatitis cases.

The prevalence rates of AST alterations were always significantly higher and showed lower variation among the various studies than those of ALT (Table 1). In the study where the types of histopathologic alterations were not differentiated, the prevalence rates were 77/181 (42.5%) for AST and 22/52 (42.3%) for ALT.

Prevalence of AST abnormality was significantly higher in cases with than without histopathologic alteration (P = 0.002; 95% CI 1.88-184.58; odds ratio 15.75). The relationship between

prevalence of AST alteration and histopathologic damage indicate an 87.5% sensitivity, 77.8% positive predictive value, and 81.8% negative predictive value (Table 3).

Mean levels of AST were greater than 2N (twice the upper limit of normality) in all cases with histopathology of hepatitis, averaging 2.6N (range 2.1N-3.6N), while those of ALT, in the same cases, were 1.48N (range 1.09N-1.87N) (Table 4).

II. Alkaline phosphatase

In studies with defined histopathologic examinations, prevalence of alkaline phosphatase (AP) increases were 484/650 (74.5%) globally, 129/182 (70.9%, range 45%-75%) in cases of steatosis, and 355/468 (75.9%, range 59.5%-84%) in cases of hepatitis. Where histopathologic abnormalities were not differentiated, altered AP prevalence was 20/52 (39%).

In all cases of hepatitis, average AP levels were above the upper normal level, which was not observed where patients had the histopathologic types of lesions not differentiated. An average above 2N was reported in only 1 of the studies of alcoholic hepatitis patients (Table 4).

III. Total bilirubin

Prevalence of bilirubin alterations in studies with defined histopathologic data were 499/666 (74.9%) globally, with 127/187 (67.9%, range 20%-72%) in steatosis cases and 372/479 (77.7%, range 9%-94.5%) in cases of alcoholic hepatitis. Where the type of histopathologic alteration was not defined, prevalence was 30/139 (23.3%, range 6.9%-28%).

In 4 studies on patients with alcoholic hepatitis, the average of total bilirubin (TB) was above normal, but was above 2N only in 3 of them. In one study of patients with steatosis and hepatitis, and in another where the types of lesions was not differentiated, the average value was below the upper limit of normality (Table 4).

IV. Association of enzymes and bilirubin alterations

Patients presenting 1 or more biochemical abnormality in liver tests (AST, ALT, AP, TB) showed a significantly higher prevalence of histopathologic alteration than those with normal tests (P = 0.001; 95% CI range 1.99-20.31; odds ratio 5.78). Under these criteria, sensitivity was low (49.1%), but the positive predictive value was high (91.4%) (Table 5).

Comparing results from tables 3 and 5, it can be concluded that considering only the aminotransferases increases related to presence of histopathologic alteration, irrespective of type, there is a gain in sensitivity and negative predictive value but a loss in specificity. The probability of diagnosing liver damage is increased when other alterations are considered, including any of the aminotransferases plus AP and TB (Tables 3 and 5).

The low probability of occurrence of liver enzymes and bilirubin values above 2N (Table 6) was noticeable.

Table 3 - Distribution of prevalence of histopathologic lesions and of aspartate-aminotransferase alterations in chronic symptomatic or oligosymptomatic alcoholics.

Aspartate-aminotransferase	Histopathology					
	Altered		Normal		Total	
	n	%	n	%	n	%
Above the upper reference limit	14	48.8	4	13.8	18	62.6
Inside the normal reference limit	2	6.9	9	31.0	11	37.9
Total	16	55.7	13	44.8	29	100.0

Adapted from Green[3]. *P* = 0.002, 95% CI 1.88 to 184.58, odds ratio = 4.28; sensitivity 87.5%; specificity 69.2%; predictive values: positive 77.8%, negative 81.8%

Table 4 - Ratios between the average liver enzyme and total bilirubin values, and the upper limit of normality for the respective test.

