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Acute Viral Hepatitis

Harvey L. Atin

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ACUTE VIRAL HEPATITIS
Clinical Course and Laboratory Aids in Diagnosis in Thirty-five Consecutive Cases
Adrenal Steroid Therapy in Seven Cases

HARVEY L. ATIN, M.D.*

Introduction:

The assertion has been made that the correct diagnosis of acute hepatitis can be made at the bedside by means of a careful history and physical examination in 80 per cent of the patients who present themselves with this disease. With the aid of appropriate laboratory studies this percentage can be increased to 90. The percentage rises to 98 if liver biopsy is also employed. Expectant treatment and observation, along with patience, will add to the accuracy of diagnosis still further. In an attempt to assess the aid from laboratory diagnosis in this disease, and to evaluate the course of the patient and response to treatment, 35 consecutive patients with viral hepatitis and icterus were studied; these patients were admitted to the Henry Ford Hospital during 1956 and 1957. There was no evidence of underlying chronic liver disease in this group. There were 22 males and 13 females and the cases were divided into those due to infectious hepatitis virus (IH) and those due to homologous serum hepatitis virus (HSH). If the patient had received an injection from two weeks to six months prior to the onset of his symptoms, he was considered to have serum hepatitis; we realize that this is not necessarily true, as the IH virus can be transmitted also by the parenteral route. We are also aware of the possibility that the IH and HSH viruses are not necessarily separate strains.

The incubation period calculated from the time of the injection to the onset of symptoms, in the HSH group, varied from 35 to 147 days with an average of 80 days. The patient ranged from 8 to 67 years with an average age of 35 in the IH group compared with 52 in the HSH group. Not only were the patients in the latter group older, but the majority of them suffered from associated disease which necessitated the previous blood or parenteral medication. Whether due to these reasons or due to the inherent greater virulence of the B virus, as some have postulated, the patients with serum hepatitis appear to suffer a more severe form of the disease, as the data will indicate. It has long been said that serum hepatitis has a more insidious onset, and this may be reflected in the longer duration of symptoms prior to admission, i.e., 13.5 compared with 9.9 days.

Method and Results:

Many different methods could have been used to evaluate the laboratory data. The method used here was to record the peak abnormality, if any, and determine the number of days this occurred from the onset of symptoms and from the date of admission, and then note how long it took after onset of symptoms for this abnormality to return to normal. The data has been summarized in Table I.

*Resident, Division of Gastroenterology.
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Table I

Peak values of laboratory tests in 35 patients with viral hepatitis.

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35 Patients; 22 Males, 13 Females

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>IH</th>
<th>HSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs.)</td>
<td>8 - 66 (Av. 35)</td>
<td>20 - 67 (Av. 52)</td>
</tr>
<tr>
<td>Symptoms Prior to Admission (days)</td>
<td>1 - 28 (Av. 9.9)</td>
<td>4 - 28 (Av. 13.5)</td>
</tr>
<tr>
<td>Bilirubin (mg.%)</td>
<td>2 - 15 (Av. 8.1)</td>
<td>6 - 46 (Av. 16.2)</td>
</tr>
<tr>
<td>White Blood Count (x 1000)</td>
<td>3.3 - 11 (Av. 5.6)</td>
<td>4.5 - 10.5 (Av. 8.0)</td>
</tr>
<tr>
<td>Cholesterol Esters (%)</td>
<td>21 - 58 (Av. 41)</td>
<td>24 - 63 (Av. 39)</td>
</tr>
<tr>
<td>Prothrombin Time (%)</td>
<td>Av. 91</td>
<td>Av. 82</td>
</tr>
<tr>
<td>Alkaline Phosphatase (Bodansky units)</td>
<td>2.6 - 15.1 (Av. 7.4)</td>
<td>5.0 - 20 (Av. 9.5)</td>
</tr>
</tbody>
</table>

Flocculation Tests

Ceph. Chol. Flocculation | 5/35 less than 3+ throughout course. |
Thymol Flocculation | 6/35 less than 3+ throughout course. |
Thymol Turbidity (Units) | 3/35 less than 4 throughout course. | Av. 13.4 | Av. 11.9 |

Bilirubin:

In HSH the bilirubin peaks were generally much higher (reaching 46 mg. per cent in one case) and, although generally occurring in the first week in the hospital, frequently took much longer (up to 21 days after admission or 31st day of illness). In IH the peaks were lower, rarely over 12 mg. per cent, and usually but not invariably occurred within the first week in the hospital.

