A clinicopathological study of liver disease in haemophiliacs.

P M Mannucci, G Ronchi, L Rota and M Colombo

doi:10.1136/jcp.31.8.779

Updated information and services can be found at:
http://jcp.bmj.com/cgi/content/abstract/31/8/779

These include:

References
1 online articles that cite this article can be accessed at:
http://jcp.bmj.com/cgi/content/abstract/31/8/779#otherarticles

Rapid responses
You can respond to this article at:
http://jcp.bmj.com/cgi/lettersubmit/31/8/779

Email alerting service
Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Notes

To order reprints of this article go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to Journal of Clinical Pathology go to:
http://journals.bmj.com/subscriptions/
A clinicopathological study of liver disease in haemophiliacs

P. M. MANNUCCI, G. RONCHI, LIDIA ROTA, AND M. COLOMBO

From the Haemophilia and Thrombosis Centre Angelo Bianchi Bonomi, and the 3rd Department of Clinical Medicine, University of Milan, Via Pace 5, 20122 Milan, Italy

SUMMARY Chronic liver disease is not often reported in patients with haemophilia. Although a high incidence of abnormal liver function tests has been reported, the clinical significance of these findings and their relation to chronic liver disease cannot be established without a liver biopsy. The results of this procedure, carried out in 11 patients with severe haemophilia A and B, in whom SGOT had been persistently raised for three years, are reported. Five patients had chronic active hepatitis, four had chronic persistent hepatitis, one had cirrhosis, and one alcoholic hepatitis. No haemorrhagic complication followed the biopsy procedure, which was carried out in patients given prophylactic clotting factor concentrates. These results suggest that duration of abnormal liver function tests is likely to represent liver disease in haemophiliacs, and that biopsy should be considered to establish the diagnosis and plan a suitable therapeutic programme.

It has recently been shown that multitransfused haemophiliacs have a high incidence of abnormal liver function tests. According to different reports, 40 to 60% of patients have raised levels of serum transaminases whether or not there is a history of jaundice (Mannucci et al., 1975; Hasiba et al., 1977; Hilgartner and Giardina, 1977). Although the majority were asymptomatic and had no physical signs of liver disease, abnormal enzyme values may be the expression of chronic hepatitis. Since the clinical significance of these findings cannot be ascertained with single measurements, we have followed 66 severe haemophiliacs with serial determinations of liver function tests over a period of three years. In patients showing increased values of serum transaminases throughout the entire study period, histological examination of the liver was deemed necessary to assess the nature of the disease. Hence, percutaneous biopsy was carried out in 11 patients given prophylactic clotting factor concentrates, and the tissue specimens showed a high incidence of chronic active liver disease.

Patients
Liver function tests were carried out at yearly intervals from 1974 to 1976 in 66 patients (51 with severe haemophilia A and 15 with severe haemophilia B) during regular follow-up visits at the Haemophilia Centre. Those patients who had serum aspartate aminotransferase (SGOT) above the upper normal limit (20 mU/ml) at all of the three visits were offered percutaneous liver biopsy after the benefits and risks of the procedure had been explained in detail. When consent had been obtained, patients were admitted to the hospital the day before biopsy. If no inhibitor to factor VIII or IX was found, patients with haemophilia A were treated with cryoprecipitate immediately before biopsy; patients with haemophilia B were similarly infused with a commercial prothrombin complex concentrate (Proconativ, Kabi, Stockholm). Dosage was calculated in order to increase the deficient clotting factor to 100% of normal immediately before the procedure, which was done using the Tru Cut® needle (Travenol Laboratories, Rome). Additional replacement therapy was given after 12 hours in order to maintain factors VIII or IX at not less than 50% of average normal for the first 24 hours, and then at 24-hour intervals for the next four days, adjusting the dose to attain at any time levels of not less than 20%. Patients were followed in hospital with routine haematological tests and then discharged if no complication occurred.