		Aspartate-aminotransferase	Alanine-aminotransferase	Alkaline phosphatase	Total bilirubin
1 - Liver steatosis					
- Green[3]	(n = 5)	1.42	-	-	0.62
2 - Alcoholic hepatitis					
- Green[3]	(n=11)	2.31	-	-	0.61
- Harinasuta et al.[24]	(n = 100)	3.60	1.47	2.15	5.70
- Helman et al.[25]	(n = 12)	2.45	1.09	1.53	4.75
- Mendenhall et al.[26]	(n = 89)	2.10	1.87	1.38	1.60
	Average	2.62	1.48	1.69	3.17
3 - Various lesions					
- Ryback et al.[27]	(n = 60)	1.60	1.57	0.70	0.84

COMMENTS

A biochemical survey of asymptomatic residents of the USA detected about 6% with abnormal levels of liver enzymes, while the prevalence of liver disease in the general population was significantly lower (about 1%)[28]. In routine examinations of Canadians, about 10% showed at least 1 abnormal liver biochemical test[29].

In studies with liver histopathology, 25%-35% of chronic alcoholics with mild or no clinical manifestation of hepatopathy were considered free of

Table 5 - Distribution of prevalence of histopathologic lesions and biochemical alterations in chronic oligosymptomatic and asymptomatic alcoholics.

Biochemical data	Histopathology					
	Altered		Normal		Total	
	n	%	n	%	n	%
One or more abnormalities	53	37.1	5	3.5	58	40.5
No abnormality	55	38.5	30	20.9	85	59.5
Total	108	75.6	35	24.4	143	100.0

Data from Bruguera et al.[7], on Aspartate-aminotransferase, Alanine-aminotransferase, Alkaline phosphatase, and Total bilirubin, in HBsAg negative and without history of viral hepatitis patients. *P* = 0.001, 95% CI 1.99 to 20.31, odds ratio = 5.78; sensitivity 49.1%; specificity 85.7%; predictive values: positive 91.4%, negative 35.3%

Table 6 - Frequency of occurrence of liver enzymes and total bilirubin values higher than the upper limit of normality in chronic asymptomatic or oligosymptomatic alcoholics.

		Aspartate-aminotransferase	Alanine-aminotransferase	Alkaline phosphatase	Total bilirubin
1 - Liver steatosis					
- Green [3]	(n = 5)	26.4	-	-	1.2
2 - Alcoholic hepatitis					
- Green [3]	(n = 11)	65.9	-	-	6.2
- Harinasuta et al.[24]	(n = 100)	66.6	40.1	54.8	26.8
- Mendenhall et al.[26]	(n = 89)	52.8	47.2	17.6	33.4
	Average	61.8	43.7	36.2	22.1
3 - Various alterations					
- Ryback et al.[27]	(n = 60)	41.3	39.7	0	2.3

All values in %.

liver disease[7,30,31]. In the present study, in the same category of patients, biochemical liver tests indicated 31% (range 21%-40%) free from liver disease.

The variations observed in oligosymptomatic or asymptomatic alcoholics among studies of prevalence rates of enzyme increases, which were relatively modest with respect to AST, as well as of histologic abnormalities, could be due to various conditions and peculiarities. These include the different sex ratios in the samples, women being more susceptible to alcoholic liver damage[32]; morphologic identification of classic alcoholic hepatitis being difficult in cases with massive adipose deposition, as well as the distribution of adipose tissue not being uniformly distributed in the liver[33]; the 3 types of liver morphologic alterations-steatosis, hepatitis, and cirrhosis-possibly being present or distributed with different intensities in the same case[13]; infection by C- type virus that may act synergistically in liver damage, provoking a more aggressive course of the alcoholic hepatitis[34,35] with elevation of serum levels of both aminotransferases[36], especially ALT[37]; tobacco-smoking alcoholics showing higher AST levels (with higher AST/ALT ratios) and also of AP levels, relative to non-smokers, suggesting synergism between alcohol and tobacco in liver damage[38]; the alcoholic beverage most utilized by Brazilian alcoholics being sugarcane spirit, which contains a chemical composition qualitatively different from those of other fermented and distilled beverages most utilized in other countries. It contains minerals (iron and copper), upper alcohols, and aldehydes[39,40], some of these in amounts higher than the allowed limits, which could act synergistically with alcohol in producing liver disease. Excessive and prolonged ingestion of beverages containing high iron contents could lead to elevations in blood iron concentrations which is associated with significantly elevated average plasma levels of AST, ALT, and AP[18]; the high (close to 100%[33]) prevalence of undernutrition in alcoholics with alcoholic hepatitis due to both proteic and caloric deficiency resulting from low ingestion and inadequate utilization of nutrients absorbed[41]; and biochemical and histologic abnormalities resulting from variations in abstinence periods before blood sampling or obtaining biopsies[6], as well as in different alcoholism regimes, with respect to time and amount of the habit. When patients look for assistance due to complications resulting from the alcoholic state or just for treatment of the alcoholism, they might comprise selected samples that would create at least partial differences in the incidence of types and severity of structural liver lesions[6] as well as in the prevalence of alterations of some types of liver enzyme activity[3,26] (for example, a proportion of alcoholics showed slight spontaneous elevation of the activity of aminotransferases soon after alcohol withdrawal[42]). In addition to these factors, genetic conditions and individual susceptibility may affect the development of alcoholic liver disease[15,43].

