

Mild abnormalities in liver histology associated with chronic hepatitis: distinction from normal liver histology

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Abstract

Background—Chronic hepatitis C virus infection associated with contaminated anti-D immunoglobulin has become an issue of recent concern. The clinical course of chronic hepatitis C infection is unpredictable and histological assessment is felt to be the most reliable means of assessing disease status. Semiquantitative scoring systems have been devised, which assess degree of necroinflammatory disease activity (grade) and extent of disease progression with fibrosis (stage) in chronic hepatitis. Often, using these systems, biopsies of anti-D associated chronic hepatitis C cases show mild changes only, with low scores. The significance of these low scores is uncertain.

Aims—To evaluate the significance of low scores in chronic hepatitis.

Methods—Liver biopsies were assessed from two groups of patients in whom liver histology would be expected to be normal: 30 cases of Gilbert's syndrome and 13 necropsy cases of young people (< 45 years) with no history or risk factors for liver disease. These biopsies were scored using the histological activity index of Knodell *et al* and its recent modification (separation of scores for grade and stage) by Ishak *et al*.

Results—Twenty of 30 cases of Gilbert's syndrome and 11 of the 13 necropsy cases had chronic hepatitis scores of 1 or 2, whereas only eight cases of Gilbert's and two necropsy cases had scores of 0. The remaining two Gilbert's cases had scores of 3 and 5. Similar results were found using both the histological activity index of Knodell *et al* and the method of Ishak *et al*. **Conclusion**—The finding of low but positive scores using these systems in people with normal liver histology questions the reliability and significance of finding such scores in patients with chronic hepatitis and is of particular concern in the evaluation of chronic hepatitis C infection.

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stranded (+) sense RNA virus and has been identified as the aetiological agent in the majority of cases of bloodborne non-A, non-B hepatitis found following blood transfusions, associated with chronic renal dialysis, and in intravenous drug abusers. A large cohort of Irish women were infected with hepatitis C virus following treatment with a contaminated batch of anti-D globulin in 1977. Hepatitis C virus infection often becomes chronic, with persisting viraemia detectable by reverse transcriptase-polymerase chain reaction. The clinical course of chronic hepatitis C infection is unpredictable but often appears to be slowly progressive. Histological assessment is felt to be the most reliable way to assess an individual patient's disease status, rather than using clinical or biochemical parameters.

The issue of disease activity in chronic hepatitis, how it should be assessed, and the reliability of assessment methods has received considerable attention in the literature.^{1,2}

Semiquantitative scoring systems have been proposed that assess the degree of disease activity in terms of necrosis and inflammatory changes (grade) and the extent of disease progression with fibrosis (stage) in cases of chronic hepatitis. Such systems in routine use by hepatic pathologists and hepatologists include the histological activity index of Knodell *et al*,³ which yields a composite score for stage and grade, and its recent modification by Ishak *et al*,⁴ which scores stage and grade separately.

Many cases of anti-D associated chronic hepatitis C infection are relatively asymptomatic and most of these show mild histological abnormalities. Such cases may be scored formally using the above methods, typically yielding a low but definite score value on the basis of identifying subtle histological changes. In practice, it may be difficult to recognise with confidence that some of these changes are abnormal. It was decided to assess liver biopsy material from two groups of patients in whom liver histology would be expected to be normal and to score them formally with the same systems used to assess chronic hepatitis to establish whether livers with chronic hepatitis C infection with very low disease activity scores could be distinguished reliably from livers assumed to be normal.

