Prevalence of Thrombocytopenia in Patients with Chronic Hepatitis C

Thesis
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Introduction

Hepatitis C virus (HCV) is a major cause of chronic liver disease with about 170 million people infected worldwide. The severity of disease varies widely from asymptomatic chronic infection to cirrhosis and hepatocellular carcinoma ***(Asselah et al, 2006).*** The overall prevalence of antibody to HCV in the general population in Egypt is around 15-20%. The risk factor for HCV transmission that specifically sets Egypt apart from other countries is the high rate of exposure to HCV as a consequence of parenteral anti-schistosomal therapy ***(Frank et al., 2000).***

Thrombocytopenia is defined as a platelet count less than 150.000/mm^3. Thrombocytopenia is a common finding in subjects with chronic hepatitis as HCV antibody-positive individuals are 2.6 times more likely to have a low platelet count than those who are HCV-antibody negative. However, controversy still exists concerning the mechanism of HCV-associated thrombocytopenia ***(Wang et al., 2004).*** Several

mechanisms have been proposed as contributing to thrombocytopenia: sequestration of platelets in the enlarged spleen (***Sanjo et al., 2003***), platelet destruction mediated by platelet-associated IgG possibly leading to the sequestration in the reticuloendothelial system and also related to hypersplenism (***Pockros et al., 2002 and Sanjo et al., 2003***), impaired hepatic production of thrombopoietin (TPO) (***Ishikawa et al., 1998 and Martin et al., 1997***) and a direct viral effect since a positive correlation between thrombocytopenia and HCV association with platelets has been found (***De Almeida et al., 2004***).

Thrombopoietin is the main stimulus for thrombopoiesis, regulates platelet production, stimulating megakaryocyte proliferation and maturation. It is produced primarily in the liver and degraded by circulating platelets ***(Streiff et al., 2002).***

Administration of thrombopoietin is currently under investigation for management of thrombocytopenia in patients with liver disease, or during treatment with interferon therapy to counteract the myelosuppressive effects of the drug ***(Garcia-Suarez et al., 2000).***

Aim of the work

To study the prevalence of thrombocytopenia in chronic hepatitis C patients.

Hepatitis C viral infection

Epidemiology of hepatitis C virus infection

Hepatitis C is a disease with a significant global impact. According to the World Health Organization (WHO) there are 170 million people infected with the hepatitis C virus (HCV), corresponding to 3% of the world's total population. There are considerable regional differences. In some countries, e.g., Egypt, the prevalence is as high as 20%. In Africa and the Western Pacific the prevalence is significantly higher than in North America and Europe ***Wasmuth J. (2009).***