Among the various series studied, independently of whether patients were symptomatic or not, the prevalence rates of steatosis varied from 50% to 55% and that of alcoholic hepatitis from 8% to 63%[32]. In a Brazilian study, histopathologic alterations were detected in 67.9%, being milder (steatosis, reactional or grades I and II steatohepatitis) in 26.8% and more severe (steato-hepatitis grades III and IV) in 41.1%[30].

The behavior of each of the enzymes and bilirubin, as well as the correlation between biochemical abnormalities and liver histopathology is detailed below.

1. Aminotransferases

In this review, among all enzymes, the prevalence of alteration in AST, especially in patients with alcoholic hepatitis, was the highest and most uniform across all series. AST abnormality was directly correlated with the presence of histopathologic liver alterations. The fact that the test for AST had high sensitivity demonstrates its capability for indicating liver damage in alcoholics; additionally, its high positive and negative predictive values allow the differentiation with high probability of individuals with and without liver disease.

Our conclusions regarding the behavior of AST do not agree with those of Rosman and Lieber[44] when they state that activities of liver enzymes, including AST, have limited diagnostic usefulness in predicting the histologic staging. These authors have generalized the results of Li et al.[45] to all types of histologic lesions; these results indicate the limitations of the enzyme values only for identification of liver fibrosis (perivenular fibrosis, septal fibrosis, and incipient cirrhosis) and for accurately discriminating liver fibrosis from non-complicated steatosis.

We found that detection of serum AST levels higher than twice the upper normal limits, irrespective of the reference values in each procedure, was correlated with high probability of alcoholic hepatitis. In another study[13], it was observed that the AST levels were correlated among alcoholics directly and exclusively with the presence and extent of hepatocellular necrosis.

Prevalence of altered levels and average values of ALT varied widely in both categories of steatosis and alcoholic hepatitis, confirming that this enzyme was not an adequate test for liver alterations in alcoholics.

The generally low values of aminotransferases in alcoholic hepatitis, relative to viral hepatitis and lesions caused by other types of drugs, could be consequent to pyridoxine deficiency, which occurs in chronic alcoholics at high frequency[43], as well as to the slow course of hepatocellular necrosis resulting from alcohol consumption and undernutrition. This contrasts with the acute cell lesions following viral infections or toxin ingestion, where there is quick release of great amounts of enzymes into the circulation [13].

2. Alkaline phosphatase

In chronic alcoholics, AP alterations are related more closely to disturbances in the free flow in biliary routes, while those of gamma-glutamyltransferase (GGT) would indicate liver enzymatic induction and hepatocellular damage[46] or difficulties in biliary excretion[47]. Therefore in alcoholics, AP alterations are more significant than those of GGT. AP activity is elevated when cholestatic processes are present[48]. Elevation in AP is detected in liver steatosis and in alcoholic hepatitis in a frequency of about 2/3 of the cases.

