Review

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Management of hepatitis C virus genotype 4: Recommendations of An International Expert Panel

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HCV has been classified into no fewer than six major genotypes and a series of subtypes. Each HCV genotype is unique with respect to its nucleotide sequence, geographic distribution, and response to therapy. Genotypes 1, 2, and 3 are common throughout North America and Europe. HCV genotype 4 (HCV-4) is common in the Middle East and in Africa, where it is responsible for more than 80% of HCV infections. It has recently spread to several European countries. HCV-4 is considered a major cause of chronic hepatitis, cirrhosis, hepatocellular carcinoma, and liver transplantation in these regions. Although HCV-4 is the cause of approximately 20% of the 170 million cases of chronic hepatitis C in the world, it has not been the subject of widespread research. Therefore, this document, drafted by a panel of international experts, aimed to review current knowledge on the epidemiology, natural history, clinical, histological features, and treatment of HCV-4 infections.

Introduction

Hepatitis C virus (HCV), a member of the Flavivirida family of RNA viruses, is characterized by a high spontaneous mutation rate with an estimated frequency of $1.4–1.9 \times 10^{-3}$ mutations per nucleotide per year [1,2]. As a result, HCV exists as a heterogeneous group of viruses sharing approximately 70% homology. On the basis of nucleotide sequence homology, HCV has been classified into no fewer than six major genotypes and a series of subtypes [3]. Each HCV genotype is unique with respect to its nucleotide sequence, geographic distribution, and response to therapy [4]. Genotypes 1, 2, and 3 are common throughout North America and Europe. HCV genotype 4 (HCV-4) is common in the Middle East and in Africa, where it is responsible for more than 80% of HCV infections. It has recently spread to several European countries [5,6]. HCV-4 is considered a major cause of chronic liver disease and cirrhosis, which leads to liver failure and is the root cause of hepatocellular carcinoma. Because of these complications, extended cirrhosis during chronic infection is a primary cause of liver transplantation in these regions. Although HCV-4 is the cause of approximately 20% of the 170 million cases of chronic hepatitis C in the world, it has not been the subject of widespread research. Therefore, this document, drafted by a panel of international experts, aimed to review current knowledge on the epidemiology, natural history, clinical, histological features, and treatment of HCV-4 infections.

Epidemiology

Approximately 34 million people are chronically infected with HCV-4. The Iinfection is common in the Middle East and Africa, where it accounts for more than 80% of all hepatitis C cases [5–8]. The risk factors for HCV-4 transmission are determined by the geographical distribution of this genotype.

Egypt has the highest prevalence of HCV worldwide (15%) and the highest prevalence of HCV-4, which is responsible for 90% of infections, with a predominance of subtype 4a (55%) [5–9]. Epidemiological and molecular evolutionary analysis on Egyptian genotype 4a isolates suggest the origin of the HCV-4 epidemic arises from the antischistosomal campaign, which was administered parenterally, and only stopped in the mid-1960s [10,11]. However, other risk factors, mostly related to prevailing social and cultural conditions, are responsible for maintaining the high

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rates of HCV-4 transmission even after the treatment campaign was stopped. Currently, the major route of transmission appears to be health-related procedures with inadequately sterilized instruments. Procedures performed by non-medical professionals and traditional healers have been identified as important risk factors for HCV transmission in Egypt [12–14]. Intrafamilial and sexual transmissions also play a role in the high prevalence of HCV-4 in this country [15,16].

The prevalence of HCV in Saudi Arabia is 1–3%, [17] with a predominance of genotype 4 (62%). Unlike the predominance of subtype 4a in Egypt, subtypes 4c/4d are the most prevalent subtypes among Saudis, followed by subtypes 4h, 4e, and 4a, suggesting that the origin and transmission of HCV-4 is different from that in Egypt [17]. Similarly, studies from other parts of the Middle East also suggest a high prevalence of HCV-4. For example, 36–46% of HCV-infected Lebanese patients have HCV-4 [18], 59% of Syrian patients [19] and 27% of HCV-infected Jordanian patients on dialysis have HCV-4 [20].

HCV-4 is also endemic throughout Central and West African countries such as the Congo, Liberia, and Uganda (where it accounts for 100% of HCV infections), as well as Gabon, Tanzania, and Cameroon (97%, 50%, and 36% of HCV infections, respectively) [21–25]. Scarification, circumcision practices, and sexual transmission may contribute to the persistence and propagation of HCV transmission in these countries [21,25].

