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Kaiser Permanente Medicine 50 Years Ago:

Acute Catarrhal Hepatitis: A Study of Twenty-Two Cases, With Current Day Commentary

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Epidemiology

The etiology of catarrhal jaundice has not been definitely determined up to the present time.[1] A filterable virus has been accused, but the various means used to isolate or transmit this ultramicroscopic organism to the various laboratory animals have all met with failure. At no time has an animal or insect vector been found, nor has it been accepted that food or fomites are the agents of transmission, although an outbreak in Scotland was attributed to milk. Anderson claimed that swine were a source of hepato-trophic virus. Water also has been incriminated by Bellandes and Hallgren, and by Frazier, who attributed to this source an outbreak following a waterborne salmonella epidemic.[1]

It has been observed that outbreaks have followed tonsillitis and upper respiratory infection resembling an influenza syndrome.

Epidemiologically, it is justified to presume that a virus is the infecting agent because of the suspected mode of transmission, incubation period, age group involved, character of the epidemics and failure to isolate the organism.

The suspected mode of transmission is by means of droplet infection and that rather close personal contact is necessary. For an example, an epidemic[2] occurred in a school and as long as the children remained in school the disease was localized to that one group, but with the coming of vacation, the infection spread to schools in the surrounding area. Usually two to three members of a class or two members or more of a family became ill. This is typical of an epidemic of infectious jaundice. To further substantiate that it usually has spread among groups in close contact, Hunter[3] described the observations of epidemics of World War I. He stated, "The usual history in any battalion affected commenced with one to two isolated cases. Then there was an interval of about three to four weeks; then a large number of cases for three weeks; finally an occasional case for another few weeks."

The highest incidence reported was between the ages of six to 10, and 20 to 30 years, and was evenly distributed between the sexes.[2] The incidence was highest in the fall and winter, decreasing in the spring, and nearly absent in summer. No age group was immune, as was pointed out by Bloomfield,[4] who felt that the older group was also quite susceptible.

Our series did not show an even distribution between the sexes, and only 15.8 percent were below twenty years of age. However, this was not true representation of the surrounding area because our study included only adult shipyard workers.

Kerr,[5] in a simultaneous study of epidemic jaundice in this area, covering the entire population group, based upon cases reported to the Department of Public Health between March 1943 and April 1944, noted that the highest incidence fell in the five- to nine-year-old group. The 20- to 29- and 30- to 39-year-old groups were equal in number and were found to be next in frequency. There was no study made to compare the incidence between the sexes. In all, 80 cases were studied by Kerr, and all worked or attended school in Richmond. There were 70 cases in the Richmond area, which included San Pablo, El Cerrito, and vicinity. Most of the people observed resided in the new war housing projects. The remaining ten were distributed among people living in Oakland, Berkeley, San Francisco, and Vallejo.

Leptospira agglutination tests, performed on blood sera secured at different stages of the disease, were all negative.

An attempt was made to discover possible contacts in all cases, but usually none were found. In three instances, it was noted that apparently parents had contracted the disease from their children. To make the study more difficult, many may have had the prodromal signs but not the icteric stage.

It was emphasized by Kerr that more than one attack of jaundice has been known to occur in the same individual, which suggests various strains of hepatotoxic virus.

Homologous Serum Jaundice

Following yellow fever vaccination in the armed forces, many cases of jaundice appeared among the men. It resembled catarrhal hepatitis in every respect except epidemiologically, and the occasional prodromal appearance of urticarial eruption and severe joint pains. The incubation period was two to four months.

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Investigations revealed that those men who developed jaundice were inoculated with certain lots of vaccine, whereas other lots caused no such difficulty.[6]

Most cases were mild. Some only presented symptoms of the prodromal period and did not develop jaundice. This occasionally has been noted when catarrhal jaundice has been suspected during epidemics. The period of recovery was four to eight weeks, and in the fatal cases death occurred in two to six weeks.

