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Epidemiological Dynamics of Hepatitis C Virus among 747 German Individuals: New Subtypes on the Advance

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This study demonstrates the dynamics in the epidemiology of hepatitis C virus subtypes. Subtypes 3a and 4a have become increasingly prevalent in patients where an infection within recent years can be assumed. Evidence is presented that the subtypes observed among younger patients can spread rapidly and lead to significant changes in the subtype distribution.

Hepatitis C virus (HCV) isolates can be divided into genotypes and more closely related subtypes (15). The prevalences of these genotypes and subtypes vary significantly among different parts of the world. It has been shown earlier that in Europe and the United States genotype 1 with its subtypes 1a and 1b prevails by far (1, 4), while HCV subtypes 2a, 2b, 3a, 4a, and others are only seen occasionally. However, in certain risk groups like intravenous drug users (IVDU) subtype 3a isolates occur regularly (4). Furthermore, the rare subtypes can be observed in higher percentages among people who have immigrated from countries where these subtypes are common. Type 2 with its subtypes is known to be one of the dominant types in Asia and can also be observed to a high degree in the Mediterranean countries and northern Europe (2, 6, 17). The subtype 4a is predominant in the Middle East and North Africa (7, 15). However, the prevalence of HCV subtypes within a population may vary due to introduction and spread of new or rare subtypes. A shift of HCV subtype distribution within a patient population would influence the spectrum of clinical HCV manifestations and the efficiency of antiviral treatment (14, 18). Because of its significant impact on practical medical issues, we have addressed this topic by determining the current HCV genotype and subtype distribution in a population of 747 (334 female and 413 male) unselected, untreated patients.

Serum samples were collected consecutively from July 2000 to January 2001. They originated from inpatients of the University Hospital Hamburg-Eppendorf and from outpatients of different general practitioners in northern Germany and around the city of Frankfurt. All patients had been interviewed regarding risk factors for acquiring HCV infection (IVDU, transfusion of blood and blood products, hemodialysis, and high-risk sexual behavior [HRSB]) (Table 1). Although only a very low transmission rate of HCV is documented among spouses (16), HRSB is strongly associated with HCV infection (1) and comprises multiple sexual partners, prostitution, and homosexuality.

Genotypes were determined serologically by nonstructural 4 (NS-4) region immunoblot assay (NS-4 IBA) as described recently (12). Genotypes of samples which could not be typed serologically due to low or absent antibodies against the NS-4 region were determined by nucleotide sequencing as described earlier (4). All samples with serologically determined HCV genotypes other than genotype 1 were also retyped by nucleotide sequencing.

Genotype 1 prevailed by far and was observed in 583 of the patients (78%). Among these patients, 208 (28%) had HCV subtype 1a and 375 (50%) had 1b. The frequency of subtype 1a declined with increasing age, while subtype 1b became more frequent (Fig. 1).

In the younger individuals (age < 40 years), among whom a more recent time point of HCV infection must be assumed, two other HCV subtypes were detected with significant prevalences. With a frequency similar to the genotype 1 subtypes, subtype 3a was observed in individuals under age 40 (90 of 348; 26%) (Fig. 1). This is only partly due to the high prevalence of this subtype among IVDU, which was found as the most likely route of transmission in 47 (52%) of the subtype 3a-infected patients. The other 43 samples were derived from non-IVDU patients. In the age group of 40 years and older, subtype 3a was found less frequently, accounting for only 6.5% of infections (26 of 399). IVDU as the most probable mode of transmission was found in 7 of them (27%). HRSB was the next most common risk factor in the subtype 3a-infected patients and was found in 17 (40%) and 9 (47%) of the non-IVDU in the groups aged <40 and ≥ 40 years, respectively.

