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Liver histopathology of the hepatitis A virus infection: a comparison with hepatitis type B and non-A, non-B*

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SUMMARY Liver biopsies from 86 patients with serologically established acute hepatitis A were evaluated for quantitative and qualitative light microscopic features together with biopsies from 78 patients with acute hepatitis type B and 76 patients with acute hepatitis type non-A, non-B. Hepatitis A was characterised by more pronounced portal inflammation than hepatitis non-A, non-B ($p<0.01$) but less conspicuous parenchymal changes (focal necrosis, Kupffer cell proliferation, acidophil bodies, ballooning) than found in hepatitis type B ($p<0.01$). Steatosis occurred in 10% of the hepatitis A biopsies compared with 26% ($p<0.01$) and 6% (not significant) in the hepatitis non-A, non-B and B groups, respectively.

A comparison between the histological findings in women and men revealed that iron deposits occurred in more than half of the men compared to <20% of the women ($p<0.01$) irrespective of hepatitis type. Histological and biochemical follow-up was available in 36 patients with hepatitis A. For the majority of these patients the bilirubin concentration reached normal values within one month of the initial biopsy. The activity of serum transaminases showed good correlation with the degree of histological resolution. Non-specific reactive hepatitis with slightly raised serum transaminases were often seen during recovery from hepatitis A. These patients may be misinterpreted as cases of acute non-A, non-B hepatitis.

Specific and sensitive serological techniques for the diagnosis of acute hepatitis A and B infections are now available. Liver biopsy is therefore no longer a standard procedure in the diagnosis of acute viral hepatitis type A and B. It is, however, still very important in chronic cases of hepatitis B and in the diagnosis of non-A, non-B hepatitis.

In the future it may be difficult to obtain large unselected material of liver biopsies from patients with hepatitis A because the diagnosis can be made by serological methods and because the disease does not progress to chronic hepatitis or cirrhosis.

However, the precise nature of the morphological lesions during hepatitis A infection in man is not fully established. The information previously reported about liver changes in hepatitis A concerns a limited number of often highly selected patients,[1–3] and may therefore not be representative for hepatitis A in general.

Until 1980 liver biopsy was performed routinely in three medical departments in Copenhagen on a large number of patients who were clinically and biochemically suspected of acute viral hepatitis. We have re-evaluated these biopsies and here report the histological findings of patients with acute hepatitis A infection compared with patients with hepatitis B and non-A, non-B, and the morphological events during the convalescence after acute hepatitis A.

Material and methods

Until 1980 liver biopsy was performed routinely in hepatitis patients admitted to three medical depart-

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ments in the Copenhagen area and all patients with a clinical and histopathological diagnosis of acute hepatitis were included in the Copenhagen Hepatitis Acuta Programme.[4] Patients whose liver damage was suspected to be caused by alcohol or hepatotoxic drugs were excluded. All patients were at regular intervals offered follow-up liver biopsies until complete histological resolution or development of chronic liver disease. In the present study 86 consecutive cases of acute hepatitis A found during the period from August 1975 to February 1978 were selected for further histological examination. The patients fulfilled the following criteria:

1 A liver biopsy obtained during the acute phase of the disease showed fully developed acute hepatitis.
2 No serological evidence of acute hepatitis B virus infection: Hepatitis B surface antigen (HBsAg) negative by radioimmunoassay (AUSRIA, Abbott Diagnostic Division, North Chicago, Illinois, USA) and negative for IgM antibodies against hepatitis B core antigen (anti-HBc IgM) by enzyme-linked immunosorbent assay (ELISA).[5]
3 Serological evidence of acute hepatitis A infection: Presence of IgM antibodies against hepatitis A by ELISA.[6]

The mean age of the 86 patients (26 women and 60 men) was 31 yr (range 17–64 yr). Paraffin sections from the liver biopsies were stained by standard methods with haematoxylin and eosin, van Gieson-Hansen, PAS after diastase (ceroid), orcein (ground glass changes), Gomori silver impregnation for reticulin fibres, Perls' stain (iron) and methyl green pyronin (plasma cells).

The authors blindly evaluated the 86 biopsies together with biopsies from 78 patients with HBsAg positive and anti-HBc IgM positive acute hepatitis (B hepatitis) and 76 biopsies from patients without serological evidence of hepatitis A or B (non-A, non-B hepatitis). Detailed information about the histological findings in the biopsies from the patients with acute non-A, non-B hepatitis has been published previously.[7]

The following histological features were registered using a 0–3 scale (0 = absent, 1 = slight changes, 2 = moderate changes, 3 = severe changes): Focal necrosis, Kupffer cell proliferation, acidophil bodies, ballooning, portal inflammation, piecemeal-, bridging- and confluent necrosis, ceroid and iron accumulation, cholestasis, abnormal bile duct epithelium and steatosis. Piecemeal necroses were classified into small and large necroses. Periportal necrosis comprising an area of five or more hepatocytes were defined as large piecemeal necrosis.