White Blood Count:

In no patient was there a white blood count above 11,000. Several patients had white blood counts below 5,000, particularly in the IH group. The absence of prominent leukopenia in the HSH may be due to the longer duration of the illness prior to admission and testing. A white blood count of over 11,000 in uncomplicated viral hepatitis is extremely unusual.

Cholesterol esters:

The esters were usually below 50 per cent in 2/3 of the patients. The sickest patients usually had the lower values, but there is not enough data or correlation to make any further statement in this regard.
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**Prothrombin Time:**

The lowest value was 41 per cent and only two patients had values below 55 per cent. This should not detract from the great prognostic value of a markedly abnormal prothrombin time in hepatitis. A value below 20 per cent is a grave sign of a severely diseased liver.

**Alkaline Phosphatase:**

There was great variability in the peak values obtained and the number of days required for the peak to be reached. In 24 patients with two or more determinations, five reached values greater than 12 Bodansky units, i.e., approximately 20 per cent reached values in the range of so-called obstructive jaundice.

**Flocculation Tests:**

Approximately 17 per cent of the patients had one test negative and about 12 per cent had two out of the three tests negative throughout the course of the illness. Only one patient, or about 3 per cent, had all tests negative throughout the course of the illness. Two patients, or about 6 per cent, had all tests negative during the first week in the hospital. Generally the cephalin cholesterol flocculation is the first and the thymol turbidity the last of these tests to be elevated.

**Serum Iron and Serum Glutamic Oxaloacetic Transaminase:**

According to Rinaldo, in jaundiced patients, values of serum transaminase greater than 250 units and serum iron greater than 200 micrograms are almost diagnostic of hepatitis. Both tests appear to be of particular value early in the disease. About 60 per cent of those tested reached serum transaminase levels greater than 250 units, and 33 per cent serum iron levels greater than 200 micrograms per cent. Since many were admitted some time after the onset of the disease, these percentages are probably far lower than the true yield. The transaminase value in those with serial tests reached the peak about the 16th or 17th day of the illness or within the first week of hospitalization. Since elevated serum transaminase levels did occur in patients with the cholangiolic variety of hepatitis, a serum transaminase level greater than 250 units, even in the presence of a high alkaline phosphatase and negative flocculation tests, still points strongly to the diagnosis of hepatitis.

**Serum Protein:**

Total serum proteins and A/G ratios were done on many patients but were all normal. This does not detract from the value of low total protein and particularly a low albumin as an indication of a poor prognosis in patients with hepatitis. Furthermore, although no electrophoretic data was obtained on our patients, it is worth mentioning that a rising gamma globulin is frequently associated with prolonged and chronic hepatitis, while a markedly elevated alpha globulin level is usually indicative of extra hepatic obstructive jaundice or metastatic disease in the liver, rather than hepatitis.
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Biliary drainage and Oral Cholecystograms:

There were nine biliary drainages performed. Five of these could be considered abnormal by usual criteria, but only one had calcium bilirubinate pigment. In no case were there both cholesterol crystals and bilirubinate pigment. Three of these nine cases had cholecystograms. Two of these confirmed negative biliary drainage findings. The other case yielded a negative cholecystogram in a patient with microcalculi in the biliary drainage. Of the five oral cholecystograms performed, (these were performed when jaundice was minimal), only one patient had an abnormal x-ray. That was a patient in whom calculi were demonstrated and who had classical biliary colic while in hospital. It is difficult to draw any conclusions from this data but it is suspected that the biliary drainage must be interpreted with caution in patients with hepatitis.

Complete Suppression of Bile Flow:

Twenty-nine patients had urinary urobilinogen or stool bile examinations on one or more occasions. There were 13 patients or about 40 per cent who exhibited complete suppression of bile flow at some time during their course. Five patients, or about 16 per cent, had complete suppression for greater than 10 days. The longest period of complete suppression in this series was 17 days. The frequency of prolonged biliary suppression in this series again calls to our attention the fact that suppression for more than ten days does not preclude a diagnosis of hepatitis.