With subtype 4a, another HCV subtype was detected with significant frequency. Its prevalence decreases with increasing age (Fig. 1). It is notable that the occurrence of this subtype was not restricted to the group of immigrants from countries where subtype 4a is known to be most prevalent. Of 27 patients infected by this subtype, 12 (45%) were German patients who had never been at risk for acquiring HCV infection in foreign countries. Eleven of these patients are in the age groups below 40 years, and in all of them IVDU could be evaluated as the

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TABLE 1. Distribution of risk factors among the 747 examined patients[a]

Age group	No. of patients with risk factor					
	IVDU	Transfusion	Hemodialysis	HRSB	Unknown	Total
1–19	5	1	0	0	9	15
20–29	45	2	1	16	39	106
30–39	83	12	1	23	112	231
40–49	35	13	3	19	114	184
50–59	4	26	2	6	62	100
≥60	0	38	11	1	64	114

[a] Distribution of the most probable risk factors for acquiring HCV infection in the different age groups. While use of intravenous drugs and engagement in HSRB account for most HCV infections in younger individuals, transfusion of blood products and hemodialysis are the main infection routes in older patients. Although thoroughly investigated, about 50% of the patients neglected to have a recallable risk factor for HCV acquisition.

most likely known risk factor for acquiring HCV. In contrast, only one sample in the age group over 40 years originated from an IVDU, while the others were all derived from immigrants from North Africa and the Middle East. IVDU accounted for 58% (11 of 19) of the subtype 4a infections in the younger individuals but for only 12.5% among the older patients.

Genotype 2 was found in 21 patients (3%), of whom 18 and 3 were infected by subtypes 2a and 2b, respectively. With this genotype, no tendency could be observed towards higher prevalences among younger or older individuals. The majority of patients infected by this genotype had IVDU as the most probable mode of infection (10 and 3 of the 2a- and 2b-infected patients, respectively). Two of the subtype 2a-infected patients had received blood transfusions in foreign countries (United States [Alaska] and Russia) before moving to Germany.

Knowledge of the epidemiology of HCV subtypes is essential not only for epidemiological reasons but also from the clinical standpoint. The subtype of the infecting HCV strain is known to be one of the main independent factors that influence the clinical course of an infection as well as the outcome of antiviral therapy (18, 19). The subtype distribution of the enrolled patients is representative for the epidemiological situation in western Europe and the United States (1, 4). It has been stated that in both settings the prevalences of certain subtypes may change over time due to different distributions in various age groups (4, 17). Moreover, certain risk populations and ethnic groups have been detected who are mainly infected by HCV subtypes that occur with very low prevalences outside these groups (4, 12).

It is well known that subtype 3a is detected with high prevalences among IVDU (3, 4, 8). It has been suggested that this subtype was introduced in European populations by IVDU who acquired their infection while traveling in Asia (5, 13, 17). The epidemiology of subtype 3a and other subtypes is so different between IVDU and non-IVDU patients that the theory of two independently developing HCV epidemics has been proposed (8).

Our data demonstrate that this situation has changed significantly. This is mainly due to the fact that subtype 3a can now be detected in non-IVDU patients to a significant degree. This shows that during recent years the subtype 3a has spread beyond the boundaries of the IVDU scene, most probably by HRSB, which is known to be one of the main risk factors nowadays besides IVDU and hemodialysis for acquiring HCV

