Distribution of hepatitis C virus genotypes in the Middle East

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Introduction

In 1999, the World Health Organization (WHO) estimated that 170 million individuals were chronically infected with the hepatitis C virus (HCV) worldwide.1 Furthermore, it is now well established that hepatitis C develops into cirrhosis of the liver and hepatocellular carcinoma (HCC) both of which are fatal diseases.2–6 These facts clearly indicate that HCV is an important public health problem globally.

To date, numerous data have been accumulated on the epidemiology of HCV infection.7,8 Accumulated data show that HCV genotypes vary in their distribution, which may have clinical significance.9–11 The WHO estimates that there are at least 21.3 million HCV carriers in the Eastern Mediterranean countries, which is close to the number of carriers estimated in the Americas and Europe combined. With such a high disease burden of HCV infection in this part of the world, and in light of the new evidence that genotypes may influence the outcome of antiviral therapy, the focus of this review is on the epidemiology and distribution of HCV genotypes in the Eastern Mediterranean countries. Accumulated data show that there are two main patterns for the distribution of HCV genotypes in the Middle East: in the first pattern, genotype 4 is prevalent in most of the Arab countries, and in the second pattern, genotype 1a or 1b predominates in the non-Arab countries. Results from the limited number of clinical trials on the treatment of chronic HCV genotype 4 using peginterferon alfa-2b in combination with ribavirin are encouraging. However, efforts to develop more effective antiviral therapies and the establishment of an effective HCV vaccine remain the largest challenges for the near future.

Summary

It is well established that hepatitis C develops into cirrhosis of the liver and hepatocellular carcinoma (HCC) both of which are fatal diseases. The World Health Organization estimates that there are at least 21.3 million hepatitis C virus (HCV) carriers in the Eastern Mediterranean countries, which is close to the number of carriers estimated in the Americas and Europe combined. With such a high disease burden of HCV infection in this part of the world, and in light of the new evidence that genotypes may influence the outcome of antiviral therapy, the focus of this review is on the epidemiology and distribution of HCV genotypes in the Eastern Mediterranean countries. Accumulated data show that there are two main patterns for the distribution of HCV genotypes in the Middle East: in the first pattern, genotype 4 is prevalent in most of the Arab countries, and in the second pattern, genotype 1a or 1b predominates in the non-Arab countries. Results from the limited number of clinical trials on the treatment of chronic HCV genotype 4 using peginterferon alfa-2b in combination with ribavirin are encouraging. However, efforts to develop more effective antiviral therapies and the establishment of an effective HCV vaccine remain the largest challenges for the near future.

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KEYWORDS

Hepatitis C virus; Genotypes; Middle East; Epidemiology
estimated in the Americas (13.1 million) and Europe (8.9 million) combined. Indeed, one of the highest prevalences of HCV infection (18.1%) has been reported from Egypt, a Middle Eastern country. With such a high disease burden of HCV infection in this part of the world and in light of the new evidence that genotypes may influence the outcome of antiviral therapy, the focus of this review is on the epidemiology of HCV infection and distribution of HCV genotypes in the Eastern Mediterranean countries and possible implications for the future. However, since there have been dramatic advances in the diagnosis of HCV infection during the past decade, this article first reviews the molecular organization and the genetic diversity of the HCV genome, and then highlights the significance and reliability of the tests available for testing and confirmation of HCV genotypes.

HCV genome

Genomic organization

HCV is an aspheric, enveloped virus classified in the Hepacivirus genus of the Flaviviridae family. The viral genome is a single stranded linear RNA of positive sense. The genome is approximately 9.6 kb in size and contains an open reading frame (ORF) flanked by both a 5'- and 3'- non-coding region (NC). Immediately downstream of the 5’ NC is the single ORF, which encodes a large protein polyprotein precursor. This precursor is subsequently cleaved by host and viral proteases into various structural and nonstructural proteins. The structural proteins are at the 5’ end and include the capsid or core protein (c), two envelope proteins (E1 and E2) and a small protein of unknown function (P7). The structural proteins are followed by at least six nonstructural (NS) proteins denoted as NS2, NS3, NS4A, NS4B, NS5A, and NS5B.

Genetic diversity of the HCV genome

Although both the 5’ and 3’ NC of the HCV genome possess highly conserved terminal sequences, HCV is characterized by a high degree of genetic heterogeneity and as such it is similar to other RNA viruses. The most heterogeneous regions of the genome are the genes encoding the two envelope proteins, E1 and E2. The N terminus of the E2 gene contains the most variable region of the entire genome and has been referred to as the first hypervariable region (HVR1). A second hypervariable region, referred as HVR2, is located just 3’ of HVR1. This genetic heterogeneity of HCV has been classified into four hierarchical strata: genotypes, subgenotypes (subtypes), isolates, and quasi-species. The degree of nucleotide sequence variation for each stratum (expressed as a percentage) is 30–50%, 15–30%, 5–15%, and 1%, respectively.