Methods

Forty three liver biopsies were examined from patients with no known risk factors for liver disease. These comprised 30 patients with

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The form of chronic hepatitis that prompted us to undertake this study is that associated with hepatitis C virus. Hepatitis C virus is a single

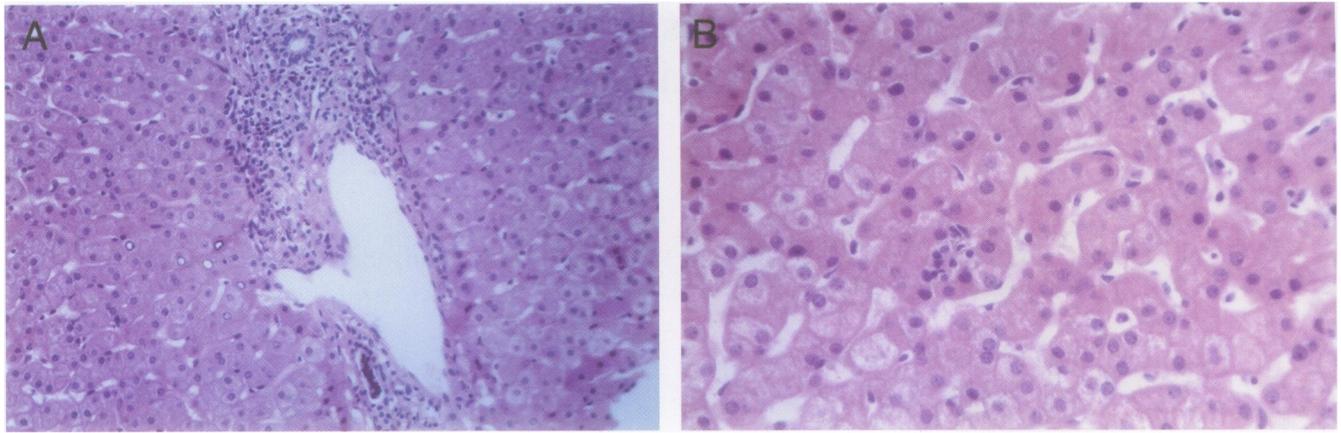


Figure 1 (A) Portal tract showing mild chronic inflammation. (B) Occasional aggregates of chronic inflammatory cells within lobule. (Haematoxylin and eosin; original magnifications (A) $\times 200$; (B) $\times 400$.)

Gilbert's syndrome, (in whom the liver biopsy had been taken originally as part of the diagnostic work up and in whom there was no clinical evidence of any other liver disease) and 13 necropsy cases of young people (aged 19–45) in whom there was no history of liver disease and in whom the needle liver biopsy was performed within 24 hours of death. These were cases of sudden death following road traffic accidents with no history of drug ingestion or blood transfusion. In the latter group the biopsy was taken from the right lobe of the liver, avoiding the subcapsular area. Each case was reviewed using one haematoxylin and eosin stained slide and one Masson's trichrome slide (for fibrous tissue).

Each case was scored using the histological activity index of Knodell *et al*³ and the system of Ishak *et al*.⁴

Results

Of the 30 patients with Gilbert's syndrome scored using the histological activity index of Knodell *et al*,³ eight yielded a score of 0, 20 a score of 1 or 2, and two a score of > 2 (one had a score of 3, the other a score of 5). Of the 13 selected necropsy cases scored using the histological activity index of Knodell *et al*, 11 yielded a score of 1 or 2 and two cases scored 0. In all cases contribution to these scores from section IV (fibrosis), was 0.

Similar results were obtained for grading of disease activity (that is, necroinflammatory activity) using the modified method of Ishak *et al*.⁴ Of the Gilbert's syndrome cases, the same eight cases yielded a score of 0, the same 20 cases yielded a score of 1 or 2, and the remaining two cases yielded a score of 3 and 4, respectively. Of the 13 necropsy cases, the same two cases yielded a score of 0 and 11 cases yielded a score of 1 or 2 for necroinflammatory activity. Assessment of disease stage using this method was consistently 0.

Using either method, the positive scores were obtained by identifying either mild inflammation in some portal tracts, focal inflammation (with or without focal necrosis) in some lobules, or both (table 1). Piecemeal necrosis was not seen (fig 1).

There was no histological evidence of further liver pathology, such as alcohol or other drug induced damage, in any biopsy.

Table 1 Breakdown of activity scores

Biopsy source	Lobular inflammation score of 1	Portal tract inflammation score of 1
Necropsy cases (n=13)	8	7
Gilbert's syndrome (n=30)	17	15
Chronic hepatitis C (n=37)*	11	12

*Unpublished results; these results are included to illustrate the degree of overlap, which highlights the problem raised when grading systems produce low or near normal scores.