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Pathological studies in fatal cases revealed the presence of acute yellow atrophy.[6,7] Those patients who died of other causes offered an opportunity to study the effect upon the liver. It was noted that the earliest lesion was frank necrosis of the central regions of the lobules. The stroma was seldom involved. There were no inclusion bodies of yellow fever seen. In the fatal cases, the cecum was inflamed, the kidney showed a biliary nephrosis, and there were hemorrhages into serous and mucous membranes.

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This type of reaction following homologous serum therapy has been observed in the past. Jaundice appeared following the use of "glycerinated humanised" lymph, measles and mumps vaccine.[8] It also has been seen following transfusions.[9] The same thing has occurred in horses immunized with homologous serum.[10]

Investigations to determine the cause of jaundice led to the conclusion that probably some infective agent was present in the vaccine and its source was probably in the serum used. When new vaccines were made without the serum, no reactions were observed. Studies were carried out in which volunteers were used as subjects, and jaundice was reproduced in these when the same lot of vaccine was used and when serum from jaundiced patients was administered.

Important conclusions derived from the study were that a virus, probably identical with that causing acute catarrhal hepatitis, was the infecting agent. It could resist drying in vacuum, storage for long periods in serum at 4 degrees C, and heating to 56 degrees C for one-half hour in the dried state.[9]

Another hypothesis which has been offered is that the liver is subject to an antibody-antigen reaction which results in hepatitis.[11]

Pathology

Acute catarrhal hepatitis is a relatively benign malady, and the pathologist infrequently is given the opportunity to study the changes which take place in the liver. However, some studies have been made, with considerable disagreement among the authors. In a passage in the Official History of the War, Medical Services, Diseases of the War,[4] Volume I, is stated: "The cause of jaundice in these cases seems to be obstruction in the biliary tract. The symptoms are not usually severe or lasting enough for there to be any involvement of the smaller ducts within the liver and are best explained by the swelling of the papilla of Vater as a part of a duodenal inflammation due to localization of inflammation in the duodenum." However, studies made by Eppinger[11] on dead jaundiced soldiers did not reveal any catarrhal changes in the duodenum or bile ducts, but he did show degenerative changes in the liver cells. Experiments by Van Rooyen and Gordon[3] also failed to substantiate any gastric, duodenal, or biliary catarrhal. Both jaundiced and normal individuals were used as subjects. Aspiration of the duodenal contents after using a cholagogue revealed no appreciable difference in the groups. Steigmann and Popper[15] found a narrowing of the common bile duct rather than dilatation as some authors describe. They reported: "The livers of two cases of acute hepatitis showed degenerative changes in the liver parenchyma, bile imbibition by the liver cells, and bile casts in the dilated bile capillaries … there was enlargement of the periportal fields with very marked fibrosis, lymphocytic and occasionally leucocytic infiltration, and bile duct proliferation … The demarcation of the periportal fields was not clear due to the extension of the proliferated bile ducts into the periphery of the lobules, where the liver cells showed irregular shape."

Popper [sic][15] and Hanger describe a pathological process which places the point of obstruction in the periportal field. The dilated bile capillaries are joined to the narrowed bile ducts by the wide but weak-walled canal of Hering, which is lined with flat epithelium. This connecting link is either ruptured or occluded by the exudate in the periportal field, thus preventing the flow of bile in the bile ducts.

Clinical Picture

Prior to the onset of jaundice, it has been stated that there is a prodromal period of three to seven days, during which time the patient may be either mildly or acutely ill. In a review of our 22 cases, this was found to be true in the majority, but four patients, or 18.2 percent of the group, had prodromal symptoms ten days to about one month, or probably longer, in duration.

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It was seldom that the temperature rose above 101 degrees F and the most common symptoms (82.8%) were anorexia, nausea and vomiting with various combinations of the following: bloated sensation, vague abdominal complaints, constipation or diarrhea, weakness, malaise, common cold and influenza-like syndrome. Vomiting was the most common symptom (68% of cases). Before jaundice made its appearance, it was noted that the urine became darker in color and the stools lighter.

In the milder cases of catarrhal hepatitis, the prodromal symptoms ceased a short time prior to the appearance of jaundice or extended up to this point, and then the patient felt very well. The more severe cases remained ill for a variable period of time after the onset of jaundice.