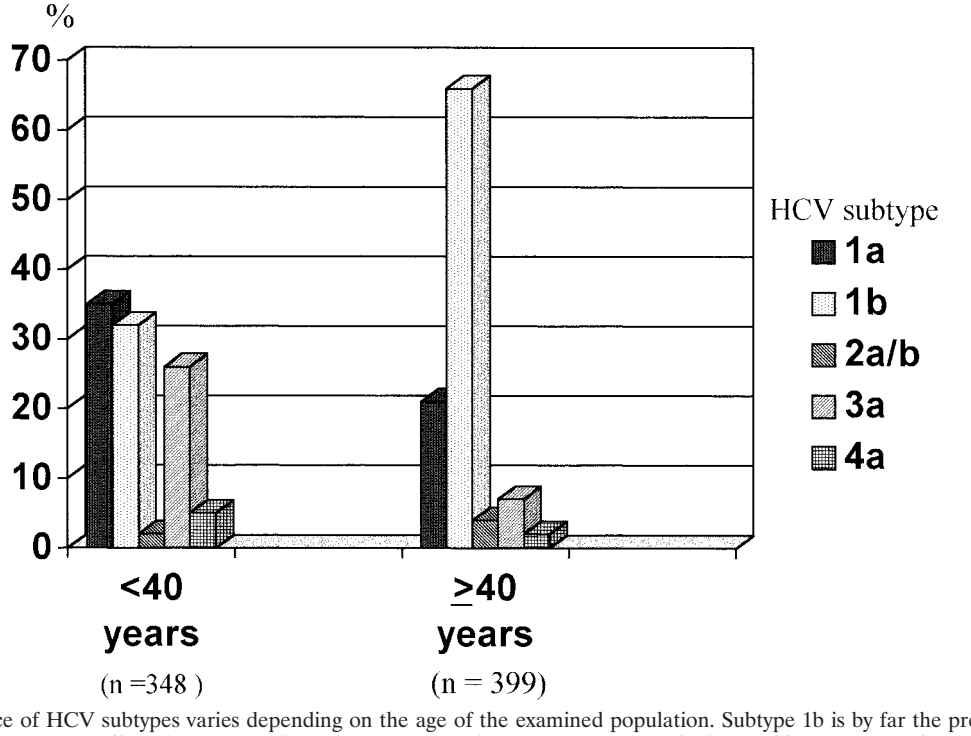

FIG. 1. Prevalence of HCV subtypes varies depending on the age of the examined population. Subtype 1b is by far the prevailing subtype in the older patient group. Contrarily, subtype 3a and to a lesser extent subtype 4a are commonly detected in younger patients.

infection (1, 11). Another significant change is with regard to HCV genotype 4, which has been described to be the most prevalent genotype in the Middle East (15). While the majority of individuals aged ≥40 years are immigrants, IVDU is the main risk factor in age groups below 40 years. This demonstrates that this subtype was obviously introduced into our patient population by immigrants who had acquired their HCV infection before moving to Germany, which has been proposed previously (4). However, now this subtype has become introduced into the IVDU scene as indicated by the detection of subtype 4a infections in young German IVDU, in whom a recent infection can be assumed. Taking the significance of IVDU for the dissemination of HCV infection (1) into account, it can be expected that this subtype will expand with accelerated speed within the next years. In analogy to the findings with the 3a subtype, the HCV subtype 4a may also spread over the boundaries of the IVDU scene with increasing prevalence.

Only in 3% of the examined samples were genotype 2 isolates detected. This is in concordance with previous studies where isolates of this genotype were also rarely found (10).

HCV genotype 2 has been observed with high frequencies in Asia, Mediterranean countries, and northern Europe (6, 15, 17). Therefore, it can be assumed that HCV type 2 strains were introduced by HCV-infected people immigrating from these countries, as formerly observed with subtype 4a. However, the majority of our patients infected by genotype 2 are locals and have never been at risk for acquiring HCV infection in one of the high-prevalence countries. In analogy to the findings regarding subtypes 3a and 4a, the genotype 2 subtypes have most probably been introduced occasionally by IVDU or immigrants and are now beginning to spread within certain risk groups. Although it has to be assumed that three patients had acquired their HCV infection before immigrating to Germany (two of them by transfusion, one IVDU), again, IVDU seems to be the most significant route for the spread of this genotype in our patient population. This is supported by the observation that three patients with type 2 isolates were previously infected by 1a subtypes. All of them were IVDU with a high risk of multiple exposure to different HCV strains. It has been shown that in patients who have been sequentially infected with different HCV subtypes, only one dominant strain can be detected (9, 12).

It has been argued that shifts in the relative frequencies of HCV subtypes occur. About 20 to 25 years ago, subtype 1b seemed to be prevailing by far (4). A shift during the last 15 to 20 years towards subtype 1a has been noted (4, 10). Now, our data present evidence that another shift towards subtypes 3a and 4a is ongoing and will change the epidemiological situation significantly within the next few years. Due to the introduction of blood donor screening, one of the former main HCV transmission routes has meanwhile lost its importance. Therefore, IVDU, hemodialysis, and HSRB are now essential risk factors for the spread of HCV (1, 11). Since both IVDU and HSRB are noted mainly among younger people, it can be assumed that the HCV subtypes which are common among these age groups will spread in the future.

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