Chronic hepatitis C in Austria, 1992–2006: genotype distribution and demographic factors

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Chronic hepatitis C is a leading cause of end-stage liver disease and, with a worldwide prevalence of up to 3%, is a pandemic infectious disease. Austria, like most western European countries can be considered as a low prevalence country. This analysis aimed to assess the distribution of hepatitis C virus (HCV) genotypes in patients with chronic HCV infection in Upper Austria. Between September 1992 and December 2006, we identified 1,318 consecutive patients who tested positive for HCV RNA. Genotyping was routinely performed in 1,239 of the 1,318 patients, and in a subgroup of 617 patients data on the source of transmission were collected. Additionally we obtained data on liver histology and body mass index in a subsample of 273 of the 617 patients. Hepatitis C genotypes 1, 2, 3, 4, 6 and co-infections were found in 80.4%, 4.5%, 12.3%, 2.7%, 0.1% and 0.2% of the patients, respectively. There was a highly significant age difference in relation to gender at the time of diagnosis of chronic hepatitis C, with women being older than men (men: 45.0 years; women: 49.3 years; $p<0.0001$). The number of new cases of chronic hepatitis C decreased substantially over the last decade, but although risk factors for obtaining HCV are well established, we did not find a decrease in the age of first diagnosis. Besides consistent screening in defined risk groups it is important to raise awareness for risk factors for HCV acquisition and liver disease progression.

Introduction

Chronic hepatitis C is one of the leading causes of liver cirrhosis and end-stage liver disease, resulting in liver failure, hepatocellular carcinoma, liver transplantation and premature death. Thanks to antiviral treatment, 50% of patients with progressive hepatitis can be cured if the infection is diagnosed in time and treatment is available [1]. Cofactors such as alcohol intake, obesity and underlying liver-related diseases (e.g. haemochromatosis) play a major role in the progression of the liver disease [2]. Infections with hepatitis C virus (HCV) are pandemic with a worldwide prevalence of up to 3% [3,4]. There is a large variation regarding the genotype distribution worldwide, the most prevalent in Europe and North America being genotype 1 [5]. The knowledge of genotypes in chronic hepatitis C is crucial for the choice of the therapeutic regimen and for the therapeutic outcome, because genotypes 2 and 3 are curable in more than 80%, whereas genotypes 1 and 4 are curable in only 40-50% of cases [6].

The most common ways of transmission in low resource countries are still inadequately screened blood products, insufficiently sterilised needles, syringes and other medical equipment [7] as well as needle sharing among intravenous drug users, unsafe tattooing and body piercing worldwide. Sexual and perinatal transmission can occur but are of minor importance [8]. In the past decade the knowledge about risk factors for HCV infection and their reduction or even elimination have reduced the number of new cases and this resulted in a stabilisation of the HCV prevalence in developed countries [9]. Nevertheless this development did not prevent the continued rise in cirrhosis and liver cancer that resulted from HCV infections acquired dozens of years before [10]. The age at the time of diagnosis is very important because patients that are older at the time of diagnosis are more likely to develop severe liver disease [11].

Austria is a low prevalence country as are most other western European countries [8]. In Austria there is underreporting and a lack of epidemiological background data such as suspected route and time of transmission and genotype in the national reporting data [12]. In view of the lack of national epidemiological HCV data the aim of this analysis was to present the data for one of four hepatitis clinics in Upper Austria, one of the nine Austrian states. We analysed the number of new cases, the distribution of HCV genotypes and demographic factors. In addition, we analysed the number of new infections with the difficult-to-treat HCV genotypes 1 and 4 over time in association with

Table 1

New cases and mean age of hepatitis C patients by year and sex, hepatitis clinic Upper Austria, September 1992 – December 2006 (n=1,318)