The usual course of the jaundice stage of catarrhal hepatitis, as a rule, was uneventful and the patient was kept in bed and on a low-fat, high-carbohydrate, high-protein diet until the jaundice cleared. Three patients in our series progressed to the point where they became intensely jaundiced, and studies of the bile pigments in the urine and stool revealed that complete hepatic obstruction had taken place. Liver function tests indicated parenchymal involvement of varying severity. The amount of toxicity seemed to bear a direct relationship to the severity of the hyperbiliurbinemia [sic: hyperbilirubinemia] (as measured by the icterus index) and hepatic insufficiency. In fulminating cases, parenchymal destruction has been reported as taking place rapidly and the patient expiring within a few weeks. In homologous serum jaundice as reported by Turner[7] et al, death occurred in 24 to 39 days. During this severe toxic stage, there have been seen neurological or personality changes, hemorrhages into the mucous membranes and gastrointestinal tract, ascites, and kidney dysfunction.

The duration of hospital stay in our patients was from three to seventeen days except in the three severely jaundiced patients, who required 21 to 62 days. Follow-up clinic visits in 13 patients revealed that the average period away from work was 31.5 days, the shortest being 11 days and the longest 73 days.

As a rule, there was a normal white cell count or a leukopenia present with an increase in the nongranular series of white cells. This was true in all of our patients but one, in whom it was observed that the leukocyte count was 26,350 cells per cubic millimeter on entrance and it later dropped to 12,550. This may have been a case of true cholangitis. The sedimentation rate in this disease has usually been reported as being normal. In ten patients in which it was determined, it varied between 12 and 89 millimeters in one hour (Westergren method). The highest rates were in our two most severe patients and in one patient who might be considered mildly to moderately ill.

The intravenous hippuric acid liver function test was performed in the majority of patients and was never found to be abnormal in the milder cases. Urine examination in all cases revealed the presence of bilirubin in the urine and also amounts of urobilinogen which were within normal limits. The prothrombin in all of the milder cases was found to be within normal limits.

It has usually been considered that no ill effects remain after a mild case of catarrhal hepatitis. However, Kornberg[17] reported liver disease to be demonstrable in persons who had catarrhal jaundice at one time and who subsequently appeared to be normal.

Case Reports

Three patients in this series are of special interest because of the intensity and duration of jaundice, the degree of hepatic involvement, and the atypical course of the illness.

Case 1. In which the patient was jaundiced for over three months, with evidence of severe liver damage and an icterus index as high as 340 units.

A 37-year-old, white, obese male, was admitted into the hospital on January 17, 1944, after being jaundiced, he stated, for six weeks. His illness began with a cold. He was able to continue work for two weeks, but on December 14, 1943, it was necessary for him to go to bed. He remained there a few days and, on rising, noted that his skin was yellow and that he was quite weak. He complained of nausea and vomiting three weeks prior to entry and had noticed that his urine had become darker and his stools lighter. Pruritis [sic] was moderately severe, but he complained of no pain. He had lost 22 pounds since the illness began.

Physical examination was not remarkable except for jaundice and right upper quadrant tenderness. The liver was not palpable.

Laboratory studies: The leukocyte count on admission was 12,800 cells per cubic millimeter and by

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February 16, 1944, it was 6150. The first icterus index was 165 units, and its highest level was 340 (17 days after admission). Prothrombin time was normal up until March 17, when it was found to be 42 percent of normal. Repeated hippuric acid liver function tests indicated parenchymal damage, and on February 5, none was formed by the liver. Examination of the urine for bile and urobilinogen disclosed a four-plus bilirubin reaction and no urobilinogen present on two occasions: first on January 24 and second on February 6. After this, the urobilinogen was found to be present in the urine in normal amounts. There was never any lowering of the serum albumin, and the serum globulin was elevated to 4.0 grams per 100 cubic centimeters on one occasion. The sedimentation rate was repeatedly elevated; the highest level was 89 millimeters in one hour (Westergren method). Stool examinations for occult blood were positive (guiac [sic: guaiac] method) on two occasions.