A total of 54 follow-up liver biopsies (range 2–4 per patient) were available from 36 of 86 hepatitis A patients. These biopsies were re-evaluated and grouped according to the stage of histological resolution into fully developed acute hepatitis, non-specific reactive hepatitis and no pathological changes. The histological criteria for the diagnosis were based on the principles given by an international group of pathologists.[8]

For statistical analysis, the Mann-Whitney U test with correction for ties and the χ^2 test were used. A 1% level for type 1 errors was chosen.

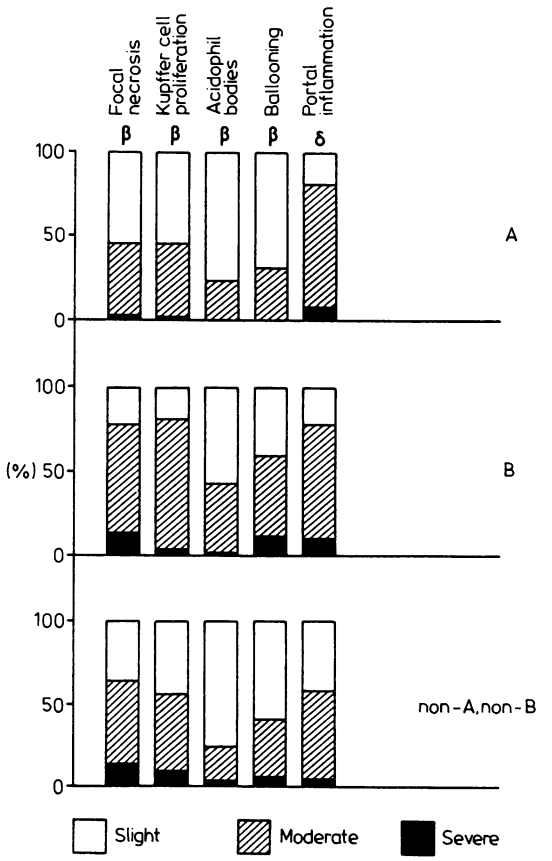

Fig. 1 *Constant histological features in liver biopsies from patients with acute hepatitis A: a comparison with hepatitis B and non-A, non-B.*

β = $p<0.01$ compared to hepatitis type B.
δ = $p<0.01$ compared to hepatitis type non-A, non-B.

Results

All liver biopsies showed some degree of the so-called constant parenchymal and portal changes that constitute the morphological criteria for the diag-

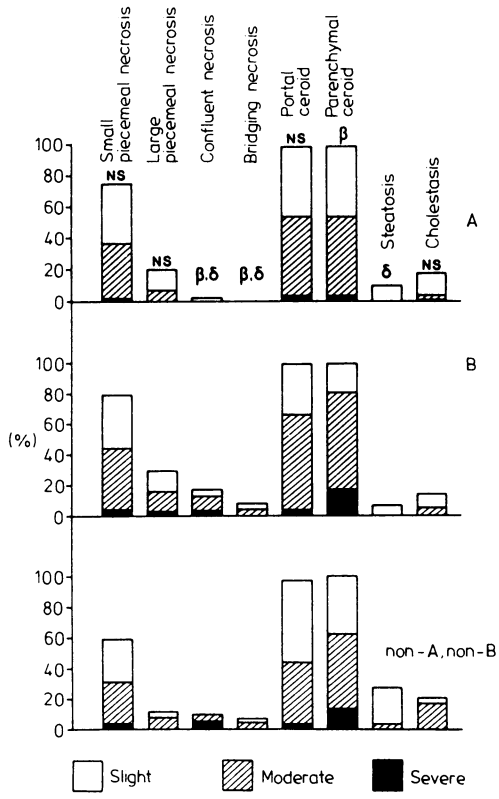

Fig. 2 *Inconstant histological features in liver biopsies from patients with acute hepatitis A: a comparison with hepatitis B and non-A, non-B.*

β = p<0·01 compared to hepatitis type B.
δ = p<0·01 compared to hepatitis type non-A, non-B.
NS: not significant.

