Natural History of Hepatitis C

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Hepatitis C virus (HCV) is the main cause of parenteral non-A/non-B hepatitis and was the major agent causing post-transfusion hepatitis. Since its discovery in 1989 (Choo et al. 1989) many isolates have been sequenced. HCV consists of a heterogeneous mix of isolates defined by genotype; each of which is further classified into subtypes (Simmonds 1998). So far about six genotypes and more than 100 subtypes have been defined (Fig. 1). HCV has a positive single stranded RNA genome of about 9,500 nucleotides in length and shows similarities to the genome organization of flavi and pesti viruses. Its single open reading frame (Fig. 2) includes three structural proteins: core and the two glycolysated putative envelope proteins E1 and E2. Previous reports suggest that E1 and E2 interact and form a complex which has been proposed to be a functional subunit of HCV virions.

From the six non structure proteins, the two protease NS2 and NS3 and the RNA dependent RNA polymerase NS5B have been characterized very well. The NS4A is an important cofactor for NS3 protease and seems to be important for the generation of replicative complexes within the infected cell. The c-terminal 456 amino acids of NS3 has in addition ATPase and RNA helicase activity. These activities have been suggested due to comparison of sequences to other helicases. The function of NS5A is not yet known. It can be found after expression in the periplasmatic membrane fraction of the nucleos and seems to be heavy phosphorylated. NS5A contained the sequence which is correlated to a sensitivity of HCV genotype 1b and interferon. NS5B contains a known amino acid sequence motive glycin, aspertate which is highly conserved in RNA dependent RNA polymerases. This gene product was early on thought to be the viral RNA polymerase of HCV. This has been proven in the recombinant barculo virus system. As there is no tissue cultures system to efficiently replicate HCV, several groups intended to generate *in vitro* replication systems. Recently, the group of Bartenschlager succeeded to generate replications in the Huh7 cell line which produce high amounts of viral RNA lacking the structural proteins (Lohmann et al. 2000).

HCV has become a major public health issue and is prevalent in most countries. HCV infection starts frequently without clinical symptoms, and progresses in the majority of patients (70 to 85%) to persistent viremia and chronic hepatitis including cirrhosis and hepatocellular carcinoma. A number of factors, which are important in predicting the outcome of disease progression, has been identified. This include age at infection, viral type/subtype, viral load, quasi species, male/female, and mode of transmission (EASL 1999). The mechanisms causing viral persistence after primary infection are not understood. One hypothesis is the inability to mount an efficient humoral and cellular response due to an immune escape mechanism of the highly variable virus. In the recent years chronic hepatitis C has caused high costs and is a leading cause of liver transplantation in the United States.

NATURAL HISTORY OF HEPATITIS C

The natural history and the prognosis of hepatitis C are still controversial. Prospective studies have not yet been conducted because of the predominantly asymptomatic onset of the disease. The existing studies differ in design, follow-up intervals, and in unintentional selection of progressive disease, therefore the knowledge on natural history of hepatitis C in the non-transfusion setting are limited (Hopf et al. 1990, Seeff et al. 1992, Vogt et al. 1999). Transfusion associated chronic hepatitis C may lead to cirrhosis in as much as 5 to 25% and to hepatocellular carcinoma in up to 8% of the cases after a chronic course over 20 years. Several large outbreaks of HCV infection have been reported recently. Among 710 Irish women with HCV antibodies only 55% had chronic viremic hepatitis C and 2% cirrhosis, after 17 years

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infection by contaminated anti-D immunoglobulin (Kenny-Walsh 1999). A similar outbreak has been observed in the former German Democratic Republic (East Germany) in 1978/1979 (Dittmann et al. 1991).

HISTORY OF THE HEPATITIS C OUTBREAK IN EAST GERMANY

The large outbreak of hepatitis C had occurred in 1978/1979 in East Germany caused by HCV contaminated anti-D immunoglobulin used for prophylaxis of Rhesus incompatibility. The source of infection in this immunoglobulin preparation could be traced back to a Rhesus positive woman, her erythrocytes had been used to boost five plasma donors for the preparation of anti-D immunoglobulin. This immunoglobulin preparation was prepared by combination of ethanol precipitation and exchange chromatography procedure. A total of 40 batches of anti-D immunoglobulin was produced and administered to 2,867 women throughout East Germany. After several cases of acute non-A/non-B hepatitis occurred, the source of the outbreak was identified on January 12th 1979. All women who had received anti-D immunoglobulin from contaminated batches were called to the regional outpatient clinics for ALT screening three times within three months. All who had shown an increase of ALT levels had received an official certificate for serum hepatitis caused by the anti-D immunoglobulin prophylaxis. They received financial compensation and medical follow-up in regional centres and treatment free of charge. The virus isolate AD78 was determined to belong to subtype 1b (Höhne et al. 1994).