Roentgenograms of the gallbladder area and upper gastrointestinal tract were normal.

The patient was in the hospital for approximately 63 days, and for a few weeks, he was acutely and severely ill. Pruritis [sic] was aggravating but never really severe. His jaundice became so deep that a slight greenish tinge to the skin became evident. He became depressed easily and would cry occasionally.

The patient's temperature during his stay in the hospital was usually within normal limits. On one or two occasions, it rose to 100 degrees F. The pulse was always relatively slow.

He was discharged from the hospital on March 21, 1944, with an icterus index of 25. He went home to New York and we have lost contact with him since.

Case 2. In which a patient was jaundiced for five weeks, with an icterus index as high as 136 units and some findings suggestive of cholecystitis with choledocholithiasis.

A 33-year-old white female, well-nourished and developed, was admitted into the hospital December 28, 1943, with complaints of jaundice, weakness and pruritis [sic]. She stated that she had influenza during the spring of the same year. Since then, she had always felt weak, and had an aggravating pruritis [sic]. Three weeks prior to entry, she noted dark urine, and for two weeks, light-colored stools. Jaundice was present for ten days. She complained of no pain but did have nausea and vomiting for two months prior to entry. Appetite had been only fair for two to three months.

Physical examination was not remarkable except for jaundice and tenderness in the right upper quadrant. The liver was not palpable.

Laboratory studies: The leukocyte count was normal on admission and always remained so. The prothrombin time was always within normal limits. The icterus index on admission was 103 units, and the highest was 136 (six days after admission). Bilirubin was present in large amounts in the urine, and urobilinogen was found to be absent on three different occasions in single specimens but not in successive samples. The hippuric acid liver function test (using 1.77 grams sodium benzoate intravenously) was very low on admission, only 0.04 grams recovered. Repeat tests on January 2 resulted in 1.38 grams being recovered, and on January 11, 0.45 grams were recovered. Blood albumin and globulin levels were never greatly disturbed; however, the globulin was 3.2 grams per 100 cubic centimeters on January 3. The sedimentation rate was 43 millimeters in one hour (Westergren). Several stool examinations showed traces of occult blood. The alkaline serum phosphatase was recorded as 5.6 units, and the heterophile antibody reaction was negative.

On one examination, a mass was thought to be palpable in the right upper quadrant, separate from the liver. Cholecystography at this time revealed a nonfunctioning gallbladder.

This patient suffered severely from itching of the skin and her entire body was covered with excoriations. On January 10, the icteric index was 114 units. On January 17, the icterus index had fallen to 51 units. She left the hospital January 20 and was subsequently seen in the clinic, where continued improvement was noted. She was seen the last time on February 17, at which time she had no symptoms.

Case 3. A patient with evidence of moderately impaired liver function and icterus index to 124 units.

A 37-year-old white male, who appeared well-nourished and developed, was admitted to the hospital January 5, 1944. He stated that 20 days prior to admission, he had chills and fever associated with symptoms of influenza. About 10 days after the onset of illness, he had the sensation of abdominal distention. This was followed by diarrhea, which for a time was quite severe. The stools were cream-colored at first but on admission were returning to normal color. He had never had pain, but epigastric tenderness was present. His appetite during this period was poor.

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Physical examination was normal except for jaundice and a moderately enlarged and tender liver.

Laboratory examinations: The leukocyte counts were always within normal limits. The icterus index on admission was 88 units; it reached a peak of 124 units on January 17 and then decreased rather rapidly. The prothrombin time was normal. Urine urobilinogen was absent on three examinations between January 7 and January 12; it was present in a dilution up to one-to-sixty on an isolated specimen on January 19. Bilirubinuria was reported as four-plus reaction in all examinations. Only 0.19 grams of hippuric acid were recovered with the first intravenous test and 0.59 grams, on the next. The sedimentation rate was three millimeters per hour. The blood albumin and globulin were reported as 3.7 grams and 2.9 grams per 100 cubic centimeters, respectively. A roentgenogram of the abdomen was normal.

