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The Long-Term Course of Non-A, Non-B Post-transfusion Hepatitis

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Patients with non-A, non-B post-transfusion hepatitis were followed from the onset of their disease until their blood tests normalized, until they died, or until the present time. Of 66 patients, 30 had a spontaneous resolution of their biochemical disease. Ten patients died or were begun on immunosuppressive therapy with transaminases still abnormal. The remaining 26 patients had abnormal transaminase levels when last seen. By actuarial analysis, only 54% of hepatitis patients are predicted to develop a spontaneous biochemical remission within 3 yr. No further resolutions have occurred after that time. Icteric and anicteric acute disease may be equally likely to progress to chronic disease. Initial and follow-up liver biopsy specimens have revealed both chronic persistent and chronic active hepatitis. Two patients showed histologic evidence of cirrhosis, and a third developed a hepatic coagulopathy and splenomegaly. No other patient to date, however, has developed overt evidence of hepatocellular failure or portal hypertension. Thus, non-A, non-B post-transfusion hepatitis frequently results in biochemical evidence of chronic liver disease, and in a few patients cirrhosis may develop slowly and in a clinically inapparent fashion.

Prospective studies of post-transfusion hepatitis (PTH) have been conducted at UCLA since 1972. The initial results[1] not only validated the usefulness of screening units of blood for hepatitis B surface antigen (HB_sAg) by radioimmunoassay (RIA), but also revealed that a substantial number of patients who received HB_sAg-negative blood developed PTH. Most of the patients in this UCLA study developed non-B hepatitis. When testing procedures for hepatitis A became available, it was found that the vast majority of patients developing PTH, both at UCLA and at other centers, had disease caused by one or more non-A, non-B hepatitis viruses.[2]

Serum glutamic pyruvic transaminase (SGPT) (alanine aminotransferase) elevations were present for more than 20 wk in over one-half of the UCLA patients who contracted PTH.[3] Other groups also subsequently observed that a large proportion of non-A, non-B PTH patients develop chronic liver disease.[4,5]

As one or more non-A, non-B viral agents are responsible for most cases of PTH, and as chronic disease often results, it is important to define the natural history of the illness. The present report describes the UCLA prospective experience with 66 patients who developed non-A, non-B PTH and who have been followed for up to 6 yr.

Materials and Methods

The 66 patients were identified from two separate prospective studies of acute PTH. The first prospective study was conducted from 1972 to 1974 to evaluate the usefulness of certain HB_sAg-screening tests. Aliquots of serum from blood units that had recently been transfused were screened for HB_sAg by the then more sensitive (but commercially unavailable) techniques of passive hemagglutination and RIA. Positive units were identified, and the recipients were prospectively followed. Matched controls who received all HB_sAg-negative blood were similarly followed. Post-transfusion hepatitis was defined as two or more consecutive, and otherwise unexplained, elevations in the SGPT that occurred in the 6-mo period after the receipt of blood. At least one of these elevations had to be more than five times the upper limit of normal. Of 125 pa-

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tients so followed, 54 developed PTH. Thirty-one* were subsequently shown to have non-A, non-B PTH based on their failure to demonstrate serologic evidence of hepatitis A (hepatitis A antibody[7]) or B (HB_sAg,[8,9] antibody to hepatitis B core antigen,[6] or antibody to HB_sAg [anti-HB_s][10]) exposure. The patients in this first study had various underlying illnesses, and each had received an average of 10 units of blood. Almost all of the transfused blood came from commercial sources. None of these 31 patients had clinical or biochemical evidence of liver disease before transfusion, although 1 had a past history of heavy alcohol consumption.

The second acute PTH study, which is still continuing, was initiated in 1974. Potential recipients were identified before transfusion and enrolled; 216 transfused patients were followed with serial specimens obtained every 2-4 wk. Patients with clinical or biochemical evidence of liver disease were excluded from the study. The criteria for PTH are the same as those of the first study with the exception that only a twofold, rather than a fivefold, elevation was necessary to establish the diagnosis. The patients were derived primarily from the surgery or surgical subspecialty services. They have received substantially less blood than those in the first study (approximately 5 units per patient) with a larger proportion (all of it since 1976) from volunteer sources. To date, 40 of these patients have developed PTH, 35 of which are etiologically of the non-A, non-B type.