Methods
Factor VIII and IX assays were carried out before and 15 minutes after each therapeutic infusion with the methods described by Wilson et al. (1971). The presence of inhibitors was checked by the method of Strauss and Merler (1967).
The liver function tests performed were serum bilirubin, aspartate and alanine aminotransferase (SGOT and SGPT), gamma glutamyltranspeptidase (γ-GT), serum protein electrophoresis, and HBsAg and anti-HBs, (radioimmunoassays, Ausris and Ausab, Abbott Laboratories); the methods used have been described previously (Mannucci et al., 1975). Tissue nuclear, smooth-muscle, and mitochondrial antibodies were detected using an indirect fluorescent-antibody technique. All of the liver specimens were examined by two clinical hepatologists (GR and MC). The histological diagnosis of chronic persistent hepatitis and chronic active hepatitis was based on the criteria established by De Groote et al. (1968) and subsequently modified by the International Association for the Study of the Liver (Levey, 1976).

Results

Liver function tests carried out three times at yearly intervals were available in 66 patients with severe haemophilia (factor VIII or IX less than 0.01 U/ml). In 17 patients, SGOT was always found to be within the normal limits (< 20 mU/ml). In 13, the enzyme was increased on one occasion but was normal on the remaining two visits; in 16, increased values were found in two instances and normal in one, whereas the remaining 20 patients showed persistently abnormal values. Three of them could not be considered for biopsy because an inhibitor was detected, six refused to undergo the procedure, and 11 accepted. All had received multiple infusions with various types of blood products (whole blood, cryoprecipitate, and commercial concentrates). Unfortunately, a precise record of the total number of infusions was not always available in all the recipients. The Table summarises liver function tests carried out at the time of biopsy, the main clinical findings, and the histological features. Four patients (1-4) showed varying degrees of chronic persistent hepatitis (Fig. 1), five (5-9) had chronic active hepatitis, and patient 10 showed features of postnecrotic active cirrhosis. In two patients with chronic active hepatitis (7 and 8) the histological signs of the disease were mild (portal mononuclear infiltration associated with periportal necrosis); patients 5 and 6 showed a more severe picture with central-to-portal bridging necrosis, whereas patient 9 had clearcut features of transition to cirrhosis (Fig. 2). Patient 11 showed cirrhotic and portal fibrosis with minimal mononuclear infiltration, and marked steatosis and siderosis; on the basis of these findings and a history of prolonged alcohol intake, a diagnosis of mild chronic alcoholic hepatitis was established. Only two patients (9 and 10) had in their history an episode of jaundice formerly diagnosed as acute hepatitis. Liver enlargement was found in patient 10 with cirrhosis, in patient 11 with alcoholic hepatitis and, to a lesser extent, in two patients (6 and 7) with chronic active hepatitis. In patients who eventually showed chronic active hepatitis at biopsy, liver function tests were usually more markedly impaired (higher transaminase and gamma globulin values) though the difference from those with chronic persistent hepatitis was not always clearcut. No treatment was prescribed for patients with chronic persistent hepatitis, who were advised to have liver function tests at more frequent intervals; patient 11 was asked to abstain from alcohol. Patients 6 and 7

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Haemophilia</th>
<th>Total bilirubin (mg/dl)</th>
<th>SGOT (mU/ml)</th>
<th>SGPT (mU/ml)</th>
<th>γ-glutamyl transferase (IU/l)</th>
<th>Flame antibodies</th>
<th>HBsAg</th>
<th>Anti-HBe</th>
<th>Concanavalin exposure (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>A</td>
<td>1.1</td>
<td>34</td>
<td>9</td>
<td>1.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&gt;200</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>B</td>
<td>0.4</td>
<td>31</td>
<td>9</td>
<td>0.9</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>100-150</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>A</td>
<td>0.4</td>
<td>22</td>
<td>3</td>
<td>1.1</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>B</td>
<td>1.1</td>
<td>67</td>
<td>10</td>
<td>1.3</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>A</td>
<td>1.0</td>
<td>38</td>
<td>6</td>
<td>0.9</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>A</td>
<td>0.5</td>
<td>40</td>
<td>24</td>
<td>1.6</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>100-150</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>A</td>
<td>0.8</td>
<td>46</td>
<td>23</td>
<td>2.1</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>50-100</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>A</td>
<td>0.4</td>
<td>67</td>
<td>9</td>
<td>1.3</td>
<td>-</td>
<td>-</td>
<td>&lt;25 &gt; 30</td>
<td>100-150</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>A</td>
<td>1.1</td>
<td>103</td>
<td>25</td>
<td>1.8</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>100-150</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>A</td>
<td>2.6</td>
<td>112</td>
<td>37</td>
<td>2.5</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>&gt;200</td>
</tr>
<tr>
<td>11</td>
<td>47</td>
<td>B</td>
<td>1.3</td>
<td>22</td>
<td>186</td>
<td>1.4</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>56</td>
</tr>
</tbody>
</table>