The clinical course of this patient was uneventful. He was discharged on January 26 and subsequently seen in the outpatient department. He was released for work on February 2, 1944.

Discussion

The prodromal periods in each of the above patients began with an upper respiratory infection, and in two there were associated symptoms of an influenzal syndrome. Each was ill longer than seven days before the onset of jaundice. The patient cited in Case 2 developed a respiratory infection in the spring and noticed the jaundice in the winter. It does not seem reasonable that such a long prodromal period could have existed. However, nausea and vomiting were present for two months, and her appetite was poor for two to three months. There is a possibility that she may have had a subicteric course during this period.

In Case 1, a period of five weeks elapsed before the highest icterus index was reached. This long period of increasing jaundice and decreasing liver function caused concern. If the patient had infectious hepatitis, it was feared he was going into the stage of acute yellow atrophy, or if he had a stone in the common duct, irreparable damage might be taking place. Surgery in the former condition would be harmful. A period of approximately 47 days elapsed before a drop in icterus index was noted in this patient.

Bloomfield[4] asserts that to wait one month before resorting to surgery is justified and cites one instance in his series in which clearing of the jaundice started after a 35 day period.

In two patients, occult blood was noted in the stools. This might be due to either [sic] bleeding into the gastrointestinal tract as a result of low prothrombin content; however the prothrombin time (Quick one-stage method) was usually normal in these patients.

Mild cases of acute catarrhal hepatitis present little or no problem in diagnosis, but those cases seen for the first time which already show evidence of complete biliary tract obstruction are a problem, and the question often arises as to whether the condition is one requiring surgery.

Ivy[13] and others[16,19] point out that in the first two to six weeks of jaundice, the less sensitive liver function tests are helpful in differentiating between "surgical" and "medical" jaundice. In the former, the tests will be negative because any liver cell damage would be negligible and would not be detected, whereas in a hepatitis, the results would be abnormal.

One characteristic noted early in infectious hepatitis is the inability of the liver cells to reoxidize urobilinogen. As a result early in the disease, it is usually found in increased concentrations in the urine. Unfortunately, the physician seldom sees the patient at this time. As the disease progresses, the amount of urobilinogen in the urine decreases, and when complete obstruction develops, urobilinogen disappears from the urine entirely. At this time, bilirubin is found in large amounts in the urine, as has been graphically brought out by Steigmann.[20] With improvement, as the obstruction is relieved, bilirubinuria decreases, and urobilinogenuria again rises above normal transitorily, finally returning gradually to normal.

Liver function tests performed in each patient in this series included: icterus index, albumin and globulin determinations, prothrombin time, hippuric acid liver function tests, and urine and stool determinations for bilirubin and urobilinogen. The galactose tolerance test was done only on very early cases. With these tests, it was possible to formulate impressions as to the cause of jaundice, degree of liver damage, and rate of progress of the disease and of healing.

Treatment

It has been well established that the treatment of catarrhal hepatitis is to be directed towards helping the individual liver cells by supplying high-protein and -carbohydrate and low-fat diet.[18] Addition of vitamins, especially of the B complex, is

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of value. The caloric intake of food must be over the daily requirements and if the patient cannot eat, these may be supplied with intravenous glucose, plasma, and amino acids.[12] In addition, vitamin K parenterally was given to help maintain the prothrombin level. Each patient was hospitalized until the jaundice had cleared. Turner[7] states that it is necessary for the liver to metabolize products necessary for muscular activity, and to keep the body at rest would tend to spare some activity on the part of the liver.

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Conclusion

The etiology of acute catarrhal hepatitis is probably a filterable virus which is hepatospecific. Differences in symptoms and prodromal periods may be due to various strains of this organism.

The relationship of vaccination jaundice to infectious hepatitis has been discussed.

A review of the symptomatology, diagnostic studies performed, and management of 22 cases of acute catarrhal hepatitis was presented. Case histories were given of three patients manifesting severe liver damage and values of icterus index over 100 units. ❖

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"In recent years, hepatitis, and especially hepatitis C, is frequently in the news. There are billboards showing patients with yellow eyes. Information can be downloaded from the Internet, and countless chat groups have been conducted on the subject. In 1944, things were different."