Liver Biopsy:

The histological features of viral hepatitis during the acute stage can be simply described as variations and degree of two features: diffuse portal area exudate and parenchymal cell injury. The diffuse portal exudate usually consists of leukocytes and a few eosinophiles. The parenchymal injury may be manifested by focal necrosis and lymphocyte satellitosis, acidophilic bodies, balloon cells, distortion of liver columns in the acute stage and by mitosis, pseudo-acini, lipofuscin pigment in Kupffer cells and bile stasis in the subsiding stage. During the latter part of the illness, the portal exudate and lipofuscin pigment may be the only evidence of liver pathology.

Liver biopsy has been said to be about 90 per cent effective in the differential diagnosis of jaundice. Of the 35 patients studied, ten or about 30 per cent, had a liver biopsy performed. Almost all of the biopsies were done during the resolving stage of the disease, and in only three, or less than 10 per cent, did they appear to be necessary for diagnosis. One biopsy revealed normal liver tissue. The other nine were reported as showing hepatitis. All of these revealed periportal lymphocytes in moderate numbers and a few leukocytes. Four revealed marked focal aggregations of lymphocytes and a few leukocytes in the parenchyma. Only two revealed focal necrosis of liver cells and a similar number showed marked cholestasis. In four patients, there was evidence of liver cell regeneration. There was mild portal fibrosis in two patients, both of whom had HSH with marked cholestasis. There was no evidence of bile duct proliferation, bile lakes and feathery degeneration, so frequently seen in the extrahepatic variety of obstructive jaundice.
Treatment, Course and Prognosis:

All of the patients were treated with high-protein, high-carbohydrate diets, vitamins, and enforced bed rest, during the acute stage of the disease. Some received lipotropic agents, liver extract, and parenteral fluids, carbohydrates and vitamins, as necessary. Two patients received steroids, and their course will be discussed later.

![Graph showing laboratory and clinical course in days in 32 patients with acute hepatitis.]

Table II

Laboratory and clinical course in days in 32 patients with acute hepatitis.

Course:

From Table II we note again the increased severity of the disease in HSH compared with IH. The bilirubin, transaminase and thymol turbidity peaks are usually reached in that order during the first week in the hospital. Towards the end of the first week or the beginning of the second week in the hospital, the patient's appetite and sense of well being begin to show a definite improvement. Transaminase appears to be the first of the laboratory tests to return to normal (about 31 days from onset of symptoms) and a persistent elevation in this test usually indicates continued hepatic disease. A secondary rise in the serum transaminase during the recovery phase usually indicates a relapse, and heralds a prolonged or chronic disease. The bilirubin and thymol turbidity take longer periods to reach normal levels. The thymol turbidity is usually the last to return to normal, not doing so until usually the latter part of the second month of the illness in the average case. It should be realized, however, that the thymol turbidity may not return to normal for several months after all the other tests have done so. The total duration of the illness in the average case is about eight weeks in uncomplicated infectious hepatitis, compared with more than ten weeks in HSH.
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There were three patients who after one year continued to have elevated flocculation tests and suggestive evidence at least of chronic hepatitis. This percentage of about 10 per cent is higher than usually expected with this disease. If we omit the patients suspected of having chronic hepatitis, we find that two, or six per cent approximately, of the remaining 32 suffered mild transient relapses. This percentage is similar to that reported by Ducci. No patient in this series died.

Although the laboratory is a useful tool in the diagnosis and treatment of viral hepatitis, it still remains but an adjunct to the all important bedside wisdom that can only be obtained by seeing and talking to the patient.

Steroid Therapy

Of the patients seen at the Henry Ford Hospital with viral hepatitis about 60 per cent are males. During the past two years, seven cases have been treated with steroids. Of these, six or 86 per cent were females. This appears to indicate the disease follows a more severe course in the female patient. Of the seven, three were treated with steroids because of delay in the onset of the recovery phase, i.e. persistent or rising bilirubin and transaminase peaks and persistent complete intrahepatic biliary obstruction. These patients, however, were reported as “feeling and eating well”, prior to the onset of steroids, and the steroids were used in an attempt to “break into the disease process”. In an attempt to evaluate the course of this group, they were compared with three patients not treated with steroids, who had exhibited complete intrahepatic biliary obstruction for more than ten days. From Table III,