Elevation in AP, especially in the absence of cholestasis signs, is suggestive of alcoholic hepatitis[15]. In this survey, we observed that in studies where alcoholic hepatitis was the fundamental lesion, AP was always elevated.

3. Bilirubin

Total bilirubin abnormalities in chronic alcoholics may result from isolated or combined increases of the non-conjugated and conjugated fractions. An increase in the conjugated fraction always denotes hepatocyte damage[15]. Elevation of the non-conjugated fraction may result from various causes, including increased absorption from enterohepatic pools for reasons that are not entirely clear[49,50]; deficient uptake and conjugation by the liver, similar to Gilbert's syndrome[51]; increased back flow of unaltered non-conjugated bilirubin to the plasma after having been taken up by the liver in a first passing due to reduced intracellular glutathione[52]; functional and structural alterations in hepatocyte organelles and plasmatic membranes due to lipid peroxidation[32]; hemolysis due to hypersplenism secondary to liver disease; and hyperlipidemia resulting from low activity of serum lipoprotein lipase in patients with alcoholic hepatitis[15,48]. Hypertriglyceridemia was observed in 56% of oligosymptomatic or asymptomatic chronic alcoholics[53].

Serum bilirubin levels were best correlated with the severity of alcoholic hepatitis[54].

4. Associated abnormalities

A recent publication analyzing results of liver laboratory tests concluded that such exams are of limited usefulness due to insufficient sensitivity or specificity[55]. Nevertheless, careful reading of the article leads to the conclusion that the authors were generalizing from observations on viral hepatopathies.

In alcoholism, the probability of diagnosing liver damage was increased when abnormalities of ALT, AP, and TB were considered in association with those of AST[7]. This increased probability was significantly reduced when the criteria for altered tests adopted the 2N cut-off limit of values.

Results in this review confirm the previous conclusion[29] that in cases of alcoholics with alcoholic hepatitis,

there are high frequencies of abnormalities in AST, AP, and TB. A conjunction of elevated bilirubin serum level, increased AP activity, leucocytosis, and increased erythrocyte sedimentation rate is suggestive of alcoholic hepatitis[15]. Association of enzyme abnormalities with other biochemical evidence of liver dysfunction (bilirubin, albumin, or prothrombin activity) indicates advanced liver disease and functional impairment of the organ[29].

Associated concerted elevations of one of the aminotransferases and of AP would favor diagnosis of cholestatic more than the hepatocellular types of liver disease. The latter type would be considered singly only when elevation of the aminotransferases was twice or more than that of AP[29].

Probabilities of occurrence of 2N enzyme values in the presence of histopathologic alterations were very low, and adoption of such criteria for considering the results abnormal could have caused biases in studies[56] attempting to investigate the occurrence of abnormal tests in specific groups or in the general population, neglecting alcoholic conditions.

CONCLUSIONS

Prevalence of increases in AST[3] was consistently related to the presence of histopathologic abnormalities and elevated levels of the enzyme; higher than twice the upper limit of normality of the determination method indicating the diagnosis of alcoholic hepatitis. The possibility of recognizing alcoholic hepatitis through laboratory tests in patients with mild or no symptoms should be an important goal that would be useful for at least 2 reasons: it would allow therapeutic intervention[32,57] and it would make preventive measures possible[58,59], with the purpose of avoiding evolution to more severe forms of liver disease[48].

The probability of diagnosing liver disease in alcoholics increased when associated abnormalities of aminotransferases, alkaline phosphatase, and bilirubin were considered.

While there is no uniformity in definitions, it can be concluded for practical purposes that values equal to, or below 2N or 3N, between 3N and 20N, or higher than 20N, for aminotransferases, and equal to, or below 1.5N or 2N, between 2N and 5N, and higher than 5N, for alkaline phosphatase, would be considered, respectively mild, moderate, and strong elevations[60]. Adoption of such criteria in analysis of results in this review indicated that in alcoholics, irrespective of the type of liver lesion, enzyme increases should be considered mild. Nevertheless, the probability of diagnosing liver disease in alcoholics was increased when associated increases of aminotransferases, alkaline phosphatase, and bilirubin were considered, irrespective of their levels.