A total of eleven major genotypes, designated according to the order of their discovery have been identified and more than 90 subtypes have been described. An increasing number of novel subtypes is emerging and more detailed phylogenetic analysis of these isolates is recommended.

Testing for HCV genotypes

Many methods have been used for HCV genotyping including genomic amplification and sequencing, restriction fragment length polymorphism (RFLP) of the PCR amplifications and differential hybridization. Among these direct methods, genomic amplification and sequencing, followed by sequence comparison and phylogenetic tree construction for confirmation is considered the gold standard. The genomic regions commonly used in this approach include core, E1, NS5 and 5’ NC.

More recently, HCV genotyping has been determined indirectly by testing for type-specific antibodies with a competitive enzyme immunoassay. However, although comparative analysis has shown a good overall agreement between serotyping and molecular genetic analysis the sensitivity of PCR-based assays over serologic assays has been distinctly higher.

Epidemiology of HCV genotypes

Worldwide

The worldwide distribution of HCV genotypes and their subtypes is shown in Table 1. Genotypes 1, 2, and 3 are the most frequently encountered genotypes worldwide. However, significant differences are noticed when subtype distribution is investigated. In North America and Northern Europe, 1a is the most common subtype followed by 2b and 3a. In contrast to Tunisia subtype 1b, although the most prevalent, had lower prevalences (47–48%) but a higher circulation of genotype 2 (29–37%). The pattern in Tunisia is reminiscent of that in Japan where subtype 1b accounts for 73% followed by genotype 2 (20%) and subtype 1a (2%).

Genotypes other than 1, 2, and 3 are actually more common among HCV-infected people in other parts of the world. Genotype 4 seems to be confined to the Middle East and Central Africa, while HCV genotype 5 has been isolated almost exclusively in South Africa where it predominates, followed by genotypes 1, 2, 3, and 4, respectively. Genotype 6 has been isolated in Hong Kong, Vietnam and throughout South East Asia. In one study from Vietnam, genotype 1 was the most common genotype followed by genotypes 6–9 and genotype 2. HCV genotypes 7, 8, and 9 have been identified mainly in Vietnamese patients, while genotypes 10 and 11 have been reported from Indonesia. It has been suggested that genotypes 7–11 are variants of the same group and should be classified as members of genotype 6.

It is interesting to note that in the Philippines, HCV subtype distribution is similar to that seen in North America and Northern Europe, where subtype 1a is the most common followed by 1b, 2a and 2b.
Middle East

Distribution of HCV genotypes and subtypes in the Middle East\textsuperscript{59–76} is shown in Table 2. Surprisingly, the accumulated data show that there are two main patterns for the distribution of HCV genotypes: one is peculiar to the Arab countries (except for Jordan) where genotype 4 predominates, while the other pattern is characteristic of the non-Arab countries (Turkey, Israel, and Iran) where genotype 1 predominates. Although varying prevalences of genotype 4 have been reported from the Arab countries, it is noteworthy that genotype 4 is quasi-exclusive (91%) in Egypt which is also a North African country.\textsuperscript{59–61} Based on only one known study in Jordan, 1a is the dominant subtype (40%) followed by 1b (33.3%) and genotype 4 (26.6%).\textsuperscript{63}

In Turkey\textsuperscript{75,76} and in Israel\textsuperscript{62,74} subtype 1b is the dominant subtype (>70%) followed by 1a, similar to the pattern seen in Eastern and Southern Europe.\textsuperscript{38,39} Subtype 1a is the most common subtype in Iran followed by 3a, 1b, and 4.\textsuperscript{72,73}

The two different patterns for the distribution of HCV genotypes in the Middle East are evident in the study conducted to determine genotypes of HCV in the Gaza Strip and Southern Israel.\textsuperscript{62} The Gaza Strip borders the southern part of Israel and Egypt, and a few thousand inhabitants cross the border daily from Gaza to both countries. The most common genotypes found were type 1b (62%) in Southern Israel and type 4 (78%) in the Gaza Strip, corresponding to the most prevalent genotype in Egypt.\textsuperscript{64} The high similarity between type 4 isolates from Gaza Strip and Egypt was demonstrated by sequence analysis of the HCV 5' NC region.\textsuperscript{62} Subtype 1b in Israel was followed by subtypes 1a, 2a/2c, and 3a, respectively, and no genotype 4 was found.\textsuperscript{62}

Although genotype 4 is generally uncommon in Western countries, varying prevalences have been reported in Southern Europe,\textsuperscript{77–79} During the past two years it has become evident that the number of patients infected with HCV genotype 4 in Europe\textsuperscript{80,81} and the USA,\textsuperscript{82} and most recently in Southern India,\textsuperscript{83} is rising. This emerging pattern might reflect changing immigration patterns in those areas.