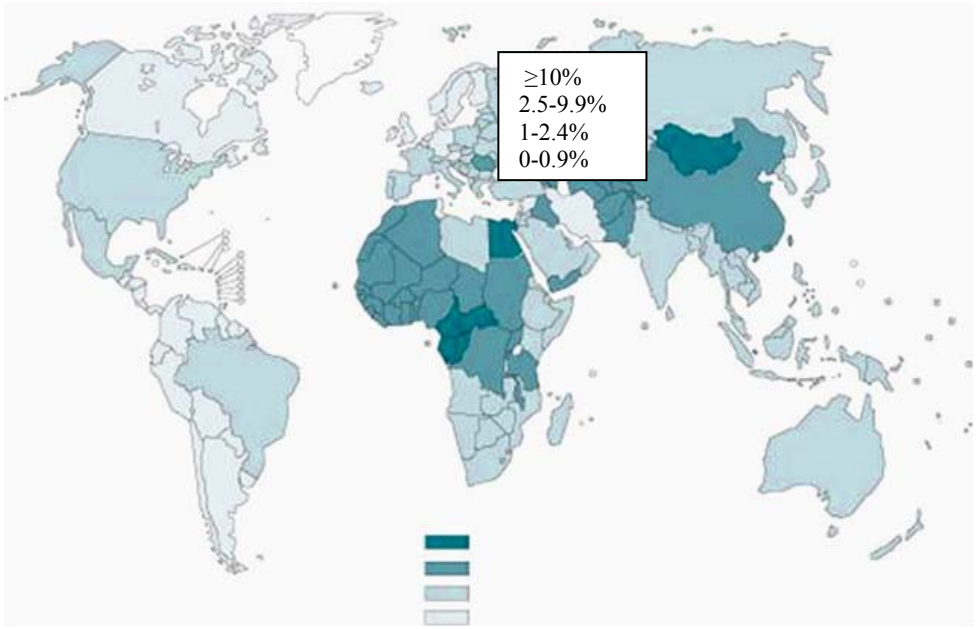

Figure 1: Global prevalence of hepatitis C.
Source: WHO, 2003(***Sharma & Sherker, 2009)***.

It is difficult to determine the number of new HCV infections, as most acute cases will not be noticed clinically. Fewer than 25% of acute cases of hepatitis C are clinically apparent. In addition, the age of infection upon diagnosis is not possible to determine in most cases.

Nevertheless, it has to be assumed that the number of new infections have considerably decreased over the past decades. For the United States it is estimated that the number of new cases of acute HCV infection has fallen from approximately 230,000 per year in the 1980s to about 20,000 cases per year currently ***(Wasley et al ., 2008).***

The causative agent and virology

Hepatitis C virus (HCV) is a small enveloped positive sense RNA virus with a diameter of 50 nm .It belongs to the family Flaviviridae and is the sole member of the genus hepacivirus. It has a single stranded RAN genome ***(Lauer and Walker, 2001).***

The genome of the hepatitis C virus consists of one 9.6 kb single-stranded RNA molecule with positive polarity. Similar to other positive-strand RNA viruses, the genomic RNA of hepatitis C virus serves as messenger RNA (mRNA) for the translation of viral proteins ***(Kupfer, 2009).***

The linear molecule contains a single open reading frame (ORF) coding for a precursor polyprotein of approximately 3000 amino acid residues (Figure 2).

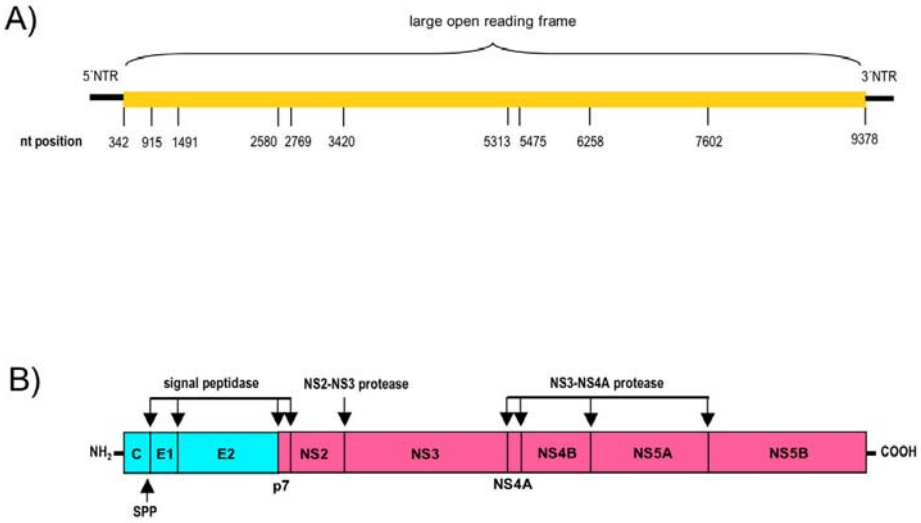

Figure 2: Genome organization and polyprotein processing ***(Kupfer, 2009).***

A) Nucleotide positions correspond to the HCV strain H77 genotype 1a, accession number NC_004102. nt, nucleotide; NTR, nontranslated region.