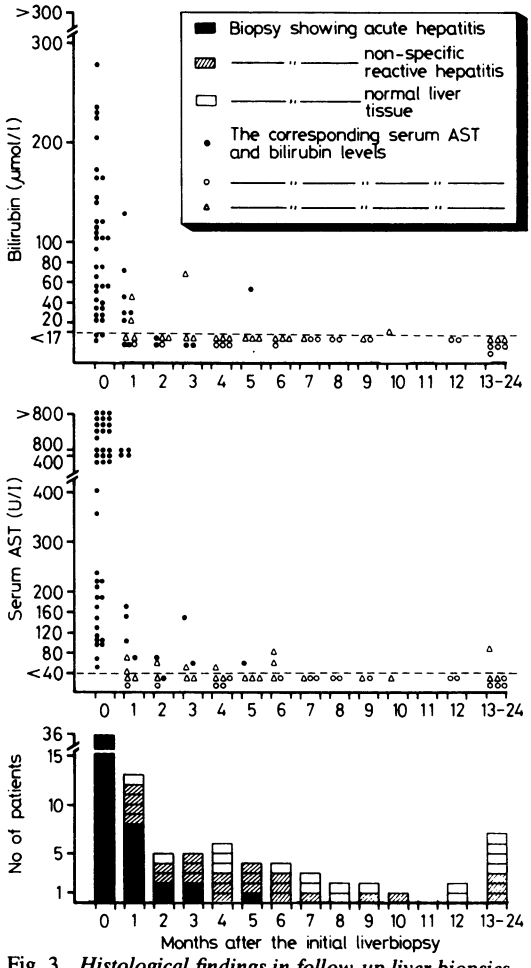

Fig. 3 *Histological findings in follow-up liver biopsies and the corresponding serum transaminase and bilirubin values in 36 patients with acute hepatitis A. (Serum AST: normal range = 10–40 U/l; serum bilirubin: normal range = 2–17 μmol/l).*

nosis of fully developed acute hepatitis (Fig. 1). For all variables the parenchymal changes were less pronounced in biopsies from patients with hepatitis A than in those from patients with hepatitis B (p<0·01). No differences in the degree of portal inflammation was seen between hepatitis A and B, while the degree of inflammation was more pronounced in hepatitis A than in the non-A, non-B group (p<0·01).

Fig. 2 shows the occurrence and degree of some of

Table *Occurrence and degree of iron in liver biopsies from 240 patients with acute hepatitis. Relation to sex and hepatitis type*

Hepatitis type	No of patients		Iron in the portal area (per cent)		Iron in the parenchyma (per cent)	
	Women	*Men*	*Women*	*Men*	*Women*	*Men*
A	26	60	23 (6/26)*	52 (31/60)	23 (6/26)**	63 (38/60)
B	19	59	16 (3/19)**	54 (32/59)	11 (2/19)**	56 (33/59)
non-A, non-B	40	36	18 (7/40)**	56 (20/36)	20 (8/40)**	56 (20/36)
Total	85	155	19 (16/85)***	54 (83/155)	19 (16/85)***	59 (91/155)

* p<0·05 compared to men.
** p<0·01 compared to men.
*** p<0·001 compared to men.

the so-called inconstant histological features. Bridging and confluent necrosis were not found in liver biopsies from patients with hepatitis A, except for a slight confluent necrosis in one hepatitis A biopsy ($p<0.01$). Steatosis occurred in 10% of the hepatitis A liver biopsies compared with 26% ($p<0.01$) in hepatitis non-A, non-B and 6% (NS) in hepatitis B. Small and large piecemeal necroses often occurred in all three types of hepatitis. Cholestasis and portal ceroid were found with nearly the same frequency in all three groups.

A comparison between the histological findings in women and men revealed that iron deposits occurred significantly more often in men irrespective of hepatitis type (Table). The iron deposits were demonstrated with the same frequency in the portal and the parenchymal area. For the total material 59% of the men and only 19% of the women had iron deposits ($p<0.01$). A comparison between age and histological findings in the hepatitis A patients showed no statistically significant differences.

The histological findings in follow-up liver biopsies and the corresponding serum transaminases and bilirubin values in 36 patients with acute hepatitis A are shown in Fig. 3. None of the patients developed chronic liver disease. For the vast majority of patients the bilirubin concentration reached normal values within one month after the initial liver biopsy. The activity of serum transaminases showed good correlation with the degree of histological resolution. All patients with normal liver biopsies, had normal serum transaminases. In contrast, one third of the patients with non-specific reactive hepatitis during convalescence from the acute hepatitis A infection had slightly raised transaminases. Histological sequelae in the form of non-specific reactive hepatitis was demonstrated more than one year after the acute episode.

Discussion

Although no single histological parameter could discriminate between the three types of hepatitis, some significant quantitative differences in the histological lesions were found. In the hepatitis A type there was less conspicuous parenchymal changes than in hepatitis type B and more pronounced portal inflammation than in hepatitis type non-A, non-B. The rather well-marked portal inflammation in the hepatitis A biopsies is in accordance with the findings in chimpanzees inoculated with hepatitis A virus reported by Dienstag *et al*[9] and the studies by Abe *et al*[2] on human beings with acute hepatitis A.

