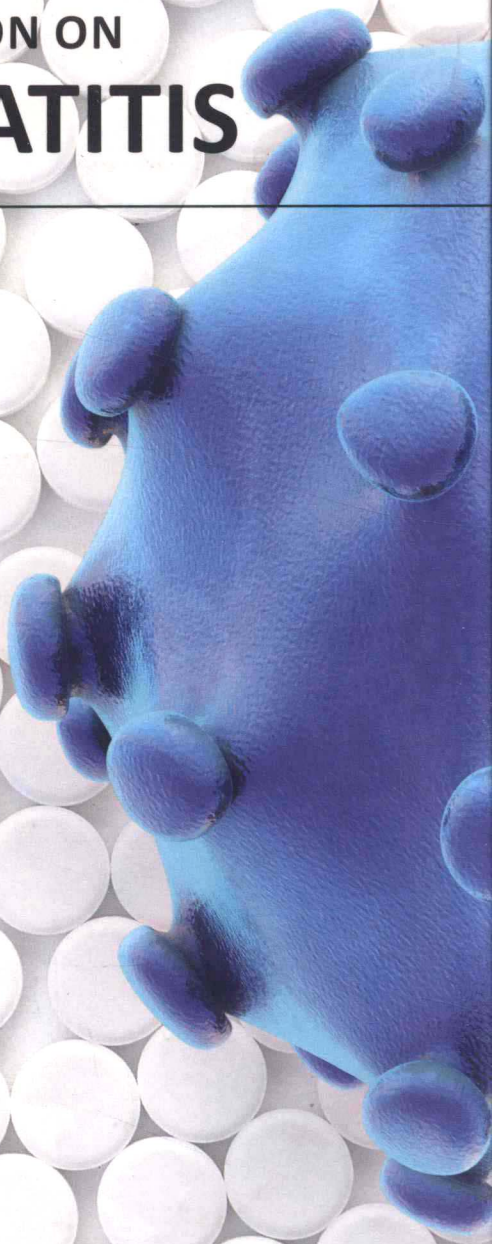
RESEARCH COLLECTION ON

VIRAL HEPATITIS



INTECH

RESEARCH COLLECTION ON VIRAL HEPATITIS

Research Collection on Viral Hepatitis

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Chapters from books edited by: **Gaetano Serviddio** and **Sergey Mukomolov**

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Preface

Millions of people across the world have to live with hepatitis virus infection, whether in acute or chronic form. The variety of transmission routes and the range of severe complications, together with the fact that some types of hepatitis infection can remain asymptomatic for many years, presents particular challenges for effective prevention, treatment and management.

A key topic discussed in this book is the practical management of chronic viral hepatitis, including the role played by viral genotype in the initial choice of treatment and the likely outcome. Reference will also be made to diagnostic techniques such as radiology and its use in assessing liver fibrosis.

In addition, the book will cover selected issues relating to pathogenesis and diagnostics, including epidemiology and molecular structure, as well as the mechanisms of immune response.

This book is a comprehensive reference work for clinicians and researchers in a variety of medical fields including virology, hepatology, immunology and public health, and will also be of interest to decision-makers in governmental healthcare departments.

PRACTICAL MANAGEMENT OF CHRONIC VIRAL HEPATITIS

Edited by **Gaetano Serviddio**

Genomic Heterogeneity of Hepatitis Viruses (A-E): Role in Clinical Implications and Treatment

Zahid Hussain

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/55231

1. Introduction

Hepatitis is an inflammation of the liver. There are at least five different viruses causing hepatitis. Each of the five major hepatitis viruses, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), delta hepatitis virus (HDV) and hepatitis E virus (HEV) belong to a separate family. Currently, all these viral hepatitis (A-E) have been classified into different genotypes and subgenotypes. Several factors, including viral genotypes have been reported to be associated with disease progression and treatment response. Consequently, documentation of genotype recently have been proved to be a valuable tool not only for epidemiological reasons but also for clinical implications and treatment.

2. Hepatitis A virus

HAV is a member of the *Hepatovirus* genus of *Picornaviridae* family. HAV is a non-enveloped (naked), linear, single stranded RNA virus of an icosahedral symmetry measuring 27-32 nm in diameter [1]. HAV infection is hyper-endemic in vast areas of the world, with approximately 1.5 million clinical cases per year [2]. The worldwide distribution is uneven and is based on determinants such as socioeconomic conditions and geographic factors [3-5]. In developing countries, the incidence of disease in adults is relatively low because of exposure to the virus in childhood. Most adults in these areas show prevalence of antibodies against hepatitis A. In developed world endemicity is usually very low and clinical cases occur almost exclusively in adults [6,7]. The variable age distribution among hepatitis A patients in developing and developed countries is a consequence of differing standards of hygiene and sanitation. In many developing countries, improved hygiene standards and socio-economic conditions have led

to a reduction in exposure to HAV in childhood and hence large non-immune adult population in the community. This leads to a shift or transition from asymptomatic childhood infections to an increased incidence of symptomatic or clinical disease in adults [8]. The persistence of circulating HAV may lead to hepatitis A outbreaks in susceptible non-immune adult population [8,9].

2.1. Disease severity

HAV causes an acute self-limited illness. The vast majority of hepatitis A patients make a full recovery and fatality rate is low. The estimated mortality rate is 0.1% for children less than 15 years old, 0.3% for adults ages 15 to 39, and 2.1% for adults ages 40 and old [10,11]. HAV does not lead to chronic hepatitis or a carrier state and only rarely leads to fulminant hepatic failure (FHF) [12]. FHF occurs during the first 4-6 weeks of illness which is characterized by sudden onset of high fever, marked abdominal pain, vomiting and jaundice followed by development of hepatic encephalopathy associated with deep coma and seizures [13,14]. Mortality is highly correlated with increasing age, survival being rare over the age 45 years [15]. The acute HAV super infection with chronic liver disease is also associated with severity and high mortality [16,17].