Year	Male mean age in years (n)	Female mean age in years (n)	Total mean age in years (n)
1992	42.3 (12)	49.6 (7)	45.1 (19)
1993	44.6 (47)	53.2 (26)	47.7 (73)
1994	46.9 (54)	49.2 (35)	47.8 (89)
1995	44.0 (61)	50.6 (31)	46.2 (92)
1996	43.2 (75)	47.9 (47)	450 (122)
1997	43.2 (73)	48.6 (48)	45,4 (121)
1998	43.4 (88)	46.2 (35)	44.2 (123)
1999	45.9 (81)	47.3 (43)	46.4 (124)
2000	46.0 (69)	50.0 (28)	47.1 (97)
2001	44.8 (51)	52.6 (36)	48.0 (87)
2002	48.9 (57)	51.3 (33)	49.8 (90)
2003	47.0 (51)	47.3 (36)	47.1 (87)
2004	44.8 (65)	50.1 (29)	46.4 (94)
2005	44.6 (33)	46.8 (20)	45.4 (53)
2006	45.1 (30)	52.2 (17)	47.7 (47)
Total	**45.0 (847)***	**49.3 (471)***	**46.6 (1,318)**

* Significantly different (p<0.0001).

Table 2

Distribution of hepatitis C virus genotypes and subtypes and patients' mean age, hepatitis clinic Upper Austria, September 1992 – December 2006 (n=1,239)

Genotype group	Genotype subtypes	Number of cases	Proportion of total (%)	Mean age (years)
Genotype 1	1b	641	51.7%	
	1a	253	20.4%	
	1a/1b	68	5.5%	
	1	31	2.5%	
	1/3a[1]	1	0.1%	
	1a/2[1]	1	0.1%	
	1b/2[1]	1	0.1%	
Genotype 1 Subtotal		996	80.4%	48.2*
Genotype 2	2	14	1.1%	
	2a	2	0.2%	
	2a/2c	29	2.3%	
	2b	11	0.9%	
Genotype 2 Subtotal		56	4.5%	43.4
Genotype 3	3	48	3.9%	
	3a	104	8.4%	
Genotype 3 Subtotal		152	12.3%	37.7*
Genotype 4	4	15	1.2%	
	4a	4	0.3%	
	4c	2	0.2%	
	4c/4d	8	0.6%	
	4h	5	0.4%	
Genotype 4 Subtotal		**34**	**2.7%**	**39.7**
Genotype 6	**6**	**1**	**0.1%**	**47.7**
Total		**1,239**	**100.0%**	**46.4**

* Significantly different (p<0.0001).

[1] Co-infections are counted as one entry.

gender, age at time of diagnosis, route of transmission, liver histology and body mass index (BMI) in the referral population of our outpatient clinic.

Figure

HCV genotype distribution 1992-2006, hepatitis clinic Upper Austria, September 1992 – December 2006 (n=1,239)