Despite the fact that none of the hepatitis A patients developed chronic liver disease as judged by biochemical and histological parameters small and large piecemeal necroses were seen with the same amount and frequency in all three types of hepatitis. The use of piecemeal necrosis as an indicator of progression to chronicity may therefore be misleading, at least in patients whose hepatitis is of unknown aetiology at the time of the biopsy.

It has long been known from clinical experience that the clinical and biochemical course of acute hepatitis A is milder in children than in adults and that the mortality rate of hepatitis A increases with age.[10] These differences in the course of hepatitis A might also be reflected in the morphological changes during the acute stage, but we were unable to demonstrate any correlation between age and degree of the histological changes.

An interesting finding was the presence of iron containing histiocytes in both the parenchymal and the portal area in the majority of the 240 patients investigated. In a recent study Teixeira *et al*[1] found iron deposits in 13 of 17 hepatitis A patients and suggested that the iron deposits were more common in hepatitis A than in other forms of hepatitis. However, in the present study iron deposits were seen with the same frequency independent of hepatitis type. On the other hand, a striking correlation between iron deposits and sex was found. Approximately 50% of the males and only 20% of the females with hepatitis had iron deposits. This difference in occurrence of iron deposits between the two sexes may have nothing to do with the actual case of hepatitis, but may be explained by a high consumption of iron containing alcoholic drinks among the men and/or a relative iron deficit among the women caused by menstrual bleeding.

The histological follow-up of 36 of the hepatitis A patients revealed that the morphological pattern correlated well with the biochemical indices of liver injury especially the raised aminotransferase values.

Histological sequelae in the form of non-specific reactive hepatitis was seen in many patients up to more than one year after the acute episode. However, non-specific reactive hepatitis is a condition that may be caused by many other diseases than acute hepatitis such as chronic peptic ulcer, cholecystitis, influenza and liver damage due to hepatotoxic drugs.[11] Therefore it cannot be ruled out that the non-specific reactive hepatitis in some of the patients may have had no relation to the acute episode of hepatitis A. The finding of slightly raised transaminases more than three months after the acute episode of hepatitis A, at a time where the histological follow-up showed non-specific reactive hepatitis, and the IgM antibodies against hepatitis A may have disappeared indicates that the aetiology of acute hepatitis in patients without a well-defined clinical course may be difficult to elucidate without

liver biopsies. Patients convalescing from hepatitis A with slightly raised transaminases may thus be misinterpreted as cases of acute non-A, non-B hepatitis.

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References

[1] Teixeira Jr MR, Weller IVD, Murray A, *et al*. The pathology of hepatitis A in man. *Liver* 1981;**2**:53–60.
[2] Abe H, Beninger PR, Ikejiri N, *et al*. Light microscopic findings of liver biopsy specimens from patients with hepatitis type A and comparison with type B. *Gastroenterology* 1982;**82**:938–47.
[3] Kryger P, Aldershvile J, Christoffersen P, *et al*. Acute non-A, non-B hepatitis—Clinical, epidemiological and histological characteristics. *Scand J Infect Dis* 1980;**12**:165–9.
[4] Petersen P, Christoffersen P, Elling P, *et al*. Acute viral hepatitis: a survey of 500 patients. Clinical, biochemical, immunological, and morphological features at time of diagnosis. *Scand J Gastroenterol* 1974;**9**:607–13.
[5] Kryger P, Mathiesen LR, Møller AM, *et al*. Enzyme-linked immunosorbent assay for detection of immunoglobulin M antibody to hepatitis B core antigen. *J Clin Microbiol* 1981;**13**:405–9.
[6] Møller AM, Mathiesen LR. Detection of immunoglobulin M antibodies to hepatitis A virus by enzyme-linked immunosorbent assay. *J Clin Microbiol* 1979;**10**:628–32.
[7] Kryger P, Christoffersen P, the Copenhagen Hepatitis Acuta Programme. Light microscopic morphology of acute hepatitis non-A, non-B. A comparison with hepatitis type A and B. *Liver* 1982;**2**:200–6.
[8] Bianchi L, De Groote J, Desmet VJ, *et al*. Morphological criteria in viral hepatitis. *Lancet* 1971;i:333–7.
[9] Dienstag JL, Feinstone SM, Purcell RH, *et al*. Experimental infection of chimpanzees with hepatitis A virus. *J Infect Dis* 1975;**132**:532–45.
[10] Mathiesen LR. The hepatitis A virus infection. *Liver* 1981; 1:81–109.
[11] Poulsen H, Christoffersen P. *Atlas of liver biopsies*. Non-specific reactive hepatitis. Copenhagen: Munksgaard, 1979:180.

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