![Viral Hepatitis Therapy Graph]

Table III

Comparison of the courses of the steroid and non-steroid treated patients.
we note that the two groups were similar with reference to transaminase peaks and days of complete biliary obstruction. The only significant difference was that two of the steroid group had exhibited transient lethargy five and seven days prior to its use. This indicates to a certain extent a more serious clinical state and will be commented upon later. The apparent lower bilirubin peaks in the steroid group may be due to the effect of steroids in lowering serum bilirubin. There was a definite decrease in liver size and tenderness along with a 50-60 per cent drop in total serum bilirubin within 72 hours of starting the steroids. This was associated with definite evidence of bilirubin in the stool within 48 hours. Although all patients in this group were apparently feeling and eating well, there was a clearcut added surge of well being, to the point of euphoria at times, and increased appetite, within 24 hours. There is some evidence that steroids do decrease the inflammatory reaction in the liver, and may improve bile flow by this method. There is, however, some other unknown mechanism by which the serum bilirubin level is lowered, since this occurs even though bile flow obstruction persists, as noted in the fourth case. The longer period of transaminase elevation in the treated group indicates these drugs do not prevent continued hepatic cell injury and this point should be kept in mind when considering their use in the hepatic coma of viral hepatitis. In spite of the sudden prompt drop in bilirubin with the use of steroids, there is apparently no significant difference in the period required for the total bilirubin to return to normal or in the total duration of the illness in the two groups. Doses of 300-400 mg. of cortisone, or its equivalent dropped gradually over a period of 7-14 days to maintenance levels, appears to be adequate when these drugs are used for the reasons described above. There was one mild relapse in the control group and one relapse with prolonged recovery in the steroid group. Recrudescences can develop in both groups and occur while the dose is being decreased or at termination of therapy in the steroid group. The reported relapse rate is about 20 per cent in the steroid treated group and about 5 per cent in those not treated with steroids.

A fourth patient has been grouped separately. Her disease began in a mild manner about five weeks before. She had carried out strenuous activity during this period, and from her history we considered her to have a severe exacerbation of the disease. While in hospital her appetite and well being decreased and bile disappeared from the stool. Her sensorium, however, remained good. Because of the progressive nature of the disease, she was started on 400 mg. of cortisone daily. The total serum bilirubin dropped from 27 to 21 mg. and her appetite and well being improved within 72 hours. Bilirubin continued to be absent in the stool for the next 14 days, however, and no further drop in total serum bilirubin occurred during this time. Once the bilirubin began to appear in the stool the serum bilirubin gradually decreased. After three weeks the patient is still on 200 mg. of cortisone daily and continues to gradually improve, although her progress has been slightly marred by transient hypomania and persisting euphoria. The early mild fall in serum bilirubin probably had nothing to do with hepatic function. The persistent absence of bilirubin in the stool and absence of progressive fall in serum bilirubin over two weeks can be considered as a partial failure of steroid therapy.

The other three patients who were treated with steroids exhibited progressive
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evidence of liver decompensation, manifested by lethargy and restlessness, decreasing well being, appetite, albumin, prothrombin and cholesterol esters, and increasing bilirubin and transaminase. They could be classed as the pre-coma stage of liver decompensation.