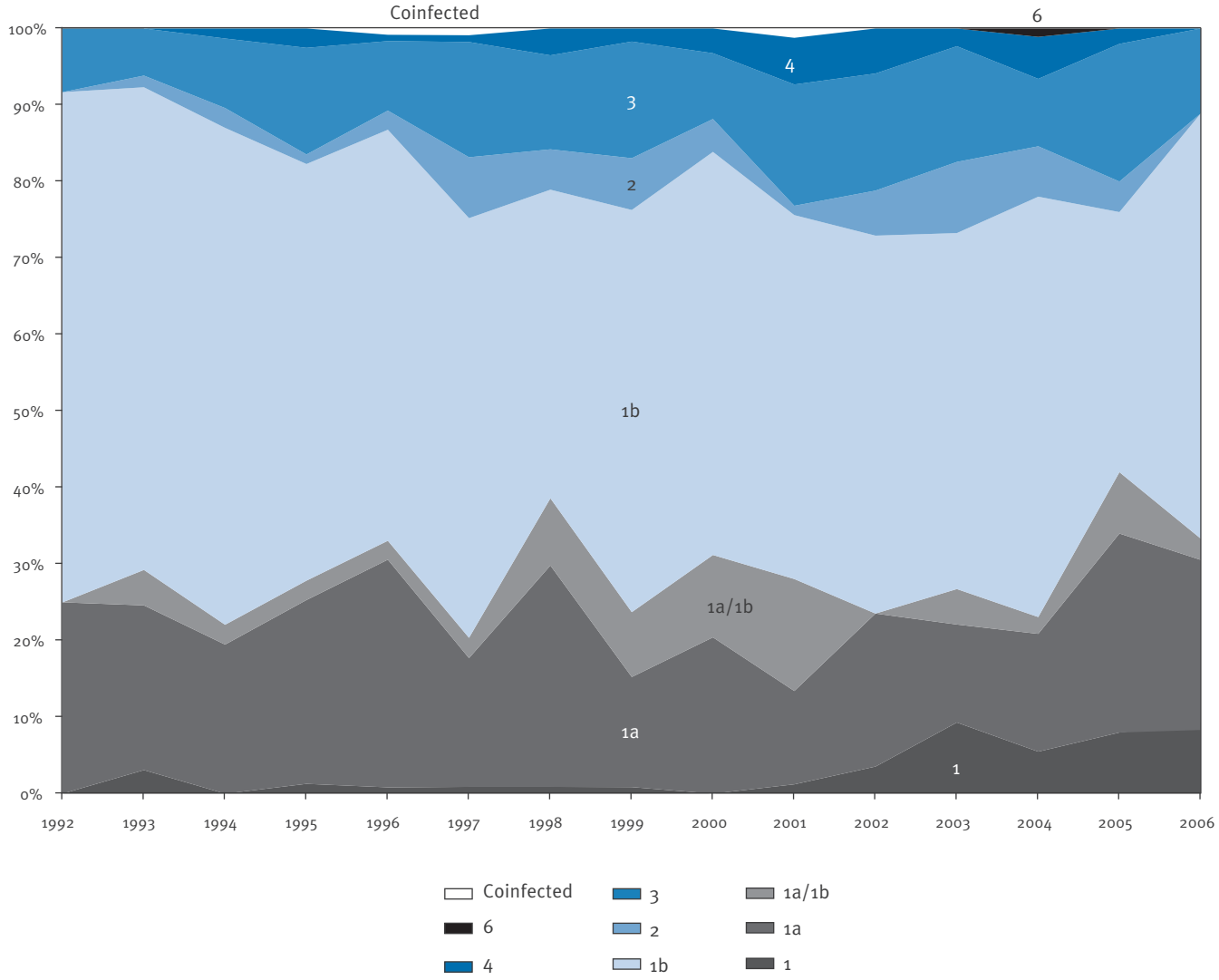

Table 3

Route of transmission for hepatitis C virus infection, by genotype group, hepatitis clinic Upper Austria, September 1992 – December 2006 (n=604)[1]

Route of transmission[2]	Genotype 1/4			Genotype 2/3		
	Number of cases	Proportion of total (%)	Mean age (years)[3]	Number of cases	Proportion of total (%)	Mean age (years)[3]
Unknown	205	41.4	46.8	29	26.6	43.6
Blood products	131	26.5	50.3	27	24.8	46.4
Plasma donation	78	15.8	49.5	4	3.7	45.4
Intravenous drug use	55	11.1	35.2	41	37.6	36.6
Piercing/tattoo	17	3.4	44.0	7	6.4	34.1
Needle stick injuries	8	1.6	47.5	0	0.0	-
Vaccination	1	0.2	38.5	1	0.9	56.3
Total	**495**	**100.0**	**46.8**	**109**	**100.0**	**41.2**

[1] For whom genotype was known.

[2] In case of more than one risk factor the one most likely to have caused the infection was assigned (e.g. in a case with unsafe tattooing and intravenous drug use, intravenous drug use was assigned)

[3] Age at the time of diagnosis.

Methods

Upper Austria has 1.4 million inhabitants and four large outpatient clinics specialised in the care of hepatitis patients. Patients are referred to these clinics mainly by general practitioners, physicians responsible for the intravenous drug substitution programmes and centres for blood or plasma donation. From September 1992 to December 2006, we identified 1,319 consecutive patients (847 men (64.3%), 471 women (35.7%) and one case of unknown sex) who were referred to our outpatient clinic and tested positive for HCV by PCR. Patients were retested within one year if the first PCR test was negative and the antibody test was positive.