These 66 patients with non-A, non-B PTH (31 from the first study and 35 from the second) were then followed until the SGPT level returned to normal (on at least three consecutive determinations generally 1 mo apart), until death occurred, until follow-up was refused by the patient, or until the present time. In those cases in whom disease lasted longer than 6 mo, this follow-up usually consisted of SGPT value determinations every 1-3 mo along with physician interviews and physical examinations every 3-6 mo. As was true during the acute phase of the study, no other cause for the abnormal SGPT level was apparent.

For the purposes of this paper, the term "chronic hepatitis" will be defined on purely biochemical grounds. No implication will necessarily exist concerning prognosis or response to therapy. In fact, the purpose of the study was to determine the prognosis in this population.

Percutaneous liver biopsy specimens were sought from patients who had SGPT levels that remained abnormal for longer than 20 wk and who had no contraindications. Each biopsy specimen was usually obtained with a double-pass technique, which provides two tissue cores for histologic examination. Chronic active hepatitis (CAH) was defined as piecemeal necrosis, increased fibrosis, and intralobular hepatocytolysis. Chronic persistent hepatitis (CPH) was characterized by portal tract inflammation with intact limiting plates, with or without intralobular hepatocytolysis. The biopsy specimens were read by both blinded and nonblinded evaluators, and agreement was reached as previously described.[3] Those who maintained abnormal transaminases for 12-24 mo from the time of the last specimen were asked to undergo repeat biopsies. Biopsy specimens were not requested from patients in whom the underlying disease(s) or condition(s) was (were) severe enough to preclude biopsy or potential immunosuppressive therapy.

The actuarial analysis performed in the 66 patients with non-A, non-B PTH was conducted in a standard manner.[11] Patients who had their last follow-up, who died with abnormal SGPT values, or who began immunosuppressive therapy in the first 3 mo of the period were excluded for that period. If one of these events occurred in the last 3 mo of the period, the patient was considered to have had an abnormal SGPT value for the entire period.

Statistical evaluations were performed either by the χ^2 or by Student's t-test method.[12]

All of the patients gave written, informed consent to participate in the study, which was approved by the UCLA Human Subject Protection Committee on August 28, 1975.

Results

The clinical characteristics of the non-A, non-B PTH seen in the patients from both studies are displayed on Table 1. There was no difference in the incidence of icteric disease occurring in each study ($P > 0.50$). More patients in the first study had symptoms ($P < 0.01$), but, in the anicteric individuals, these symptoms usually consisted only of mild fatigue. In spite of the lower SGPT abnormality used to define PTH in the second study, no significant difference was seen between the two groups with regard to the highest transaminase value observed during the acute stage ($P > 0.20$). Only 6 of the 35 non-A, non-B PTH patients in the second study failed to have their SGPT abnormalities exceed five times the upper limit of normal.

Table 1. The Clinical Characteristics of the Initial Hepatitis

Characteristics	Study 1	Study 2	Total
Jaundice	8/31 (26%)	6/35 (17%)	14/66 (21%)
Symptoms	24/31 (77%)	11/35 (31%)	35/66 (53%)
Maximum SGPT[a]			
Mean	22	18	20
Range	6-66	2-82	2-82
Abnormal SGPT persisting beyond 6 mo	23/31 (74%)	23/35 (66%)	46/66 (70%)

[a] Maximum SGPT is expressed as number of times greater than the upper limit of normal.

* Upon review of the serologic records, 2 patients initially classified as having hepatitis B in 1976[3] were reclassified as non-A, non-B. In one of these patients, an observed "anti-HB_s response" was, in retrospect, clearly the result of passive transfusion of antibody. The second patient, who demonstrated pre-existent anti-HB_s, had an eightfold rise (by passive hemagglutination) in titer during the follow-up period. However, during the period of observation, the anti-HB_s titer was observed to fluctuate for unexplained reasons over this range, and, when the patient was tested for antibody to hepatitis B core antigen,[6] none could be demonstrated.