Recently, HCV-4 has become increasingly prevalent in some southern European countries on the Mediterranean Sea, particularly Italy, France, Greece, and Spain, where prevalence rates of 10–24% have been reported in some areas [26–31]. HCV-4 infection is frequent among intravenous drug users (IVDUs) (European and non-European), HCV/HIV-coinfected patients, and immigrants from North and sub-Saharan Africa [26–31]. HCV-4 was probably introduced into Europe through immigration and the movement of IVDUs across European borders [31].

HCV-4 infections are uncommon in the United States, Canada, South America, and Asia. The prevalence of HCV-4 in the United States is about 1% [32]. Most HCV-4 cases reported from the United States were clustered among IVDUs or immigrants from countries where subtype HCV-4 is known to be most prevalent or among individuals who acquired the infection in these countries [32,33]. There are no reliable data on the prevalence of HCV-4 either in Australia or in South East Asia. However, HCV-4 appears to be rare in these regions.

Natural history

There are few data on the natural history of HCV-4. It is likely that the course of genotype 4 infection is similar to that of other genotypes [25,34].

HCV-4 represents more than 30% of the annually reported acute hepatitis cases in Egypt [35]. Very few studies address the outcome of acute HCV-4 infection. Indeed, prospective studies have shown 20–50% rates of spontaneous resolution in acute HCV-4 infections [36–38]; whereas those rates are reduced in patients with a coinfection with HIV or *Schistosoma mansoni*, as frequently occurs in Egyptians [34,37]. The presence of schistosomiasis is a negative predictor of outcome, being associated with accelerated progression of hepatic fibrosis among HCV-4 patients. In fact, the fibrosis progression rate of 0.1 ± 0.06 fibrosis units/year observed in HCV-4 patients (similar to that of patients infected with other genotypes) increased up to 0.6 ± 0.13 in patients with associated schistosomiasis [39–43]. An Egyptian origin was independently associated with severe fibrosis in two French studies, however the higher fibrosis scores in these studies might be attributed to concomitant schistosomiasis in these Egyptian patients rather than ethnicity or HCV subtype [39,40]. Insulin resistance was also found to be correlated independently with severity of fibrosis [40]. The known association between hepatocellular carcinoma (HCC) and HCV needs to be weighed against other potential risk factors for HCC like schistosomiasis and exposure to aflatoxins or pesticides [44–47].

Utility of liver biopsy and noninvasive fibrosis tests

The biopsy is assessed for grade and stage of the liver injury, but also provides information on other histological features that might have a bearing on liver disease progression [48]. The two more common non-HCV conditions that might affect disease progression and possibly impede treatment response are steatosis [49,50] and excess of hepatocellular iron [51]. The pathological findings in chronic HCV-4 are in general similar to other types of viral hepatitis C. However, certain features may be prominent in this genotype, one of which is the presence of moderate to severe steatosis [50,52,53] with no associated sinusoidal fibrosis [53]. Host and viral factors contribute to the development of steatosis in hepatitis C, but their relative importance varies with genotype [54–56]. Hepatic steatosis in patients infected with HCV-4 is mainly associated with metabolic factors and follows the same pattern as those infected with genotype 1 [50,54]. Steatosis, in particular moderate-to-severe steatosis was detected in similar proportions of patients with genotype 1 and 4 [50,52,54]. Several studies have shown that steatosis in chronic HCV-4 is macrovesicular [50,52,53] and is seen without any prominent zonal preference [53]. More detailed studies are needed to determine if there is a characteristic histological pattern that might distinguish chronic HCV-4. Efforts are ongoing to seek alternative means focusing on noninvasive blood marker panels. In a recent study, the combination of hyaluronic acid, YKL-40, platelet count and serum aminotransferases provided information about the amount of hepatic inflammation and steatosis in Egyptian patients and achieved this cost-effectively [57].

Hepatocellular carcinoma

HCC is a major cause of cancer death worldwide [58], with evidence that its incidence has sharply increased in many countries as a consequence of the accumulation of patients with chronic liver disease caused by viral hepatitis or alcohol abuse [58,59]. The incidence of HCC in Egypt is also increasing [60–62] and is now the second most frequent cause of cancer and cancer mortality among men [63]. Hospital based studies have reported an increase in the relative frequency of all liver-related cancers in Egypt (>95% as HCC), from ~4.0% in 1993 to 7.3% in 2003 [60–62].

Data from the National Cancer Registry of Egypt, the National Cancer Institute and the Middle East Cancer Consortium recently reported that the incidence rate among males was 7 times greater than the next highest rate (among Israeli Jews) and more than 3 times that reported in the United States Surveillance Epidemiology and End Results summary [63,64].

A possible association has been suggested between HCV-4 and HCC based on the similarity of distribution of HCC and HCV-4 in