Commentary

By Leon Kaufman, MD

In recent years, hepatitis, and especially hepatitis C, is frequently in the news. There are billboards showing patients with yellow eyes. Information can be downloaded from the Internet, and countless chat groups have been conducted on the subject. In 1944, things were different. Hepatitis was still a mysterious disease. I enjoyed the article by Dr Phillip Raimondi—much has changed since then. I have selected five areas to illustrate how our understanding of viral hepatitis has developed over the years.

1. Pathogenesis: Dr Raimondi's title itself is of interest. The pathogenesis of "acute catarrhal hepatitis" was still controversial. Dr Raimondi notes that some continued to believe that jaundice was secondary to common bile duct obstruction due to a mucous plug associated with duodenal and ampullary inflammation—hence the term "catarrhal." It was Hans Popper who demonstrated that viral hepatitis was clearly an inflamed liver.[16]

2. Etiology: In 1944, the etiologies of "acute catarrhal hepatitis" (hepatitis A) and "homologous serum jaundice" (hepatitis B) were obscure. There was some insight into the parenteral source of postvaccinal jaundice. Yellow fever vaccine was contaminated with serum containing the hepatitis B virus. This resulted in 40,000 cases of acute hepatitis in the United States Army during that time. (It is said that Winston Churchill was offered the vaccine but refused. His

vaccination might have changed the course of World War II!) Baruch Blumberg was awarded the Nobel Prize for the discovery of the Australia Antigen (hepatitis B) in the mid-1960s. The molecular cloning of the hepatitis C virus by Michael Houghton of the Chiron Corporation in 1989 was another milestone. We now know of hepatitis viruses A though G. However, there are some caveats; hepatitis F has not been clearly defined, and it is a relief to know that hepatitis G is probably not a pathogen.

3. Diagnosis: The differential diagnosis of hepatitis in those days was sometimes difficult. It was the time of "medical" versus "surgical" jaundice. Patients often underwent exploratory surgery when jaundice was prolonged. This was not a good thing. With the advent of liver biopsy, hepatitis serologies, sonography, CT, ERCP, and most importantly, a better understanding of the course of the disease, the diagnosis can now be made with precision.

4. Sequelae: Although the article refers to acute hepatitis, it is interesting to note that there is no discussion of chronic hepatitis. Nothing was known then about the subsequent course. Today, we know that hepatitis B and C often develop into chronic diseases that affect millions of patients in this country. Understandably, this has resulted in much public anxiety. However, long-term follow-up studies of up to 50 years have shown that most patients have a benign course.

5. Treatment: I found the section on treatment most interesting. There are only 10 lines of discussion. Included are: A) admission to the hospital: Icteric patients were routinely admitted then (Case #1, for 63 days). This was the time before Utilization Review committees. B) High-protein diet with vitamin B complex: During the 1940s, this sounded therapeutic. C) Bed rest to spare some activity on the part of the liver. This was advised until the jaundice cleared!

Today, admission is not indicated unless the patient is very ill. No particular diet is prescribed unless the patient is in liver failure. Although most patients recover from acute hepatitis A and B, current treatment includes interferon, ribavirin and lamivudine for chronic viral hepatitis; and liver transplantation for acute and chronic liver failure. Moreover, vaccines against hepatitis A and B, like the polio vaccine, will eventually eradicate these disorders.

We have come a long way in our understanding of viral hepatitis since 1944. There are probably additional human hepatitis viruses to be discovered. Up to 10% of transfusion-associated hepatitis and approximately 5% of community-acquired viral hepatitis have no identifiable etiology. What do you tell the patient with acute non A through E hepatitis? ❖

"We now know of hepatitis viruses A though G. However, there are some caveats; hepatitis F has not been clearly defined, and it is a relief to know that hepatitis G is probably not a pathogen."

Small Inside Big

"What we're trying relentlessly to do is to get that small company soul—and small company speed—inside our big company body."

Jack Welch,
CEO, General Electric