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ACTIVITY OF CHRONIC HEPATITIS CORRELATION OF CLINICAL, BIOCHEMICAL AND HISTOLOGICAL PARAMETERS IN 32 CASES

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SUMMARY

The Authors studied thirty two cases of chronic hepatitis and cirrhosis, with variable degrees of activity as measured by clinical, biochemical and histological parameters. The etiology was predominantly viral. 15 Histological variables were semiquantitated "blind", and correlated with biochemical data v.g. ALT, AST, Gamma-GT, total bilirubin and Gamma-globulin. Among the histological parameters, bile-ductular proliferation and plasma-cells proved not to be valuable features for the study. The covariance analysis showed that total bilirubin correlated in significant statistical levels with 11 histological variables. The aminotransfera ses, both ALT and AST correlated with general impression of activity and AST also with portal expansion and peri-portal piece-meal necrosis. The lack of significant correlations with gamma-globulin, in a material composed of chronic liver disease, could be due to the inclusion in the survey of cases of chronic persistent and to the absence of auto-immune chronic hepatitis.

INTRODUCTION

The diagnosis, therapeutic orientation and evolution of the activity of chronic hepatitis is primarily based on morphological criteria [2]. As, for obvious reasons, the patient cannot be submitted to liver biopsies at short intervals, biochemical control is currently used and, for that purpose, transaminases are considered to be useful tools. Some Authors state that Aspartate aminotransferase (AST) and gammaglobulin would be an expression of liver cell necrosis and inflammation [7] and, therefore, would evaluate the extent and duration of hepatic injury. However, it is a very well known fact that there is not always an evident correlation between biochemical and histological data [3,5,13]: one can find striking morphological alterations in patients whose enzyme levels are very close to normal, and, conversely, patients with abnormal liver function tests may have normal biopsies, although this is exceptional and inadequate sampling cannot be excluded [20].

As publications about well conducted statistical studies on the subject are not frequent in medical literature, it is the purpose of this paper to study the correlation between histolo gical variables and clinico-biochemical data.

MATERIAL AND METHODS

From 117 consecutive cases of chronic liver disease taken from the files of the Liver Unit of São Paulo from 1977 to 1980, 32 were analysed. In all of them, there was no evidence of alcoholism, or of immunossuppressive therapy. A full set of histological slides were available, as well as clinico-biochemical data,

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recorded up to 15 days before the liver biopsy. In 6 cases, however, the intervals between biochemical tests and liver biopsies varied from 16 to 23 days.

In 30 cases, the hepatitis B surface Antigen (HBsAg) was investigated, and it was positive in 10 (33.3%). Auto antibodies were negative in all of the 20 cases in which these tests were performed. The final diagnosis had been chronic persistent hepatitis in 10 cases, chronic active hepatitis in 15 and fully developed cirrhosis in 7.

The clinical parameters were age, hepatomegaly and splenomegaly, as measured in cm below the costal margin. The biochemical parameters were aspartate-aminotransferase (AST), alanina-amino-transferase (ALT), gamma-glutamiltranspeptidase (GGT), total bilirubin (TB) and gamma-globulin (GG). The histological sections were submitted to impregnation of the reticulin framework by silver salts and to 3 colorations: hematoxylin and eosin, Masson's trichrome and Perl's, for iron. Morphological analysis was semi quantitative, and the following variables were graded from 0 (absent) to 3 (marked):

— Portal tract expansion
— Porto-portal septa
— Porto-central septa
— Nodules
— Overall fibrosis
— Bile ductular proliferation
— Inflammatory infiltrate
— Plasma cells
— Peri-portal piece-meal necrosis
— Peri-bridging piece meal necrosis
— Liver cell damage
— Sub massive colapse
— Spotty necrosis
— Regeneration
— General impression of activity (GIA).

Two pathologists (LCCG and VAFA) analysed separately each one of these parameters "blind", in the sense that they did not have any information about clinical and biochemical data as well as about the diagnosis previously made. Differences of grading never exceeded one plus, and in those instantes a new approach was made by both pathologists together.

The purpose of the inclusion of a large number of morphological variables was to search for other markers of histological activity in chronic hepatitis and cirrhosis, besides those widely accepted, such as piece meal necrosis, inflammatory response, bridging necrosis, or, even, irregular regeneration [2,5,15].

Most parameters are self explanatory, but additional information is needed about some of them: liver cell damage included both liver cell swelling and shrinkage. Sub-massive colapse was understood as hepatocellular confluent necrosis, involving large areas of the hepatic lobule and not only "bridging" [1]. General impression of activity (GIA) was the pathologist's overall view of aggressivity of the disease without any analytical concern. The statistical analysis was based upon Spearman's non-parametric correlation coefficient, due to the interval nature of the histological variables. A Statistical Package for the Social Sciences, Burroughs 6.700, was used in the Computer Centre of the University of São Paulo.