2.2. Genomic organization

Like all picornaviral genomes, HAV is divided into three parts: (i) 5′ non-coding region (NCR) that comprises approximately 10% of the genome (ii) single open reading frame (ORF) of 2227 amino acids, that encode all the viral proteins, with regions designated as P1 for capsid proteins, P2 and P3 for non-structural proteins and (iii) short 3′ non-coding region (Fig. 1).

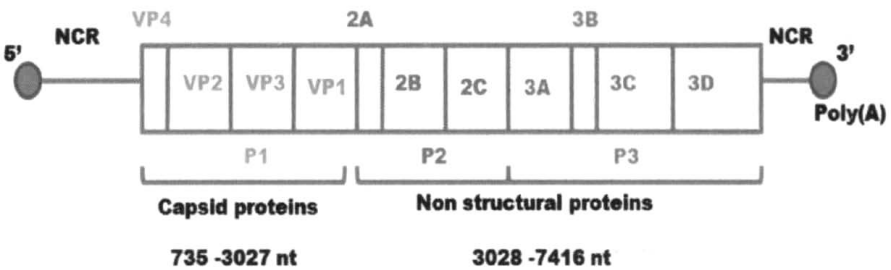

Figure 1. Genomic organization of hepatitis A virus: HAV genome is divided into a 5′ non-coding region (5′ NCR), a giant open reading frame, and a 3′ non-coding region (3′ NCR). The coding region is subdivided into regions P1, P2 and P3. (Adapted from: Ref. 20)

HAV RNA genomes lack the cap assembly found at the 5′ end of mRNA species that normally guides the ribosomal complex to the translation start site [18]. Instead, an internal ribosome entry site (IRES) formed by the 5′NCR functions to initiate translations in HAV including other picornaviruses [19, 20]. However, unlike other picornavirus IRESes, the HAV IRES requires an intact eukaryotic initiation factor 4G for its optimal activity [20]. Several other host proteins

are found to be associated with synthetic RNAs representing segments of the 5′ NCR [21]. The viral capsid protein (P1) is further divided into VP4, VP2, VP3 and VP1 regions. The non-structural P2 and P3 polyproteins are divided into 2A, 2B, 2C and 3A, 3B, 3C, 3D respectively (Fig. 1). HAV polyprotein is processed into precursor intermediates and mature proteins by the proteolytic activities of encoded viral proteins. HAV 2A, 2B, 2C protein encodes 45, 251 and 335 amino acids respectively. The 2A and 3C are identified as processing enzyme in hepatitis A virus. The translated 2A regions function as intermediary, partially located on the surface (VP1) and some are assembled inside the virion [20]. Both 2B and 2C proteins play an important role in the replication of the viral RNA. P3 polyproteins encodes 3A, 3B, 3C and 3D proteins with 74, 23, 219 and 489 amino acids respectively. 3C protein acts as sole protease for HAV protein processing, while 3D is the RNA dependent RNA polymerase [22].

2.3. HAV genotypes and geographic distribution

Genetic heterogeneity of hepatitis A has been revealed by sequencing different genome regions, including VP3 carboxyl terminus, the VP1 amino terminus and the VP1/2A junction [23-25] (Fig. 2). The VP3 C-terminal region is relatively conserved, the VP1 amino acid terminus presents an intermediate variability, while VP1/2A junction is more variable and is used to distinguish one strain from another [25]. The genetic variability observed within the putative VP1/2A junction (168 nucleotides) initially defined seven (I-VII) genotypes [26-29]. However, recently new classification of HAV has been done based on the complete sequences of the 900 nucleotides of VP1 region [30] (Fig. 2).

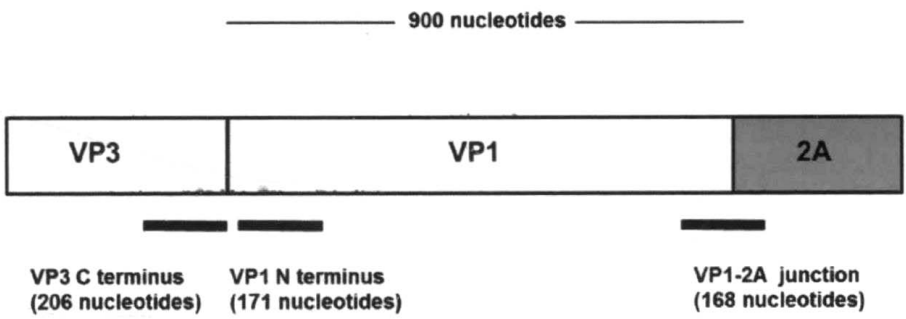

Figure 2. The genomic organization of VP3 C-terminal, the VP1 amino acid terminal and VP1/2A junction region of hepatitis A virus. The complete sequence of the 900 nucleotides of the VP1 gene has been used for new classification of HAV. (Adapted from: Ref. 30)

The phylogenetic analyses of VP1 sequences identified six genotypes (I-VI) that differ among themselves 15-25%. Three isolated from humans (I-III) and three from a simian origin (IV-VI). The genotypes I, II and III were further subdivided into sub-genotypes A and B, which differ in approximately 7.5% of base positions. The worldwide genotype distribution showed genotype I and III comprise the vast majority of human strains within the studied population (Fig. 3). Sub-genotype IA comprises the majority of the human strains studied and constitutes