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A comparison between previous and present histologic assessments of chronic hepatitis C viral infections in humans

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Abstract

AIM **To compare the previously employed classification of liver histology (minimal, chronic persistent hepatitis, chronic active hepatitis and cirrhosis) with a new classification recently described by Sheuer *et al* (activity grade and fibrosis stage) in percutaneous liver biopsies from patients with chronic hepatitis C viral infections.**

METHODS **Liver biopsies from** 79 **untreated patients were reviewed. Anti-HCV testing had been performed by ELISA and confirmed by a recombinant immunoblot assay. With respect to the new classification, all the specimens were evaluated using the Knodell score for activity.**

RESULTS **A good correlation was revealed between the previous and more recent histologic classifications in patients with abnormal liver enzyme tests. However, in** 13/15 (87%) **of patients with normal aminotransferase values, changes were consistent with chronic persistent hepatitis whereas normal activity and no fibrosis were demonstrated by the Sheuer classification.**

CONCLUSION **The old classification is more often misleading but correlates well with the new classification and thereby permits comparisons between historically clinical studies.**

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INTRODUCTION

Despite recent advances in biochemical, serologic and radiologic techniques, liver biopsies remain an essential component of diagnostic and management decisions in patients with chronic viral hepatitis. The importance of liver biopsies in this patient population has been emphasized by the International Hepat ology Informatics Group, the METAVIR group in France, and a working group of the International Congress of Gastroenterology who address the terminology, grading, staging and related histologic aspects of chronic viral hepatitis[1-3]. Liver biopsy provides information about the extent and distribution of inflammation and allows grading and staging of the disease (the amount of fibrosis). Furthermore, the liver biopsy enables some assessment of the rate of disease progression whenever the date of onset of infection is known. The presence of diffuse fibrosis or cirrhosis correlates with a lower likelihood of response to antiviral therapy, and the finding of severe necroinflammatory and fibrotic changes is helpful in determining the relative importance of early treatment rather than deferring therapy[4].

Recently, Desmetts and colleagues proposed a new classification for chronic hepatitis which incorporates the first three components of the Knodell score for grading activity and a description of sta-ging the extent of fibrosis as none, mild, moderate, severe, or cirrhosis[3,5]. This new classification is intended to replace the longstanding descriptions of chronic hepatitis as nonspecific hepatitis, chronic persistent hepatitis, chronic active hepatitis, and cirrhosis. Such a change in nomenclature is advantageous, in that the previous classification is largely confined to a system of grading rather than staging and is thus less complete. Nonetheless, as the previous classification has been widely employ ed for many decades, it is important for comparative purposes to determine whether there is a reasonable correlation between the two forms of classification. Thus, in the present study, we classified percutane ous liver biopsies from 79 patients with chronic hepatitis C viral infections by both classifications and compared the results using a Speerman rank test and crosstabulation method for correlation.

PATIENTS AND METHODS

Liver biopsies from 79 untreated patients (47 males, 32 females) were reviewed for the purpose of this study. The mean age of the study population was 44±11 years. A total of 49 patients were believed to have acquired their infections from needle sharing, 25 from previous blood transfusions, and 10 were considered sporadic infections. Anti-HCV testing had been performed by a second or third generation ELISA test and confirmed by a recombinant immunoblot assay (Ortho Diagnostic System, Raritan, NJ).

Paraffin-embedded sections of specimens were stained with hematoxyline and eosine, masson tricome, reticulin, and periodic acid-shiff after diastasde digestion. Descriptions of normal, nonspecific, chronic persistent hepatitis, chronic ac tive hepatitis and cirrhosis were as described originally[6]. With respect to the new classification, all specimens were evaluated using the first three components of the Knodell score for activity[5]: periportal ± bridging necrosis (range of score 0-10), intralobular degeneration and focal necrosis (score 0-4), portal inflammation (score 0-4). Thus, the total score for activity could range from 0-18. Total scores of 1-3 indicate minimal chronic hepatitis, 4-8 mild chronic hepatitis, 9-12 moderate chronic hepatitis, and 13-18 severe chronic hepatitis. The scoring system for staging fibrosis included: no fibrosis, 0; periportal fibrous expansion (mild) without septa formation, 1; portal portal septa (>1 septum) with intact architecture (moderate), 2; portal-cent ral septa (>1 septum) with architectural distortion (severe), 3; and cirrhosis, 4. To eliminate inter-observer variability, biopsies were interpreted by one observer (NA.) unaware of the clinical or laboratory status of the patients.

Statistics

A Spearman rank test and crosstabulation method for correlation were used. Discriminative analyses were made to relate serum AST and ALT values (independent variables) to histologic features (dependent nominal variables with more than two values). Differences were considered significant when *P* va-lues were <0.05.All statistical analyses were performed with Statisca and Winstat computer programs (Statsoft Inc, Tulsa, OK and Kalmia Co, Cambridge, MA respectively).

RESULTS

Table 1 shows the frequency of different histologic features in both the traditi onal and the new classification system. Thirty-four pat ients (34/41, 83%) with normal activity according to the new classification, had chronic persisten t hepatitis by the old classification and twenty-seven patients (27/29, 9 3%) with mild activity according to the new classification had chronic active hepatitis by the old classification system, suggesting that the old classification was more often misleading than the new classification system.