Normal values: 0-4-1-0

CPH = chronic persistent hepatitis; CAH = chronic active hepatitis.
with chronic active hepatitis as well as patient 10 are now on continuous oral treatment with 0-2-0-3 mg/kg of prednisolone, which appears to be well tolerated. Treatment was followed by a marked improvement of subjective symptoms (fatigue and malaise) in all; SGOT returned to normal in patients 6 and 7, who are now on steroids for six and four months respectively, but it remained unchanged in patient 10 with cirrhosis. No specific treatment is now being given to the remaining three patients with chronic active hepatitis (5, 8, 9) because it was thought that their ages and lack of symptoms would require a serial histological monitoring of the evolution of the hepatitis before any therapy could be started. This approach is tentative and will be reconsidered in the future according to the course of the disease.

Discussion

At the time of starting this study we hesitated before undertaking liver biopsy, which had not then been

<table>
<thead>
<tr>
<th>Sex and symptoms of liver disease</th>
<th>Liver histology</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Mononuclear infiltration</td>
<td>Spotty necrosis</td>
</tr>
<tr>
<td>Male</td>
<td>Mononuclear infiltration</td>
<td>Spotty necrosis</td>
</tr>
<tr>
<td>Male</td>
<td>Mononuclear infiltration</td>
<td>Spotty necrosis</td>
</tr>
<tr>
<td>Male</td>
<td>Mononuclear infiltration</td>
<td>Spotty necrosis</td>
</tr>
<tr>
<td>Male</td>
<td>Mononuclear infiltration</td>
<td>Spotty necrosis</td>
</tr>
<tr>
<td>Male</td>
<td>Mononuclear infiltration</td>
<td>Perportal and central-portal bridging necrosis</td>
</tr>
<tr>
<td>Male</td>
<td>Mononuclear infiltration</td>
<td>Perportal and central-portal bridging necrosis</td>
</tr>
<tr>
<td>Male</td>
<td>Mononuclear infiltration</td>
<td>Perportal necrosis</td>
</tr>
<tr>
<td>Male</td>
<td>Mononuclear infiltration; ductular proliferation; fibrosis</td>
<td>Perportal necrosis; central-portal and portal-in-portal septa; nodular regeneration</td>
</tr>
<tr>
<td>Male</td>
<td>Mononuclear infiltration; ductular proliferation; fibrosis</td>
<td>Sinusoid and siderosis; central biliary cirrhosis</td>
</tr>
<tr>
<td>Male</td>
<td>Mononuclear infiltration; fibrosis</td>
<td>Alcoholic hepatitis</td>
</tr>
</tbody>
</table>
reported in haemophiliacs. There were the risks of a
closed surgical procedure in patients with severe
bleeding diathesis, as well as the high cost of replace-
ment therapy needed to minimise such a risk. How-
ever, since the most difficult and traumatic operations
are now being successfully carried out in haemop-
ophilics, it was thought that biopsy could be justified
provided that the expected benefits outweighed the
hazards. Several factors eventually supported this
decision. Previous reports had shown that multi-
transfused haemophiliacs have a high incidence of
mildly to moderately increased transaminases, but
lack of information on the duration of such ab-
normalities left unsolved the problem of their
clinical significance (Mannucci et al., 1975; Hasiba
et al., 1977; Hilgartner and Giardina, 1977). Patients
such as haemophiliacs, who are frequently exposed
to the causative agents of hepatitis, are expected to
mount a state of immunotolerance conditioning the
development of a 'tolerating hepatitis' characterised
by mild clinical expression and a favourable course
(Grady, 1974; London et al., 1969). However, there
is also evidence that chronic active hepatitis and
cirrhosis may ensue even in the absence of (or in
association with) minimal alterations of liver function
tests (Grady, 1974; Simon and Patel, 1974; Woolf et
al., 1974). Once it had been shown that in a number
of patients SGOT remained increased for three
years, histological examination became mandatory
to define the nature and extent of the liver involve-

