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Post-transfusion non-A, non-B hepatitis in Finland: a prospective study

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To study the frequency of post-transfusion non-A, non-B (NANB) hepatitis in Finland, we have followed prospectively 65 patients after open-heart surgery. The total number of transfused blood units was 652. Blood samples were obtained from the patients during the first 6 months after the operation and were studied for transaminase levels. The NANB diagnosis was based on exclusion of viral hepatitis of known etiology by serological tests for hepatitis A, B, cytomegalovirus and Epstein-Barr virus infections. We found three cases of post-transfusion NANB, all of which were subclinical and unicteric. The frequency of NANB hepatitis was 4.6%, and the proportion of infective blood units was 0.5%.

Key-words: blood transfusion; hepatitis; non-A; non-B

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The frequency of post-transfusion hepatitis has significantly decreased along with the screening of donor blood for hepatitis B surface antigen (HBsAg) [7]. However, post-transfusion hepatitis has not been completely eliminated. The majority of these cases are referred to as non-A, non-B (NANB) hepatitis.

It is not known whether NANB hepatitis is caused by one virus or several different viruses, and there are no reliable tests for this disease. Consequently, the diagnosis of post-transfusion NANB hepatitis is based on the exclusion of other causes of hepatitis in patients who have received blood within the highly variable incubation period of the disease and who have signs of viral hepatitis. Since NANB hepatitis is usually unicteric and asymptomatic [4, 8], it is mainly diagnosed only by the observation of elevated transaminase levels in the serum.

There is no exact data on the frequency of NANB post-transfusion hepatitis in Finland but there is data that indicates the frequency may be lower in Europe than it is in the USA [9, 13]. In the USA close to 3% of transfused blood units give rise to NANB hepatitis [1].

We have followed 65 patients after open-heart

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surgery. A total of 10 blood samples were taken during the first 6 months after the operation from each patient. They were studied for elevated transaminase levels as well as for markers for hepatitis B virus infection. The patients received a total of 652 units of blood, and we found three cases of post-transfusion hepatitis, all of them NANB. All three cases unicteric and subclinical.

PATIENTS AND METHODS

We gathered our material from the patients who were hospitalized at the Third Surgical Department of the University Hospital in Helsinki between February 1980 and August 1981 for open-heart surgery. Sixty-five patients aged 19–64 years gave their consent and were followed during the whole period of investigation. Patients who had received blood or plasma up to 6 months before the cardiac operation were excluded from the study.

All blood donors were negative for HBsAg as tested by radioimmunoassay (FRC-RIA) [8]. The donors were not tested for transaminase levels at the time of transfusion. The number of blood units transfused to one patient varied from 5 to 40 with a mean of 10.2. The total number of transfused units was 652.

Blood samples were obtained from the patients before transfusion, biweekly during the first 3 months and monthly during the next 3 months after transfusion. The follow-up time was 6 months if no pathological laboratory values were found.

All samples were measured for alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) by a kinetic assay [5]. According to several earlier prospective studies [3, 6] acute hepatitis was diagnosed when the ALAT value exceeded 100 IU/l. All samples were tested for hepatitis B surface antigen (HBsAg) and antibody (anti-HBs) by radioimmunoassay [10]. The sera from patients who had elevated transaminase values were tested for antibodies against hepatitis A virus (total and IgM class antibodies by Havab and Havab-M, Abbott), hepatitis B core antigen (anti-HBc) by radioimmunoassay (Corab, Abbott), cytomegalovirus by standard complement fixation method and by enzyme-immunoassay for IgG and IgM antibodies (kindly performed by Dr J. Suni, Aurora Hospital, Helsinki) using nuclear antigen from infected cells [12], and Epstein-Barr virus by immunofluorescence using infected cells and anti-human-IgG-FITC conjugate.

RESULTS

Preoperative values of ALAT and ASAT that were normal were found in 58 patients. Five patients has ALAT values of 42–75 IU/l and two patients had values that exceeded 100 IU/l; after operation these values decreased to a normal level. Elevated transaminase levels were found from seven patients out of 65 and three of them had a rise in the ALAT level which exceeded 100 IU/l, the level we regarded as the criterion for post-transfusion hepatitis.

All seven patients with elevated transaminase values had had Epstein-Barr virus antibodies before transfusion and the titres did not change during the follow-up. Six patients out of seven were positive for hepatitis A antibody before transfusion, but none of them had IgM antibodies as a sign of acute hepatitis A infection. Two of the seven studied were positive for anti-HBc before and after transfusion and none had HBsAg or anti-HBs. Three patients with moderate rises in the ALAT level (below 100 IU/l) showed seroconversion and presence of IgM-class antibodies for cytomegalovirus. Therefore, all three cases with ALAT levels exceeding 100 IU/l could be classified as NANB hepatitis, and three out of four patients with slightly elevated ALAT probably had cytomegalovirus infection.