Two of these were started on what might be considered average doses of steroids, that is, 400 mg. or less of cortisone or its equivalent. Both exhibited transient improvement in appetite, sensorium and general well being. In one patient, this lasted only 24 hours and the patient subsequently expired on the twelfth day of steroids, despite antibiotics and arginine. This patient had exhibited progressive lethargy for three days, ascites, shrinking liver, and abdominal distention prior to the use of steroids. At post mortem, the patient was found to have diffuse and almost total hepatic necrosis and superficial gastric ulcers, with moderately severe upper gastrointestinal bleeding. The possible role of the steroids in the GI bleeding is of interest, but any answer at present can only be speculative in this regard. The other patient had a fluctuant course with ups and downs of lethargy, state of appetite, and well being for five days prior to steroids. She showed a good response to steroid therapy with marked increase in well being, sensorium, and appetite within 24 hours, and clearing of the obstructive phase with a 60 per cent drop in bilirubin within 72 hours. After 11 days of steroids, when the dose of cortisone was down to 50 mg. daily, she developed a relapse, associated with decreased appetite and well being, rising bilirubin and transaminase, and recurrence of the obstructive phase. The dose was then increased to 800 mg. daily with increase in appetite and well being and cessation of the obstructive phase within 72 hours. The transaminase, which after rising had begun to fall prior to the increase in dosage, continued to fall to normal levels in an uninterrupted fashion. The serum bilirubin level, however, remained elevated without significant change for almost three weeks. The total serum protein continued to fall to a low of 4.8 grams per cent over the next two weeks, in spite of doses of cortisone ranging from 800 to 400 mg. daily. After five weeks on high doses of cortisone, only complicated by mild depression and homesickness, the patient was discharged on 200 mg. of cortisone, eating well, with increasing energy, but still manifesting visible but mild icterus. Although the cortisone resulted in clinical improvement and appeared to stop and reverse the clinical downward trend of the illness, it did not result in sufficient laboratory evidence to indicate improvement in hepatic function and was associated with a clinical exacerbation when the dose was being lowered.

The third patient treated in the pre-coma stage was started on 800 mg. of cortisone daily. She had exhibited progressive hepatic deterioration at another hospital in spite of 15 mg. of meticorten daily. When first seen at Henry Ford Hospital, a "hepatic flap" could already be demonstrated. There was no change in the downhill course with increase in steroid dosage and the patient expired several days later. A request for post mortem examination was denied.

The work of Ducci indicating the value of high doses of cortisone (1 gram of cortisone or its equivalent) in hepatic coma due to viral hepatitis has been an important contribution to the treatment of this almost invariably fatal situation. Evidence to date, however, indicates that lower, more average doses of these steroids...
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will not alter the outcome of the patient in the coma stage. The doses apparently must be high. Furthermore, the earlier the steroids are used, the greater the chance of survival. The importance of low albumin and prothrombin levels as indicators of hepatic disease does not require re-emphasis at this time. It is interesting to note, however, that only two patients in the original series of 35 exhibited lethargy and both of these received steroids later, after the lethargy had cleared, but when they exhibited a failure to enter the recovery stage of the ailment. Since lethargy occurs when the liver is severely diseased and had appeared from three to seven days prior to the date of beginning of steroid therapy in five out of seven of our patients, we may in this sign find one of the important indicators for those patients who should receive steroids. It is, therefore, suggested that any lethargy, severe enough to be clinically evident, should be met with steroid therapy. The dose at this point should be about 400 mg. of cortisone daily or its equivalent. If the lethargy progresses or clinical state remains stationary after 48 hours, then the daily dose should be increased to 800 to 1000 mg.

Conclusions:

From the work to date, the routine use of steroids in acute, benign, viral hepatitis seems inadvisable. Its use in the patient with persistent, complete, intrahepatic biliary obstruction or cholangiolitic hepatitis is open to question. If the patient appears to be handling the disease well in spite of the absence of bilirubin in the stool, since we are probably not improving liver function or shortening significantly the total duration of the illness with the use of these drugs, the decision to employ them must be weighed very carefully. The possibility of untoward effects of steroid therapy along with a false sense of improvement must be weighed against the possible good results of their use.

Steroid therapy does definitely appear to be indicated in the patient with prolonged and/or progressive liver disease due to acute viral hepatitis. The patient's ability to handle and respond to the disease appears to be the prime consideration here. The important factor is the patient himself, and the decision to use steroids must be made at the bedside where clinical judgment must take precedence over results of laboratory tests. The use of steroids in the pre-coma and coma stages of acute hepatitis has already been discussed and appears well established at present.

The tendency for the disease to run a more severe course in the female and the effectiveness of steroids in many severely ill patients with acute hepatitis brings into focus once more the interrelationship of the endocrines and the liver. Would the use of steroids, other than adrenal, e.g. androgens, be more effectual in the treatment of viral hepatitis?

SUMMARY:

Thirty-five consecutive cases of acute viral hepatitis have been studied in an attempt to determine the average clinical and laboratory course of the disease. The laboratory tests useful in diagnosis and in following the course of the disease are stressed.
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Seven cases of acute viral hepatitis treated with steroids are carefully evaluated and the relative value of these agents under various circumstances is discussed.

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