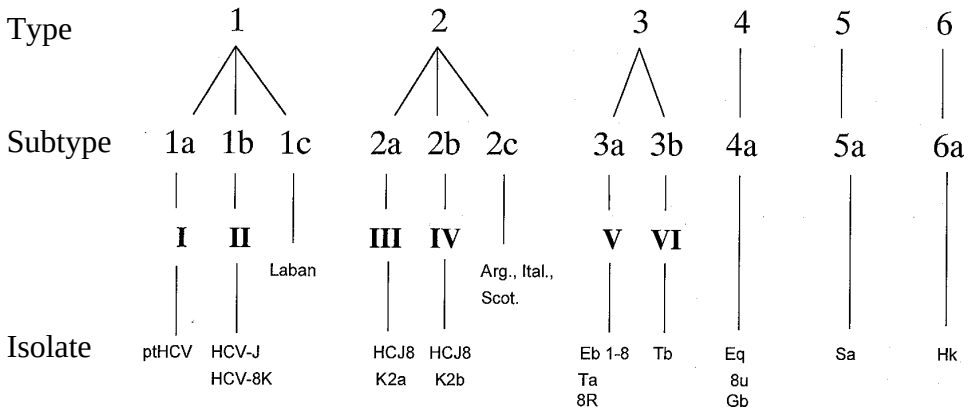

Fig. 1: nomenclature of hepatitis C virus genotypes and subtypres

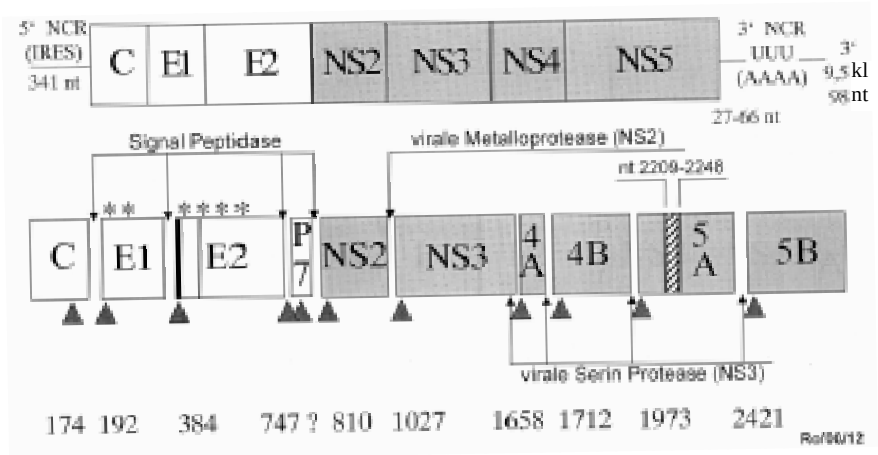

Fig. 2: hepatitis C virus - Genome Organization and viral structural and non-structural proteins

LONG-TERM FOLLOW-UP OF ANTI-D PATIENTS

In a long-term follow-up study women followed since infection were prospective. Clinical data and sera were collected for the acute course and once per year after HCV infection. Prospective screening had revealed an increase in ALT levels in 90% of these women within four months after intramuscular injection of HCV contaminated anti-D immunoglobulin. Forty-nine percent reported some symptoms but only 33% got medical care. Acute hepatitis took an icteric course in 22% of this cohort, a total of 101 women (10%) did not exhibit increased ALT levels after inoculation and were tested negative for markers of HCV (HCV RNA and anti-HCV negative) twelve to twenty years later (Weise et al. 2000).

Twenty years after infection, 85% of the cohort were still positive for anti-HCV and 49% had HCV RNA by polymerase chain reaction. Twenty years after acute HCV, 55% of all cases with documented acute hepatitis showed persistent viremia with HCV genotype 1b. Sustained clearance of HCV genotype 1b after IFN-α treatment was surprisingly high (29%), presumably because a favourable productive factors (young age) persistently elevated ALT levels in most women and probably a low concentration of HCV quasi species.

The viremic women had hepatitis of minimal or moderate grade in more than 83%. Septic fibrosis was present only in 3% and clinical evidence of cirrhosis was seen in less than 1% of the viremic women. Over all the rates of chronic hepatitis C and a progressive liver disease was surprising low in this cohort.