Discussion

Necessarily, all semiquantitative scoring systems used to assess histological changes convert a spectrum of continuous changes into discrete discontinuous scores. Well designed systems with defined criteria should allow maximum comparability of samples and generate information that is clinically useful. However, all scoring systems have to have their reliability assessed by studies of inter- and intraobserver variability. Furthermore, the distinction between subtle changes that are considered to be abnormal and those that are felt to be within the range of normal appearances may be difficult and subjective. For example, in cervical cytology, the difficulty in differentiating between mildly dyskaryotic changes and smears without dyskaryosis is recognised by allowing a specific diagnostic category (borderline nuclear abnormality) for smears in which such a definite distinction is impossible.

Similar difficulties are encountered on a day to day basis when assessing liver biopsies that show minor abnormalities. The scoring systems for chronic hepatitis in common use all define categories of minimally disturbed histology that may be difficult to separate from normal histology. For example, the scoring systems recognise mild portal inflammation with a sprinkling of inflammatory cells in a minority of tracts as abnormal. On the other hand, most discussions of normal liver histology suggest that portal tracts contain a few inflammatory cells, with distribution varying between portal tracts, and increasing numbers being found in older persons. It has been stated that: "Focal aggregation [of inflammatory cells] only within some portal tracts should be regarded as probably not significant".⁵ The purpose of this study was to assess whether so called normal

livers generate a low score on the Knodell and modified Ishak scoring system.

The scoring systems for assessment of chronic hepatitis were formulated originally to assess more objectively those biopsies with minimal or no clinical and biochemical abnormality, to allow monitoring of disease progression, and response to treatment, in particular in the context of clinical trials. In individual patients, their usefulness may be compromised by the element of sampling variability inherent in liver biopsies. However, they are still felt to be of use in indicating the degree of abnormality in a given patient with chronic hepatitis. The necroinflammatory activity or grade of the disease is an indicator of severity that may evolve in either direction with time, whereas the stage of the disease is assumed to be irreversible and potentially progressive.

Assessment of histological changes in cases of anti-D associated chronic hepatitis C infection often gives low scores. A recent review in this department of liver biopsies from 37 women with hepatitis C infection from contaminated anti-D globulin showed that one third had a necroinflammatory score of 1 or 2 (unpublished results). Inevitably, such changes may overlap with appearances that (perhaps in a different context) might be considered normal. Therefore, we decided to assess the significance of a low score by formally scoring biopsies from two groups of patients who would be assumed to have normal histology. Our finding that, commonly, such cases give low scores using these scoring systems indicates that liver biopsies from patients with chronic hepatitis C infection showing minimal or mild abnormality may not necessarily be distinguished reliably from normal biopsies. This raises particular difficulties in patients with chronic hepatitis C infection where health authorities are attempting to use these scoring systems to stratify patients for treatment and, in the context of anti-D related hepatitis C infec-

tion, for compensation. Furthermore, there is a tendency on the part of involved clinicians to use such scoring systems to monitor response to treatment. The findings of this study would suggest that, at least at the lower end of the scale, pathologists cannot distinguish normal from mild abnormality reliably using the present systems.

It is notable that most of the scores in both Gilbert's disease and apparently normal livers relate to either portal tract inflammation or very mild lobular inflammation. Whether or not portal tract inflammation should be included in scoring systems is questionable. The distinction between focal aggregation of inflammatory cells⁵ and mild inflammation of pathological significance poses obvious difficulties. The same question might well be raised regarding mild lobular inflammation. As with all grading systems, the more significant abnormalities (in this context lobular inflammation with liver cell loss and piecemeal necrosis) are recognised easily and scored reliably. Milder degrees of abnormality are more difficult and this study suggests that they cannot be distinguished reliably from normal liver tissue. Cell subset analysis might facilitate such a distinction. Until some such distinction is available the significance of these low scores in the context of a potential to develop long term liver damage must be open to question.

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