In the three NANB cases, the peak activities of ALAT were 152, 412 and 580 IU/l and they were always higher than the ASAT levels (Fig. 1). The incubation period, defined as the interval between transfusion and the first significant increase in ALAT level, was between 8 and 10 weeks. In all three patients with NANB hepatitis the ALAT activities showed fluctuation and remained elevated for the whole time of the follow-up. We were only able to follow two of these patients for 4 months after the appearance of the disease, but the third patient still had a high ALAT level 16 months after transfusion.

Four patients had moderate rises in ALAT values 8 weeks after transfusion. The peak

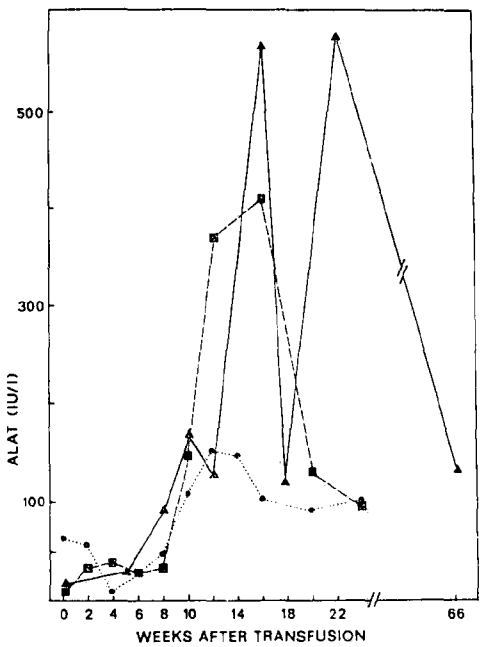

FIG. The alanine aminotransferase (ALAT) levels of three patients with NANB post-transfusion hepatitis.

activities were between 64 and 82 IU/l and the values decreased to a normal level during the study period.

The donors of two NANB cases were contacted and 16 donors out of the total of 21 were studied for ALAT and ASAT levels. All nine donors of the third patient were studied, one of them had an ALAT value of 78 IU/l and an ASAT value of 180 IU/l. The other donors had normal ALAT and ASAT values.

DISCUSSION

Non-A, non-B hepatitis remains the most important infectious complication of blood transfusion. It has been estimated that up to 95% of post-transfusion hepatitis cases are of type NANB. In a large multicentre study in the USA, 156 out of 1513 patients (10%) had NANB hepatitis after transfusion [1]. In another study in the USA, 35 out of 283 had NANB hepatitis (12.4%) [2]. The number of donors in the former study was 5564, i.e. 2.8% of them were infectious if it is presumed that each patient received only one infectious unit. The corresponding percentage in the latter study with 3359 donors was 1.1%. Similarly, in a Japanese study of 3735 transfusions, 116 out of 1082 patients got NANB hepatitis (10.7%), i.e. at least 3.1% of the donors were infectious [14]. The corresponding percentage of infectious donors, when calculated from a Dutch study, was approximately 1% [9].

NANB hepatitis has approximately the same incubation period as hepatitis B, but the acute phase of the infection seems to be somewhat milder [4, 8]. However, there is evidence that an appreciable number of NANB hepatitis cases develops into a chronic disease, with elevated transaminase values persisting for years [4].

In our series of 652 units of blood transfused to 65 patients, the frequency of NANB hepatitis was low. Only 4.6% of the patients got NANB hepatitis, which means that the proportion of infective blood units was 0.5%. This is about six times less than in the USA [1], and coincides with the clinical experience of blood transfusion in Finland. Hepatitis is known to be less prevalent in the northern parts of the world than it is in the southern parts, and in Finland blood transfusion has traditionally been based on a voluntary, non-remunerated national programme, which may, at least in part, explain this significant difference.

In our three patients the clinical course of the disease was typical of mild NANB hepatitis. None of them were icteric or had subjective symptoms, but the transaminase values remained high throughout the period of the follow-up. The incubation time of the infection was from 8 to 10 weeks, which is in accordance with earlier reports [3, 6, 8].

In addition to the three NANB hepatitis cases, four patients had mild transient elevations of the transaminase values. In addition three of them developed antibodies against cytomegalovirus, which is known at times to cause mild hepatic disease after open-heart surgery [11].

In Finland, there are annually approximately 150,000 transfusions of blood components. The Finnish Red Cross has organized a national program, and in recent years, the yearly amount of 0–3 cases of clinical transfusion hepatitis have been reported. Since 1978, none of the cases have been hepatitis B. However, if the frequency of infectious blood units is 0.5%, there should be at least 500 cases each year. This difference indicates that the vast majority of the cases are very mild and subclinical thus passing recognition.

Possible ways of preventing of NANB post-transfusion hepatitis have been recently discussed. There seem to be no good serological screening tests available, although several reports on antigen–antibody systems involved in NANB hepatitis have been reported [15]. Elevated ALAT values in blood donor samples are often associated with NANB hepatitis in the recipients, and screening of all blood donors for transaminase levels has been taken into consideration [1, 2]. However, the magnitude of this problem varies in different parts of the world, and it seems that, in this respect, blood transfusion is safer in Finland than in many other countries, even with an all voluntary, non-remunerated blood donor programme.

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