B) Cleavage sites within the HCV precursor polyprotein for the cellular signal peptidase the signal peptide peptidase (SPP) and the viral proteases NS2-NS3 and NS3-NS4A, respectively

During viral replication the polyprotein is cleaved by viral as well as host enzymes into three structural proteins (core, E1, E2) and seven nonstructural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B). An additional protein (termed F [frameshift] or ARF [alternate reading frame]) has been predicted as a result of ribosomal frameshifting during

translation within the core-region of the genomic RNA ***(Branch et al ., 2005) .***

The structural genes encoding the viral core protein and the viral envelope proteins E1 and E2 are located at the 5' terminus of the open reading frame followed downstream by the coding regions for the non-structural proteins p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B (Figure 2). The structural proteins are essential components of the HCV virions, whereas the non-structural proteins are not associated with virions but are involved in RNA replication and virion morphogenesis.

The ORF is flanked by 5' and 3' nontranslated regions (NTR; also termed untranslated regions – UTR or noncoding regions - NCR) containing nucleotide sequences relevant for the regulation of viral replication. Both NTRs harbor highly conserved regions compared to the protein encoding regions of the HCV genome. The high grade of conservation of the NTRs makes them candidates

i) For improved molecular diagnostics,

ii) As targets for antiviral therapeutics

iii) As targets for anti- HCV vaccines ***(Kupfer, 2009).***

Transmission

Parenteral exposure to the hepatitis C virus is the most efficient means of transmission. Accordingly, the majority of patients infected with HCV in Europe and the United States acquired the disease through intravenous drug use or blood transfusion ***(Wasmuth, 2009).***

The latter has become rare since routine testing of the blood supply for HCV began in the early 1990s. Other types of parenteral exposure are important in specific regions in the world. The following possible routes of infection have been identified in anti-HCV positive blood donors (in descending order of transmission risk):

- Injection drug use
- Blood transfusion
- Sex with an intravenous drug user
- Having been in jail more than three days
- Religious scarification
- Having been struck or cut with a bloody object
- Pierced ears or body parts
- Immunoglobulin injection

Very often in patients with newly diagnosed HCV infection no clear risk factor can be identified (***Wasmuth, 2009).***

1. **Injection drug use**

Injection drug use has been the most commonly identified source of acute HCV infection. It is estimated that most newly acquired infections occur in individuals who have injected illegal drugs ***(Sutton et al., 2008).***

2. **Blood transfusion**

In the past, blood transfusion or use of other blood products was a major risk factor for transmission of HCV. The risk is now estimated to be between 1:500,000 and 1:1,000,000 units **(*Pomper et al., 2003)***.

3. **Organ transplantation**

Transplant recipients who receive organs from HCV-positive donors have a high risk of acquiring HCV infection. Transmission rates in different cohorts vary from 30 to 80% ***(Roth et al., 1994).***

4. **Sexual or household contact**

The efficiency of HCV transmission by sexual contact is very low. However, there is no doubt that sexual transmission of hepatitis C is possible.

The exact risk of HCV transmission in monogamous heterosexual relationships has been difficult to determine. It appears that the risk in long-term partnerships is very Low. In prospective cohorts of monogamous, heterosexual couples, there was a long-term transmission risk of 0.01% or lower ***(Vandelli et al., 2004).***

5. **Perinatal transmission**

The risk of perinatal transmission of HCV in HCV RNA positive mothers is estimated to be 5% or less. In mothers coinfected with HIV this risk correlates with immunosuppression and has been described to reach up to 20%. Today, there are no specific recommendations for prevention of perinatal transmission ***(Pembrey et al., 2005).***

6. **Hemodialysis**

Patients who participate in chronic hemodialysis programs are at increased risk for hepatitis C. The prevalence of HCV antibodies in such patients reaches 15%, though it has declined in recent years ***(Fissell et al., 2004).***