The baseline examination of our patients included a thorough medical check-up, the recording of the medical history and the assessment of risk factors for HCV infection which was carried out by performing standardised interviews. For the majority of the patients, our clinic was the first referral centre, only few (‹5%) consulted our clinic for a second opinion.

Genotyping was performed in blood samples from 1,239 of the 1,319 patients. In a subgroup of 617 patients (410 men (66.5%) and 207 women (33.6%)) data were collected on the source of transmission, BMI, co-infection with hepatitis B virus (HBV) and co-infection with human immunodeficiency virus (HIV). Additionally, we obtained data on liver histology and BMI in a subsample of 274 of these 617 patients.
All patients primarily identified as infected with chronic hepatitis C (n=1,319) were considered in the overall analysis, but in the subgroup analysis, patients with missing data on genotype or other demographic factors were excluded.

The data were stored and analysed using MS Access, MS Excel and SPSS software 13.0. The Mann-Whitney U Test and the chi-square test were used for non-parametric statistical testing.

HCV RNA from samples collected before September 1998 was detected with the Amplicor HCV test system (Roche) [13]. Samples collected between October 1998 and March 2006 were tested with the Cobas Amplicor HCV test (Roche) [14]. Since April 2006, the Cobas AmpliPrep/Cobas TaqMan HCV test (Roche) has been used for qualitative as well as quantitative detection of HCV RNA [15]. To determine the viral load in samples collected before April 2006, the Cobas Amplicor HCV monitor test, version 2.0 (Roche) [16] was used. HCV genotyping and subtyping (including detection of mixed genotypes) were carried out with the line probe assays (Innogenetics or Bayer HealthCare). The following systems were used: INNO LiPA HCV genotype assay, INNO LiPA HCV II genotype assay and Versant HCV genotype assay (LiPA) [17-19].

Results

After we began diagnosing HCV infections in September 1992, we identified 19 chronic hepatitis C patients by December 1992. Subsequently, the number of annual new cases changed over time and reached a maximum of 121-124 patients per year between 1996 and 1999 (Table 1). In each year, the majority of patients were men and there was a significant age difference with respect to gender (45.0 years in men versus 49.3 years in women; p<0.0001).

Since the variation in the number of new cases was substantial over the years we decided to check whether the catchment area of our outpatient clinic had changed. There was no statistical significant variation in postal codes of patients (p=0.14) and therefore we assume that our catchment area has not changed considerably over time.

Genotype distribution

HCV genotypes (gt) 1, 2, 3, 4, 6 were found in 80.4%, 4.5%, 12.3%, 2.7%, and 0.1% of the patients, respectively, and co-infections in 0.2%. The major subtypes were 1b (51.7%), 1a (20.4%) and 3a (8.4%), (Table 2). Three patients had a co-infection with two genotypes

Table 4

Relation between body mass index, liver fibrosis score and hepatitis C virus genotype group, hepatitis clinic Upper Austria, September 1992 – December 2006 (n=273)

		Genotype 1/4/6			Genotype 2/3		
Fibrosis	**Fibrosis score**	**Number of cases**	**Proportion of total (%)**	**Mean BMI**	**Number of cases**	**Proportion of total (%)**	**Mean BMI**
Fibrosis 0-2	0	51	22.2%	25.4	10	23.3%	24.0
	1	51	22.2%	25.6	8	18.6%	25.3
	2	56	24.3%	26.1	18	41.9%	23.6
Fibrosis 0-2 Subtotal		**158**	**68.7%**	**25.7**	**36**	**83.7%**	**24.1**
Fibrosis 3-4	3	20	8.7%	26.6	2	4.7%	21.9
	4	52	22.6%	26.9	5	11.6%	25.7
Fibrosis 3-4 Subtotal		**72**	**31.3%**	**26.8**	**7**	**16.3%**	**24.6**
Total		**230**	**100.0%**	**26.1**	**43**	**100.0%**	**24.2**

BMI: Body mass index.