Table 1 The frequency of histologic features of chronic HCV viral infection in 79 **adults classified by the new and the old classification ***

Old classification	New classification			
	Normal	Mild	Moderate	Total
Normal(minimal)	7	0	0	7
CPH	34	4	0	38
CAH	0	27	2	29
Cirrhosis	0	4	1	5
Total	41	35	3	79

* Number of patients, Chi-square = 66.9, $P<0.001$.

Table 2 provides the results of comparisons between the old and new histologic classifications. In general, the grading of activity and staging of fibrosis in the new classification tended to correlate with the histologic classifications employed with the old classification system. Not surprisingly, correlation coefficients were stronger when activity was graded rather than fibrosis staged (r = 0.6 and r = 0.48 respectively).

Table 2 Correlation of traditional histologic diagnosis with aminotr ansferases, activity grade, and fibrosis stage in 79 **patients with chronic HCV viral infection ***

Old classification	ALT	AST	Activity score	Fibrosis score
Normal	57.6±31.4	39.0±0.0	1.0±0.0	0.0±0.0
CPH	94.0±67.5	59.7±31.8	2.0±1.1	0.2±0.5
CAH	153.8±67.8	112.9±42.0	5.4±1.4	1.8±1.2
Cirrhosis	144.3±49.2	142.0±52.7	5.5±1.7	4.0±0.0

Values are presented as mean ± SD. Activity grade; 1-3 normal, 4 - 8 mild, 9 - 12 moderate, 12 - 18 severe. Fibrosis stage; 0 non, 1 mild, 2 moderate, 3 severe, and 4 cirrhosis.

As shown in Table 3, in patients with persistently normal aminotransferase values, the old classification was more often misleading than the new classification. Specifically, 13/15 patients with normal AST values were found to have ch ronic persistent hepatitis on liver biopsy whereas according to the new classification, the overall activity in these patients (1.8 ± 0.8) was still within the normal range (0-3).

By descriminative regression analysis, serum AST values correctly classified the grade of activity

in 59/79 (75%) patients and the stage of fibrosis in 50/79 (63%) patients when employing the Desmet etal classification. How ever, when the 'traditional' classification was employed, serum AST values predicted the histology in only 34/79 (43%) of cases. Serum ALT values correc tly classified the grade of activity in 53/79 (67%) patients and the stage of fibrosis in 43/79 (54%) patients by the Desmet *et al* classification as compared with 41/79 (52%) patients by the traditional classification. Serum ALT values did not add to the predictive value of AST determinations using either histological classifications.

Table 3 Histologic distribution of chronic HCV viral infection according to aminotransferases levels

	Normal AST *n* = 15	Abnormal AST *n* = 64
Old classification*		
Normal	2	0
CPH	13	30
CAH	0	29
Cirrhosis	0	5
New classification		
Overall activity	1.8±0.8	3.7±2.2
Fibrosis	0.06±0.2	1.2±1.4

* Number of patients.

DISCUSSION

The new recommendations for nomenclature, grading, and staging of chronic hepatitis and related biliary and other disorders are attempts to standardize the criteria and simplify the terminology used in making these diagnoses. The inclusion of a system of grading and staging, whether it is numerical or descriptive, simple or complex, matters less than the need for it to communicate important information about the degree of necroinflammatory activity (grade) and the extent of the disease (stage of fibrosis) that are likely factors of prognostic and therapeutic significance[7].

To our knowledge, this study represents the first attempt to determine whether the previously employed classification of histologic disease in patients with chronic viral hepatitis correlates with the proposed classification by Desmet and colleagues. The fact that a good correlation does exist between these two methods indicates that comparison between natural history and treatment studies performed hereafter with studies reported using the old classification system are likely to be valid. The results also indicate that in general, nonspecific histologic disease correlates with Desmett activity scores of 1, chronic persistent hepatitis with 2,chronic active hepatitis with 5, and cirrhosis with 5.5. Similarly, by the old classification, normal or nonspeci fic findings are associ ated with a Desmett fibrosis score of 0, chronic persistent hepatitis with 0.2, chronic active hepatitis with 2 and cirrhosis with 4.

The reason(s) why AST but not ALT values correlated better with certain histolog ic findings is unclear. One possible explanation is that co-existing non-viral related fatty infiltration of the liver disproportionately contributes to the ALT elevations in some of these patients. Another possible explanation concerns the intracellular trophism of HCV. Because AST is a mitochondrial enzyme whereas ALT is predominantly cytosolic, a stronger correlation would be expected with AST values if HCV-induced liver injury was more extensive in the mitochondrial fr action of hepatocytes. The recent detection of HCV antigens in the microsomal but not mitochondrial fraction of hepatocytes argues against that possibility[8]. Nonetheless, isoenzyme analyses of the AST elevations would be of interest. Finally, ALT activity may be less stable than AST activity and therefore the findings may be artifactual in origin[9].

Numerous previous studies have documented that serum ALT levels are increased in the majority of patients with chronic hepatitis C viral infections and decline to the normal range with spontaneous or treatment-induced remissions[10,11]. However, these and other studies failed to demonstrate that ALT values reliably reflect the histologic severity of the disease as graded by more traditional histologic classifications[12,13], and the degree of viremia based on HCV-RNA quantitation[14,15]. Only changes in ALT values over time appear to reflect changes in the severity of disease[16]. Our findings that ALT values do not predict efficiently the histologic activity according to the new classification is in accordance with these previous studies.

In conclusion, these results show a good correlation between the old and new histologic classifications of liver disease in patients with chronic hepatitis C viral infections. Aminotransferases correlates better with the necroinflammatory activity according to new classification than the traditional classification.

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