Table 2. Risk Factors for Developing Chronic Hepatitis[a]

Factor	Duration of SGPT Abnormality <6 Mo	>6 Mo
Symptoms	9	26
No Symptoms	11	20
Jaundice	7	7
No Jaundice	13	39
SGPT > 20 times upper limit normal	6	19
SGPT < 20 times upper limit normal	14	27

[a] Arbitrarily defined as an abnormal SGPT persisting longer than 6 mo.

Table 3. SGPT Abnormalities (66 Patients)[a]

Outcome	Number	Duration (mo) Mean	Range
Resolved			
spontaneous	30	7	1-30
treatment	4	27	12-41
Died, SGPT abnormal	6	8	3-13
Abnormal, last follow-up	26	39	4-77

[a] SGPT = Serum glutamic pyruvic transaminase (alanine aminotransferase).

For ease in presenting the remainder of the data, all 66 patients will be considered as one group. The results of treating them all as one group are identical to those obtained by analyzing each group separately, with the exception of the longer follow-up in many of the patients from the first study. The 6 patients whose SGPT levels failed to rise to more than five times the upper limit of normal are also included, as separating them out failed to alter any of the results or conclusions.

Chronic hepatitis will be arbitrarily assumed to have occurred if the SGPT level remained abnormal for longer than 6 mo, as previously noted. This phenomenon was seen in 70% of the patients. It has been speculated that icteric or very active acute disease may be less predisposed to result in chronic hepatitis. As shown in Table 2, however, symptomatic disease could not be shown to be less likely to result in prolonged transaminase elevations than was asymptomatic disease ($P > 0.20$). Although only 7 of the 14 icteric patients (50%) developed chronic disease, compared with 39 of 52 anicteric patients (75%), this difference was not statistically significant ($P > 0.10$). The level of the initial SGPT bore no predictive value as to the subsequent occurrence of chronic disease ($P > 0.50$). These data, therefore, do not support the premise that icteric disease is less likely to pursue a chronic course.

The biochemical follow-up of the 66 patients is detailed in Table 3. Thirty patients had spontaneous resolutions of the abnormal SGPT level after an average duration of disease (as measured by this biochemical parameter) of 7 mo. Four other patients had their SGPT abnormalities disappear only after varying courses of immunosuppressive therapy. Another 6 patients died with their SGPT levels still above normal—they all died of their underlying diseases (3 with heart disease and 3 with cancer)—and none had hepatic decompensation at the time of death. The final 26 patients, after an average follow-up time of 3 yr, had abnormal transaminase levels when last seen.

The data are presented graphically in Figure 1, which displays the probability of spontaneously developing a normal SGPT level. Only 30 of the 66 have developed a normal SGPT level to date, and the cumulative probability of such an occurrence after 3 yr is only 54%. No patient whose SGPT level remained abnormal after 3 yr (11 patients) has yet had a spontaneous resolution.

Only 4 patients reported persistence of the symptoms beyond the first few months. One of these 4

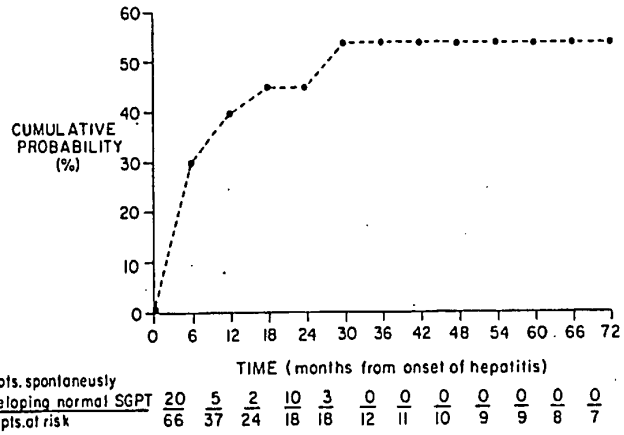

Figure 1. The cumulative probability of the patients spontaneously (i.e., in the absence of immunosuppressive therapy) developing a normal SGPT level is shown as a function of time.