(1a/2, 1/3a, 1b/2). Two patients, a couple with a history of intravenous drug use, underwent successful antiviral treatment and eliminated virus genotype 3a. Both were re-infected after needle-sharing with a mutual friend with genotype 2a. Genotypes 4 and 6, which are rarely detected in central Europe, were found in patients originating from other continents, mostly immigrants from Egypt (genotype 4 in 32 patients) and Vietnam (genotype 6 in one patient). Patients with genotypes 4 and 6 were mostly men (three women with genotype 4).

Between 1992 and 1996, we observed a high prevalence of genotype 1, ranging between 83.1% and 92.2%. After that period, the prevalence of genotype 1 decreased, varying from 73.7% to 78.4%, whereas the prevalence of the other genotypes increased or remained relatively stable (gt 2: 0-2.7%; gt 3: 9.1-16.2%;gt 4: 0-2.7%; gt 6: one patient) (Figure).

There was a continuous increase in the proportion of HCV patients who were not native Austrians, from 0% in 1992 to 15.8% in 2006. This did not influence the number of genotype 1 cases because migration was from countries with similar genotype distributions as Austria such as the Balkans, Turkey and the territories of the former Soviet Union, now known as the Commonwealth of Independent States. In 2006, 10-12% of the inhabitants of Upper Austria had been born abroad [20].

Characteristics and risk factors

Patients infected with genotype 1 were significantly older at the time of diagnosis than patients with genotype 3 (mean age: 48.2 years versus 37.7 years, $p<0.0001$; see Table 2) and they showed a different distribution of risk factors for HCV acquisition in the subgroup analysis. Blood products and plasma donation were the most frequent risk factors for HCV acquisition in genotype 1 and 4 patients, but in the majority of patients the mode of transmission was unknown. In patients with genotype 2 or 3, the most common risk factor was intravenous drug use. The risk factor distributions and the mean age relating to genotype group are given in Table 3.

72 patients (11.6%) had overcome an infection with HBV. Three patients still suffer from chronic hepatitis B infection and only one patient was co-infected with HIV. We did not observe any connection between the HCV genotype group and the proportion of HBV-co-infected patients (gt 1/4: 10.7%; gt 2/3: 11.0%).

For a subgroup of 273 patients we also obtained histological information. It was notable that more than 30% of patients with genotype 1 or 4 showed bridging fibrosis or cirrhosis. In patients with genotype 2/3 advanced fibrosis was noted in 16.3% only. The results also revealed that a higher BMI coincided with an advanced liver fibrosis. Patients infected with HCV genotype 1, 4 or 6 showed a mean BMI of 26.1 kg/m² and patients with genotype 2 or 3 a mean BMI of 24.2 kg/m² (Table 4).

Discussion

Austria is one of the countries in Europe with the lowest HCV prevalence; less than 0.5% of the total population are infected. According to this estimation our data represent around 20% of all HCV-infected patients in Upper Austria [21]. Overall our results show a change in the number of cases diagnosed over time reaching a maximum between 1996 and 1999 (121-124 patients per year) and a drop between 2000 and 2006 (10). This decline in new HCV cases is in line with Austrian reporting data published by the Federal Ministry of Health, Family and Youth [22], although it has to be mentioned that the reporting data are biased by underreporting as shown by Strauss *et al*. [12].

The sensitivity of the PCR test improved over the study period. This should not have caused a bias in our results, but a very few patients may have been missed due to the detection limit of PCR testing. The number of newly diagnosed HCV cases might be influenced by migration. The proportion of individuals not born in Austria has increased over the years among the patients in our analysis as well as in the general population. A considerable number of our patients were from Egypt and from the Commonwealth of Independent States.

Regarding the distribution of HCV genotypes, our results are very similar to those from other European countries. In our data, genotype 1 was the most prevalent (80.4%), followed by genotype 3 (12.4%). Genotype 1b was the most frequent subtype and accounted for more than 50% of all HCV-infected patients in our clinic. Observations by Haushofer *et al*. for Vienna and surrounding areas in the year 2001 [23] and by Ross *et al*. (2000) and Goeser *et al*. (1995) for Germany [24,25] yielded very similar results. The rate of genotype 3 in Germany ranged from 33.6% in 2003 to 35.7% in 2005 [26]. In a report from Slovenia from 1997, genotype 3 accounted for approximately 20% of cases [27] and in Italy in 2003, genotype 3 was found in about 12% of chronic hepatitis C patients [28]. All genotype 4 patients in our population came from Egypt (2.8%), where the prevalence of genotype 4 is nearly 90% [29] due to insufficient sterilisation of the needles used for intravenous treatment of schistosomiasis in the 1960s and 1970s [30]. The prevalence of genotype 4 outside of Egypt varies from 1% in Germany [18] to 10% in Spain [31].