In half of these patients, biopsy showed the
presence of chronic active hepatitis which could not
easily be predicted by liver function tests. The
pathological features of chronic active hepatitis
varied from minimal and potentially regressing
disease (patients 7 and 8) to obviously developing
cirrhosis in case 9 (Fig. 2).

The incidence is similar to that in a very recent
study by Lesesne et al. (1977), who found chronic
active hepatitis in three out of six biopsies carried
out in severe haemophiliacs. A peculiar feature of
our series is the younger age of the patients, whereas
the incidence of positive hepatitis B virus markers,
of a history of jaundice, and of clinical symptoms of
liver disease is similar to that of Lesesne et al. (1977).

Since the natural history of chronic active
hepatitis is at present unknown and many clinical
trials of drug treatment are in progress (Summerskill
et al., 1975; De Groote et al., 1976; Tygstrup et al.,
1976), no established therapeutic and prognostic
guideline can be given at the moment in non-
haemophiliac patients. Symptomatic and HBsAg-
negative patients seem to benefit from long-term
corticosteroid administration (Cook et al., 1971;
Sherlock, 1974), although the hazards and side
effects of this treatment make it less advisable in
asymptomatic patients. There is also preliminary
evidence that the HBsAg-positive subgroup fared
worse with steroids (Schalm et al., 1976) but this
contraindication must be confirmed in larger series
of patients. On the basis of this knowledge and of the
A clinicopathological study of liver disease in haemophilia

awareness that long-term steroid therapy carries a higher risk of gastrointestinal bleeding in haemophiliacs, we have chosen to avoid steroids in patients with chronic active hepatitis (5, 8, 9) who were younger and asymptomatic; the natural history of the disease will be closely followed (by monitoring the evolution of the chemical and histological abnormalities) and a further biopsy might be carried out in the next few years. On the other hand, steroids were prescribed for patient 10 (with active cirrhosis) and for patients 6 and 7, who were symptomatic, HBsAg-negative, and aged more than 10 years. It is at present difficult to assess any therapeutic benefit because the follow-up period is too short (4-12 months); there were no adverse symptoms or side-effects, the patients felt better, and SGOT showed a marked decrease in patients 6 and 7 (but not in patient 10 with cirrhosis).

If one assumes that significant liver disease was present only in patients with persistently increased transaminases and not in those showing sporadic elevation, its general incidence appears too small to justify withdrawal or limitation of concentrate administration in haemophilia. This would inevitably be accompanied by a consistent deterioration of their present pattern of life at a time when the natural history of chronic active hepatitis is unknown and a benign course cannot be ruled out. However, it is essential that those involved in haemophilia care become aware that liver disease is probably the most frequent 'secondary' disease in haemophilia and that liver function tests should be carried out at frequent intervals. Biopsy is advisable in patients who have persistent liver function test abnormalities and symptoms of liver involvement; a trial period of corticosteroids should be given to those with symptomatic, HBsAg-negative chronic active hepatitis.

References


Requests for reprints to: Prof. P. M. Mannucci, International Training Centre Angelo Bianchi Bonomi of the World Federation of Haemophilia, I 20122 Milan, Via Pace, 15, Italy.