had marked fatigue, anorexia, and weight loss while the other 3 complained of mild malaise. Only 1 of the 66 patients has developed any overt evidence of portal hypertension (splenomegaly). This same patient developed a prolongation of his partial thromboplastin time after 5 yr of follow-up and subsequently has demonstrated recurrent skin ecchymoses. A hematologic evaluation revealed that the coagulopathy was related to a decreased concentration of several hepatic clotting factors. (This patient has not undergone biopsy.) He represents the only patient with any clinical evidence of hepatocellular failure. When last seen, none of the other patients had hepatosplenomegaly or any other evidence of chronic liver disease.

Of 18 patients who underwent an initial liver biopsy 5–30 mo after the development of PTH, 8 had CAH, and the other 10 had CPH. Follow-up histologic specimens were obtained at 1- to 2-yr intervals in 8 of these individuals. Two of the patients with initial CPH underwent two subsequent biopsies each, and 1 other patient underwent one follow-up biopsy. All repeat biopsy specimens continued to demonstrate CPH.

All 8 CAH patients had piecemeal necrosis, but none had bridging necrosis. One of the 8 also had histologic evidence of cirrhosis on the initial biopsy specimen. Five of the 8 patients with CAH received immunosuppressive treatment while under the care of their own attending physician. (No attempt was made to perform a prospective, randomized controlled study of the effect of immunosuppressive therapy in non-A, non-B CAH.) Two of them subsequently demonstrated CPH, while a third has continued to show CAH. This third patient became the second individual in the series to display histologic evidence of cirrhosis. However, cirrhosis has been identified only on his fourth liver biopsy specimen, obtained 5 yr after the onset of his illness. (This patient had a past history of substantial alcohol usage, although he has denied any since before the transfusion.) The other 2 patients received only brief courses of therapy and subsequent biopsies have not been done.

One of the untreated patients with CAH died of cancer shortly after the liver biopsy. (He was the other patient with cirrhosis.) The other 2 have remained asymptomatic. One of these patients had two follow-up biopsies performed, the first specimen continuing to demonstrate CAH, but the second, performed 3 yr after the onset of disease, showing CPH. The other patient demonstrated CPH on the follow-up specimen obtained 2.5 yr after the onset of the illness.

Two patients not undergoing biopsies had postmortem liver specimens available for analysis. One had the SGPT values return to normal 3 mo before death and had only mild fatty changes in the liver. The second died with the SGPT value still abnormal, and had only severe hepatic congestion (from acute heart failure) without histologic evidence of chronic hepatitis.

Histologic information is thus not available in 28 of the 46 patients whose SGPT abnormalities lasted more than 6 mo. In 6 of them, the SGPT values returned to normal before a biopsy was performed. Eight others refused even biochemical follow-up prior to or concomitant with the request to perform a biopsy, and 4 others declined the biopsy. Finally, 4 patients died of their underlying disease before biopsy, and 4 others were thought not to be appropriate candidates for this invasive procedure.

Discussion

Evidence is beginning to accumulate that non-A, non-B hepatitis often results in chronic liver disease. In 1976, the present authors reported a high frequency of chronic liver disease after non-B PTH.[3] Purcell et al.[4] also reported 21 cases of non-A, non-B PTH at the National Institutes of Health, 7 of whom were observed to have protracted courses (more than 6 mo). Three of these 7 underwent liver biopsy; 2 demonstrated CAH and 1 CPH.

In 1977, Knodell et al.[5] observed 16 cases of protracted abnormalities in liver enzyme values among 44 patients with non-A, non-B PTH. Six of these patients had their enzyme abnormalities return to normal shortly thereafter, but the remaining 10 continued to demonstrate biochemical evidence of chronic hepatitis for 12–36 mo. Liver biopsies performed on these 10 revealed CAH in 8, CPH in 1, and "relatively inactive" cirrhosis in the tenth.

Tateda et al. in Japan have also noted this prolonged period of SGPT level elevation.[13] However, only 19 of 116 (16%) of their patients were so affected.