As ALT values were available in 29 cases, AST in 29, GGT in 30, BT in 22 and GG in 19 cases, a missing values routine was employed, with an option for pairwise deletion.

RESULTS

Twenty-three out of the 32 cases were male (69%) and 11 were female (31%). Age ranged from 10 to 73 years, and the median was 39.5.

The liver was palpable in 20 patients, up to a maximum of 7 cm below the right costal margin and the median was 1,5 cm. The spleen was palpable in 10 patients, up to 12 cm below the left costal margin.

Biochemical results are listed in Table I. In Table II, the modes of the histological variables can be seen, as well as the highest degree after the mode, so that emphasis could be put into the trends of the several variables. The positive results ($p < 0.05$) of the clinico-histological correlations are listed in Table III and in Table IV the positive results ($p < 0.05$) of the correlations between biochemical and histological variables are displayed.

COMMENTS

It is worth mentioning that different forms of chronic liver disease with variable degrees of activity were, on purpose, included in the

T A B L E I

Biochemical results

	Number	Median (*)	Limits
ALT	29	86.00	4.00 — 859.00
AST	29	54.00	2.00 — 462.00
Gamma GT	30	48.50	11.00 — 762.00
Total bilirub.	22	1.38	0.30 — 5.40
Gamma glob.	19	1.59	0.85 — 3.30

(*) International units for enzymes and mg% for bilirubin and gammaglobulin

T A B L E II

Distribution of histological markers (%)

Histologic variables \ Grades	0	1	2	3
Portal tract expansion			40.63*	37.50
Porto-portal septa			50.00*	21.88
Porto-central septa			37.50*	25.00
Nodules	34.38*		31.25	
Overall fibrosis			46.88*	25.00
Bile-ductular proliferation	31,25	53.13*		
Inflammatory infiltrate		28.13	62.50*	
Plasma cells	18.75	75.00*		
Periportal piece-meal necrosis		40.63*	34.38	
Peri "bridging" piece-meal necrosis	34.38	40.63*		
Liver cell damage		53.13*	37.50	
Submassive collapse		50.00*	28.13	
"Spotty" necrosis		65.63*	25.00	
Regeneration		62.50*	28.13	
General impression of activity		37.50	46.88*	

(*) Modes

present survey, so that a wide range of figures would be achieved and an adequate dispersion reached.

From the clinical point of view, a wide range of age was obtained, with a median of 39,5 years, and there were more males than females. This could be due to the absence of auto-immune hepatitis [18], besides the facts that

T A B L E III

Correlation of clinical and histological parameters of activity (Significant values — $P < 0.05$)

	Age (years)	Liver (palpation)	Spleen (palpation)
Portal tract expansion			
Porto-portal septa			
Porto-central septa	0.010	0.026	0.060
Nodules	0.042		0.010
Overall fibrosis			0.052
Bile-ductular proliferation			
Inflammatory infiltrate	0.036 (n)		
Plasma cells			
Periportal piece-meal necrosis			
Peri "bridging" piece-meal necrosis	0.016		
Liver cells damage	0.028		
Submassive collapse			0.022
"Spotty" necrosis			
Regeneration		0.040	0.004
General impression of activity			0.030

(n) = negative correlation

chronic persistent forms were included [6] and that 1/3 of the cases were positive for the HBsAg [10].

As far as biochemical parameters are concerned, it is noteworthy that the values of the aminotransferases were not high: the median of the ALT was 4 times the upper normal limit, whereas the median of the AST did not exceed 2,5 times the upper normal limit. These results were similar to those found by KALLAI et al.[11] and could be explained by the variability of degrees of activity in our material. Moreover, there were no cases of autoimmune chronic active hepatitis, in which the values of these enzymes can reach up to 10 times their upper normal limits [18]. The alterations of the GGT were even less marked, reaching no more than twice the normal upper limit. The same happened to the GG, which varied below the figures usually seen in auto-immune chronic active hepatitis.