Table 1 Worldwide distribution of hepatitis C virus genotypes and subtypes

<table>
<thead>
<tr>
<th>Region</th>
<th>Genotype/subtype</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Most common</td>
<td>Less common</td>
</tr>
<tr>
<td>North America</td>
<td>1a</td>
<td>1b, 2b, 3a</td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern Europe</td>
<td>1a</td>
<td>1b, 2, 3a</td>
</tr>
<tr>
<td>Southern and Eastern Europe</td>
<td>1b</td>
<td>1a, 2, 3, 2c</td>
</tr>
<tr>
<td>Japan</td>
<td>1b</td>
<td>2a, 2b, 3b</td>
</tr>
<tr>
<td>Africa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North Africa\textsuperscript{*}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tunisia</td>
<td>1b</td>
<td>1a, 2a, 2b, 3a, 4</td>
</tr>
<tr>
<td>Morocco</td>
<td>1b</td>
<td>2a, 2c, 1a</td>
</tr>
<tr>
<td>Central Africa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabon</td>
<td>4</td>
<td>1a, 1b, 2a, 2b</td>
</tr>
<tr>
<td>Nigeria</td>
<td>1, 4</td>
<td>2</td>
</tr>
<tr>
<td>Cameroon</td>
<td>4</td>
<td>1, 2</td>
</tr>
<tr>
<td>South Africa</td>
<td>5</td>
<td>1, 2, 3 and 4</td>
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<td>South East Asia</td>
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</tr>
<tr>
<td>Throughout the region</td>
<td>1</td>
<td>6, 7, 8, 9, 2</td>
</tr>
<tr>
<td>Vietnam, Thailand and Myanmar</td>
<td>7, 8, 9</td>
<td>10, 11</td>
</tr>
<tr>
<td>Indonesia</td>
<td>10, 11</td>
<td>1a</td>
</tr>
<tr>
<td>Philippines</td>
<td>1a</td>
<td>1b, 2a, 2b</td>
</tr>
</tbody>
</table>

\* Excluding Egypt.

Table 2 Distribution of hepatitis C virus genotypes and subtypes in the Middle East

<table>
<thead>
<tr>
<th>Region</th>
<th>Genotype/subtype</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Most common</td>
<td>Less common</td>
</tr>
<tr>
<td>Arab countries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egypt</td>
<td>4</td>
<td>1a, 1b, 2a</td>
</tr>
<tr>
<td>Gaza Strip</td>
<td>4</td>
<td>1, 3a</td>
</tr>
<tr>
<td>Jordan</td>
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<tr>
<td>Lebanon</td>
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<td>Saudi Arabia</td>
<td>4</td>
<td>1a, 1b, 3a</td>
</tr>
<tr>
<td>Syria</td>
<td>4</td>
<td>1b, 1a</td>
</tr>
<tr>
<td>Non-Arab countries</td>
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<td></td>
</tr>
<tr>
<td>Iran</td>
<td></td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>1a</td>
<td>1b</td>
</tr>
<tr>
<td>North West</td>
<td>3a</td>
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</tr>
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<td>Israel</td>
<td>1b</td>
<td>1a, 2</td>
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<tr>
<td>Turkey</td>
<td>1b</td>
<td>1a</td>
</tr>
</tbody>
</table>
Implications for the future

Clinical significance of HCV genotypes

The significance of HCV genotyping as an epidemiological marker has been clearly substantiated, particularly in tracing the sources of infection and elucidating the possible modes of transmission. However, the issue of pathogenicity of the different genotypes/subtypes is still controversial. Several environmental, genetic, and immunological factors may contribute to the profound differences in disease progression observed in HCV infected patients. Therefore, long-term prospective studies in various population groups are still needed to generate reliable data on the clinical significance of HCV genotypes.

Antiviral therapy

In addition to the importance of HCV genotyping as an epidemiological marker, most investigators agree on the significance of HCV genotypes as independent predictors of response to antiviral therapy. Major clinical trials of antiviral therapy for chronic HCV have been performed in Western countries and in Japan. Hence, existing published data largely deal with patients with HCV genotypes 1, 2, and 3, and there are now clear-cut guidelines for the type of treatment and duration of antiviral therapy in such patients. However, there have been relatively few studies that have targeted patients infected with HCV genotype 4, and combination therapy clinical trials (interferon and ribavirin) for these patients have not been promising. Encouraging results are now being reported on the efficacy of peginterferon in combination with ribavirin given for 48 weeks for the treatment of chronic hepatitis caused by HCV genotype 4 with a sustained virologic response ranging from 63 to 82%. It is evident that more randomized controlled trials of the combined peginterferon plus ribavirin are needed to assess the optimal dosage and duration of therapy and for the eventual establishment of appropriate treatment protocols for these patients.

Challenges

It is now clear that HCV genotype 4 is the predominant genotype in the Middle East where one-fifth of the estimated 170 million HCV carriers live. In addition to the possible development of the infection into cirrhosis and HCC, it has been recently observed that there is an increased risk of liver-related death and demand for liver transplantation in patients infected with HCV genotype 4. These facts indicate that the treatment of carriers and prevention of HCV infection are very urgent problems. Efforts to develop more effective antiviral therapies and the establishment of an effective HCV vaccine remain the largest challenges for the near future.

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Conflict of interest: No conflict of interest to declare.

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