The development of non-A, non-B viral induced chronic liver disease may also occur in the non-post-transfusion situation. Eight of 29 (28%) hemodialysis patients with acute non-A, non-B hepatitis developed persistently elevated transaminases, and liver specimens revealed CAH in 3, and CPH in 2 others.[14]

Finally, in our series only about half (54%) of the patients developed a normal SGPT level after 2.5 yr of follow-up. In 10 of the 30 patients who ultimately had a spontaneous resolution, the SGPT levels remained abnormal for more than 6 mo.

It has often been stated that patients with anicteric disease are more likely to progress to chronic liver disease. Unfortunately it is often difficult to determine the exact time of onset in anicteric, asymp-

tomatic disease. If such patients are found to have abnormal transaminase levels, the entire concept of time of onset has little clinical relevance. Such patients often have chronic hepatitis, but it is unproven that such people ever had "acute" disease.

As we chose not to obtain liver specimens on our patients during the early phase, we cannot comment on the progression of histologic acute disease to a histologic chronic process. We do have a time of onset of such patients, however, and we have arbitrarily called all patients whose biochemical disease lasted longer than 6 mo "chronic hepatitis." Using this definition, a less favorable prognosis for anicteric, or even less clinically active, disease could not be demonstrated. It might be argued that 6 mo was inappropriately short, as many of these patients may have had a slowly resolving disease. However, even when 1 yr was used as the cutoff period, no statistically significant different prognosis could be shown for the initially icteric vs. anicteric disease. (In fact, even the arithmetical difference seen at 6 mo, 50% vs. 75%, became less prominent, 33% vs. 53%.)

What is the clinical significance of this chronic liver disease? If this illness is asymptomatic and does not progress to liver failure, then disease does not really exist from the patient's point of view. On the other hand, if the disorder is progressive and results in cirrhosis, then it becomes important to identify it and consider the evaluation of treatment programs.

A recently published follow-up of the National Institutes of Health experience with non-A, non-B PTH,[15] now encompassing 26 cases, reported chronic biochemical disease in 12. After 1-3 yr, the SGPT levels became normal in 4 of these 12 individuals, and none of them had significant symptoms. Liver specimens were obtained in 8 patients; 6 demonstrated CAH, and 2 revealed CPH. The authors thought this disease pursued a benign course, but did observe that 1 of the 6 patients with CAH also had a mild elevation of the serum gamma globulin and histologic evidence of early cirrhosis.

Knodell et al. reported[5] that 2 of their 10 patients had palmar erythema. In fact, 1 of these 2 also had splenomegaly. Rakela and Redeker observed the progression of acute non-A, non-B PTH to hepatic failure and death over a 42-mo period in 1 patient.[16] Iwarson et al. have recently reported a patient with presumed viral hepatitis (without serologic evidence of hepatitis A or B) who progressed from an acute phase (histologically documented) through CAH with cirrhosis to liver failure and death over a 3-yr period.[17] However, it is possible that this unrelated transfusion case represented nonviral disease.

The current study represents the longest defined follow-up evaluation of non-A, non-B PTH available. To date, most of the patients have remained asymptomatic. If this disease does progress to liver failure, it only does so over a period of time that is measured in years, and its course, thus far, does appear to be benign in most instances. On the other hand, 2 patients have demonstrated histologic evidence of cirrhosis. An additional patient now has splenomegaly and a hepatic coagulopathy. It is possible that progression to overt liver failure may still be seen in some of the other patients in future years, and that non-A, non-B PTH does not have a benign prognosis. Only continued long-term observation, however, can establish or refute this possibility. Likewise, it is unknown if corticosteroids have any place in the management of this disease, a question that can only be answered with a randomized, prospective, controlled trial.

In conclusion, non-A, non-B post-transfusion hepatitis often results in chronic biochemical liver disease. Icteric, active acute disease may be as likely as anicteric asymptomatic disease to progress to this chronic phase. Although the disease is usually asymptomatic, histologic evidence of either CAH or CPH may be seen. To date, clinical evidence of cirrhosis has been seen in only 1 of the 66 patients, although histologic evidence of cirrhosis has been observed in 2 others.

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