Therefore, the generalization of criteria and terminology established by the International Consensus[12] (that is, defining the label of *liver damage* as when increases of ALT and TB are higher than 2N; *biochemical abnormalities* as when isolated increases of AST, AP, or TB are higher than 2N; and *liver test abnormality* as when increases in ALT, AST, AP, and TB are between N and 2N) have not been backed by data in this review on alcoholics with mild or no clinical manifestation or with histopathologic lesions considered mild. Were such strict criteria applied to alcoholics, one would be misled and risk not being able to identify occurrences of liver damage. Missed diagnoses could be construed as negligent behavior towards the therapeutic and preventive missions.

In the majority of studies attempting to evaluate the occurrence of liver disease in the general population, one of the parameters considered to be of value is the alteration of ALT, the enzyme thought to be the most sensitive and specific indicator for detecting hepatocellular damage. Considering that an average of about 10% of populations are alcoholics[61] (between 3% and 20% in Latin America[62]), and that in alcoholism the most frequently altered enzyme is AST, it can be said that the choice between the two aminotransferases may constitute an important factor of statistical bias.

More than a proposition for specific terminological attribution to alterations in complementary clinical exams, this study points to the need for revision of generalizations and established concepts regarding liver enzyme tests in chronic alcoholics with mild or no clinical manifestation.

A more detailed study of other methodologic aspects and a qualitative evaluation of the heterogeneity in the samples reported in the reviewed bibliography, as well as a possible expansion of the searches, should improve the present state of knowledge.

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RESUMO

BORINI P e col. - Alterações histopatológicas e testes bioquímicos hepáticos em alcoolistas crônicos assintomáticos ou oligossintomáticos: uma revisão. **Rev. Hosp. Clín. Fac. Med. S. Paulo 58**(3): 147-156, 2003.

OBJETIVO: Revisar a literatura médica referente às relações entre alterações histopatológicas e testes bioquímicos hepáticos em alcoolistas crônicos assintomáticos ou oligossintomáticos.

MÉTODOS: Levantamento, a partir das bases de dados MEDLINE e LILACS e referências em publicações, das prevalências de alterações e níveis séricos da aspartato-aminotransferase, alanino-aminotransferase, fosfatase alcalina e bilirrubina total relacionados com a histopatologia hepática, com e sem discriminação do tipo de alteração histopatológica.

RESULTADOS: As taxas médias das prevalências da aspartato-aminotransferase e alanino-aminotransferase foram 86,3% e 51,1% globalmente, sendo 79,1% e 38,5% nos casos de esteatose e 90,1% e 58% nos casos de hepatite, respectivamente. As taxas das prevalências das alterações da aspartato-aminotransferase foram, em todos os estudos, significativamente mais altas e mostraram menores variações que aquelas da alanino-aminotransferase. Os níveis médios da aspartato-aminotransferase foram maiores que 2N (duas vezes superior o limite superior da normalidade) em todos os casos com histopatologia de hepatite, enquanto que os da alanino-aminotransferase, nos mesmos casos, foram 1,48N.

As prevalências de alterações da fosfatase alcalina e bilirrubina total foram 74,5% e 74,9% globalmente, 70,9% e 67,9% nos casos de esteatose e 75,9% e 77,7% nos casos de hepatite, respectivamente. Em todos os casos de hepatite, os níveis médios da fosfatase alcalina estavam acima do limite superior da normalidade. Em 4 de 7 estudos sobre pacientes com hepatite a média da bilirrubina total estava acima do normal.

CONCLUSÕES: As prevalências de alterações da aspartato-aminotransferase foram consistentemente relacionadas a presença de alterações histopatológicas e o nível elevado da enzima, maior que 2N do método de determinação, sugere o diagnóstico de hepatite alcoólica.

DESCRITORES: **Alcoolismo crônico. Alcoolistas assintomáticos ou oligossintomáticos. Testes hepáticos. Enzimas hepáticas e bilirrubina. Histopatologia.**

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