T A B L E IV

Correlation of biochemical and histological parameters of activity (Significant values — $P < 0.05$)

	ALT	AST	GGT	TB	GG
Portal tract expansion		0.03		0.002	
Porto-portal septa				0.002	
Porto-central septa				0.004	
Nodules				0.003	
Overall fibrosis				0.019	
Bile-ductular proliferation				0.023	
Inflammatory infiltrate	0.019				
Plasma cells	0.029				
Periportal piece-meal necrosis		0.048			
Peri "bridging" piece-meal necrosis				0.004	
Liver cell damage			0.010	0.046	
Submassive collapse					
"Spotty" necrosis					
Regeneration				0.002	
General impression of activity	0.011	0.010		0.001	

Some of the histological variables showed predominance of low degrees (Table II) and, therefore, were considered inadequate, either as markers of activity or to correlate with clinico-biochemical data. Thus, bile-ductular proliferation was absent or slight in 80% of the cases; it was surprising, however, that plasma cells were scanty. These results were not in keeping with the views of some authors, who claimed that plasma cells are often found in chronic active hepatitis [17]. Perhaps, once again, this fact is due to the absence of auto-immune forms, among which the so-called plasma-cell hepatitis is included [14]. The fact that the mode of nodule formation, was naught is not surprising, as our material comprised 7 cases of fully developed cirrhosis, 15 of chronic active hepatitis with various degrees of nodularity and 10 of chronic persistent hepatitis. Similarly, as expected, lobular changes, such as spotty and liver cell damage, were not marked for, as in chronic liver disease the mesenchymal component is more conspicuous; in our results, the latter was represented by outstanding variables, such as portal expansion, portoportal and portocentral septa, as well as overall fibrosis.

As far as correlation are concerned, one must consider that, within the statistical limits proposed, 5% are expected to be due to chance. Moreover, a significancy does not imply in a link of causality between then. This can only be asserted, or even speculated, on known biological grounds. One must always bear in mind that the covariance of two biological phenomena can be determined by variables not included in the study. Sampling errors must also be considered [12,16,19].

A negative correlation was detected between age and inflammatory infiltrate. A decrease of the immunological response with the ageing process would be a possible explanation for this finding.

Whereas the liver was palpable in the majority of cases, the spleen could be palpated in fewer instances. Hepatomegaly and splenomegaly correlated with regeneration and portocentral septa and, splenomegaly alone, also with nodularity, overall fibrosis, sub-massive colapse and general impression of activity (GIA). These facts seem to point out the importance of splenomegaly as a clue to activity in clinical practice.

Table IV shows that there was a correlation of serum levels of ALT with inflammatory infiltrate and not with liver cell damage, as would be expected from information of the current literature [4]. On the other hand, the correlation of ALT with GIA shows that this enzyme is a good biochemical marker of histological activity considered as a whole [7]. The same can be said of AST, which correlated also with GIA. More than that, however, there were some remarkable correlations between AST and other histological variables, such as portal expansion and peri-portal piece-meal necrosis. These findings, especially the latter correlation, give support to the widely accepted view that AST should be preferentially used as a biochemical marker in chronic hepatitis [7].

GGT showed only one significant correlation and that was with liver cell damage, and thus, we could not confirm the impression of some Authors that this enzyme is more elevated in chronic hepatitis than the transaminases [9].

Of all biochemical variables, it was total bilirubin the one which correlated with more histological markers. Some of them were expression of mesenchymal proliferation, others of liver cell injury, and even, regeneration. The latter is though to be an important marker of activity in liver diseases [15]. Besides these variables, total bilirubin also correlated with GIA and with the degree of nodular transformation of the liver. This finding seems to confirm that jaundice yields a worse prognosis in chronic hepatitis and cirrhosis, an impression lent by current medical practice.

Finally, it was somehow surprising that gamma-globulin did not correlate with any histological variables, what means that gamma-globulin levels did not vary proportionally to the degree of histological activity as measured by the analysed features, and therefore would not be a good biochemical marker. Nevertheless, it would still be possible that, in a variance analysis, gamma globulin could discrimate chronic from acute hepatitis, as was proposed by DIETRICHSON & POULSEN [8] and that a different behaviour could be found if a population of auto-immune chronic active hepatitis were studied.

RESUMO

Atividade das hepatites crônicas. Correlação de parâmetros clínicos, bioquímicos e histológicos em 32 casos.

Os Autores estudaram 32 casos de hepatites crônicas com diversos graus de atividade clínica, bioquímica e histológica. A etiologia foi predominantemente viral. Quinze parâmetros histológicos foram semiquantificados, pesquisando-se posteriormente, correlação entre os graus obtidos e os valores séricos de ALT, AST, Gama-GT, bilirrubina total e gamaglobulina. Dos parâmetros histológicos, a proliferação de ductos biliares e os plasmócitos não se mostraram úteis para esta análise. Os níveis de bilirrubina total apresentam correlação estatisticamente significante com 11 variáveis histológicas. Ambas as aminotransferases (ALT e AST) correlacionaram se com a impressão geral de atividade histológica, sendo que a AST também se correlacionou com o grau de expansão portal e de necrose "em saco-bocados". A ausência de correlações significantes com gamaglobulina pode se dever à inclusão, neste estudo, de casos de hepatite crônica persistente e à ausência de hepatites crônicas auto-imunes.

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