Most other prospective studies on the course of hepatitis C have observed a poorer outcome (Seeff et al. 1992, Kornetz et al. 1993). Acute transfusion associated hepatitis C let a cirrhosis in 8 to 24%. Genotype 1 infection in formally healthy persons which is considered as a worst subtype does not have a pure prognosis per se. HCV genotype, the size of viral inoculum, and the mode of transmission may be less important for the natural course than the immune status of the host at the time of infection. Similar observations have been made in a cohort of patients in a large outbreak of 704 HCV positive Irish women, 17 years after infection with HCV genotype 1b and anti-D immunoglobulin. These also exhibited a low disease activity (98 %) but high rates of progression to bridging septic fibrosis (15%) and cirrhosis (2%) (Kenny-Walsh 1999).

SEROLOGICAL FINDINGS DURING LONG-TERM FOLLOW-UP

Detailed serological survey revealed that antibodies to the different proteins of HCV persisted for different time periods during follow-up. There was no obvious difference in antibody response at onset in patients with asymptomatic, acute resolving, or chronic HCV infection. Antibodies were detected four to six weeks after inoculation. There was no obvious difference in antibody response at onset in patients with asymptomatic, acute resolving, or chronic HCV infection. Antibodies were detected four to six weeks after inoculation. The antibody titre in asymptomatic patients (Group A) at onset of disease was about 1:20, in acute resolving patients (Group B) 1:80. At 180 months after infection the antibody titre in group A was 1:10, however, in group B about 1:1,000. A hundred and twenty months after infection, there was a significant difference in antibody response in RIBA III in group A and C (chronic carriers) as compared to group B. There was not only a decrease in prevalence of antibodies but also the intensity of westernblots to different proteins showed significant differences. In the group of asymptomatic infections, only 11 out of 60 patients were still antibody positive (Fig. 3).

Antibodies against the core protein (c22) were in most cases the residual antibodies. Also antibodies to c33 persisted as a single marker and was present in quite a high number of patients. None of the patients had antibodies to NS5 as a single marker during follow-up (Fig. 3).

TRANSMISSION OF HCV FROM PROVIDER TO PATIENT

In the past, transfusion of contaminated blood and blood products was the main source of HCV transmission. Due to screening of blood donors this mode of HIV infection has been reduced significantly. Currently, in developed countries injecting drug-use accounts for the majority of all HCV infections (Alter 1997, Ross 2000). In general, a potential risk factor can be established for about 90% of all HCV cases. In the remaining 10%, however, no source of infection can be identified with certainty (CDC 1998), although as yet not well recognized modes of parenteral exposure are suspected. One of the concealed ways of contracting HCV infection could be the transmission from infected medical staff members to susceptible patients during medical care. Reports on provider-to-patient HCV transmission are scarce and in all known cases HCV positive surgeons performing cardiothoracic (Esteban et al. 1996, Duckworth et al. 1999) or gynaecological operations were found to be the probable source. One important lesson for the whole medical community from these cases therefore is to be permanently aware of the high risk of blood-borne pathogen transmission. This requires a high sense of responsibility from every

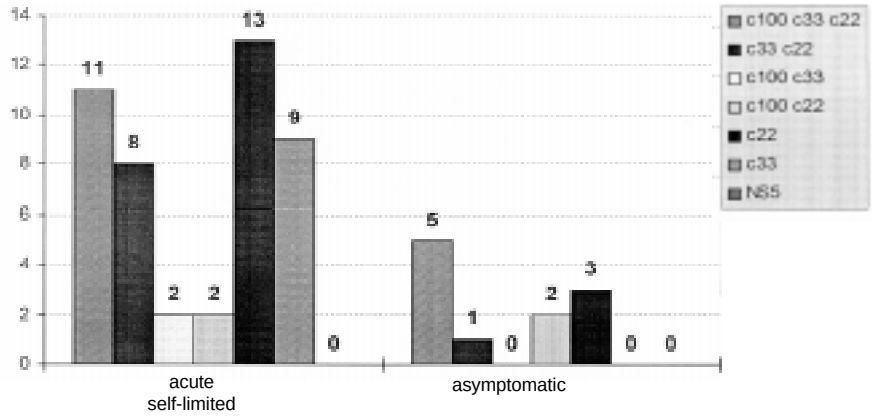

Fig. 3: anti-hepatitis C virus (HCV) pattern (RIBA 3.0) 15 years p.i. with HCV contaminated anti-D immunoglobulin

health care worker. The hospital management, on the other hand, has not only to establish appropriate hygienic guidelines and procedures, but also must implement a regular surveillance of the adherence to infection control precautions, in order to detect potential breaches and to prevent cases of blood-borne pathogen transmission.

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