In our sample, the proportion of HCV genotype 1 decreased over time, whereas the proportion of genotype 3 increased slightly. The shift of the genotype distribution may be associated with the change of risk factors for HCV acquisition, since HCV is nowadays mostly transmitted via intravenous drug use [32]. Blood products and plasma donation now play a minor role in causing new infections because of strict screening procedures, whereas the risk of acquiring HCV

through intravenous drug use has remained the same [33,34]. The overall incidence of new HCV infections has been decreasing in all developed countries including Austria. Nevertheless, the change in incidence will not prevent the increase of liver cirrhosis and liver cancer still resulting from HCV infections transmitted decades ago [10].

Surprisingly, the median age at time of diagnosis has not changed over time although the risk factors for HCV infection are well known. This might be important for therapeutic considerations because it is known that therapy is less efficient in older patients due to the progression of liver disease and longer time of being infected [11]. Unfortunately, the medical history with the time of infection given by the patient was not reliable or not available in most of the cases, and therefore the lag between the age at time of infection and age at time of diagnosis can not be given.

Another startling finding was that women were significantly older at the time of diagnosis than men. This might be because women have fewer risk cofactors such as non-alcoholic fatty liver disease (NASH) and alcohol intake, usually leading to elevated liver enzyme levels and further investigation [35]. According to Guerrini *et al*. [35], heavy drinking is overrepresented in the male population. Papatheodoridis *et al*. [36] reported that up to 15% of Greek blood donors show elevated liver enzyme levels that are most likely due to NASH. They also found a strong association of NASH with the male sex, which suggests that earlier diagnosis of HCV infection in men might be due to a higher frequency of elevated liver enzyme levels in the male population. Similar data are available for the United States, with a strong association between elevated alanine transaminase (ALT) values and risk factors for NASH [10,37]. Recent publications suggest that disease progression is strongly associated with alcohol intake, obesity, the metabolic syndrome and hepatic steatosis, all of which emphasise that the patient's age at the time of diagnosis seems to be related to the presence of these host factors [1,11,38]. We have shown here that disease progression is associated with higher BMI, higher age at time of diagnosis, and probably with risk factors that are more prevalent in men.

In general, HCV infection is detected under the following two circumstances: most commonly, a patient with chronic hepatitis C is found to have elevated liver enzyme levels, which leads to further investigation and subsequent diagnosis. Another possibility is that patients are detected by screening for HCV antibodies in well-defined risk groups. Although there have been clear recommendations (9) for HCV screening in risk groups since the late 1990s, the mean age at the time of the first diagnosis did not change in our population between 1992 and 2006. It was very surprising that the age of patients with an unknown source of transmission was significantly lower than that of patients infected via blood products or plasma donation. This leads to the question why persons with known risk factors are not diagnosed earlier. Lack of knowledge about HCV risk factors (use of blood products before 1991, haemophilia, haemodialysis, HCV-positive mother, intravenous drug use, plasma donation in the 1970s (39), piercing and acupuncture, unsafe tattooing, nosocomial infections (40)) might be the main reason for the late diagnosis of HCV infection.

Conclusions

The number of new cases of chronic hepatitis C has decreased substantially over the past decade. There has been a major change in the risk factors for HCV acquisition, with blood products and plasma donation now playing only a minor role. While the risk factors have changed over time, the genotype distribution remained relatively stable. Although risk factors for obtaining HCV are well established we did not find a decrease in the age of first diagnosis. Besides consistent screening in defined risk groups it is important to raise awareness of the risk factors for HCV acquisition and the progression of liver disease [41].

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