7. **Needle-stick injury**

There is some risk of HCV transmission for health care workers after unintentional needle stick injury or exposure to other sharp objects. The incidence of seroconversion after exposure to an HCV-positive source is generally estimated to be less than 2% ***(Anonymous, 2001).***

8. **Other rare transmission routes**

Rare sources of percutaneous transmission of HCV are contaminated equipment used during medical procedures, procedures involved in traditional medicine (e.g., scarification, cupping), tattooing, and body piercing (***Haley &Fischer, 2001).***

Clinical manifestations and natural history of HCVInfection

Effective investigation of the natural history of a disease requires specific information including the identification of disease onset, method of differentiating between acute and chronic disease, and the ability to track disease morbidity and mortality without the influence of comorbid conditions and/or treatment ***(Seeff, 2002).***

With regard to hepatitis C, the onset of disease is rarely known and patients often have comorbid conditions and available treatment options that can alter the natural course of the infection ***(Sharma & Sherker, 2009).***

Acute hepatitis

The average incubation period of acute hepatitis C, as determined in prospective studies of post-transfusion hepatitis, is 7–8 weeks, but the range varies widely (from 2 to 26 weeks or more) ***(Barrera et al., 1995).***

HCV viraemia is the first marker to become detectable during acute hepatitis C; it is demonstrable by sensitive PCR as early as 1 week after exposure. Viraemia then persists without an antibody response for a variable window period before anti-HCV seroconversion ***(Alter et al., 1992).***

The onset of liver damage, marked by variable ALT elevations, is always delayed with respect to the appearance of

viraemia and may either precede or follow seroconversion to anti-HCV.

Patients rarely have prodromic symptoms or fever. The acute phase of hepatitis C is often mild and usually less severe than hepatitis A and B; more than two-thirds of cases are asymptomatic and anicteric. A severe or fulminant course of acute hepatitis C rarely occurs, except in patients with immunodeficiency, pre-existing liver disease or the presence of other cofactors, such as hepatitis A or B or intravenous drug use.

The clinical profile of symptomatic acute hepatitis C is the same as that of any type of viral hepatitis and is often indistinguishable from hepatitis A and B. Symptomatic cases present with malaise, dark urine, nausea (with or without vomiting), abdominal discomfort and/or jaundice***(Alberti & Benvegnù .,2007).***

Chronic Hepatitis C

Chronic hepatitis C is defined as the persistence of HCV RNA viraemia for at least 6 months. Potential clinical outcomes for persons with chronic hepatitis C include cirrhosis, hepatocellular carcinoma, and death.

Progression from acute to chronic HCV occurs in 54 - 90% patients ***(Rodger et al., 2000)***.

It is unclear why infection with HCV results in chronic infection in most cases. Genetic diversity of the virus and its tendency toward rapid mutation may allow HCV to constantly

escape immune recognition. Host factors may also be involved in the ability to spontaneously clear the virus. Factors that have been associated with successful HCV clearance are HCV specific CD4 T-cell responses, high titers of neutralizing antibodies against HCV structural proteins, and specific HLA-DRB1 and DQB1 alleles ***(Lauer & Walker, 2001).***

Most patients with chronic infection are asymptomatic or have only mild nonspecific symptoms as long as cirrhosis is not present ***(Lauer & Walker, 2001).***

The most frequent complaint is fatigue. Less common manifestations are nausea, weakness, myalgia, arthralgia, and weight loss. HCV infection has also been associated with cognitive impairment. All these symptoms are non-specific and do not reflect disease activity or severity ***(Merican et al., 1993).***

Cirrhosis and hepatic decompensation

The risk of developing cirrhosis within 20 years is estimated to be around 10 to 20%, with some studies showing estimates up to 50% ***(De Ledinghen et al .,2007).***

Due to the long course of hepatitis C the exact risk is very difficult to determine, and figures are divergent for different studies and populations. In fact, chronic hepatitis C is not necessarily progressive in all affected patients. In several cohorts it has been shown that a substantial number of patients will not develop cirrhosis over a given time. It is estimated that