HEPATITIS C REARCH

Prevalence of Chronic Hepatitis C Virus Genotypes Among Patients Between 21 to 65 Years Old in Puerto Rico

FEDERICO RODRÍGUEZ-PÉREZ, MD*; ERICK SUÁREZ-PÉREZ, PhD†; MARIALI ÁLVAREZ-ROHENA, MPH†; DORIS H. TORO, MD*.

Objectives. **This is the first study done in Puerto Rico to estimate the prevalence of hepatitis C virus (HCV) genotype distribution in patients with chronic infection and to determine the statistical association between the genotype and variables such as age, sex, HCV risk factors, and viral load.**

Methods. **Chronic HCV infected patients diagnosed with ELISA, RIBA or PCR from 1990 to 2002 who were under follow up with members of the Puerto Rico Gastroenterological Association were asked to participate. Eligible patients were those without evidence of HIV or other viral hepatic infection; had no previous antiviral treatment or if previously treated, therapy ended at least six months prior to their participation in the study; had no history of organ transplant and were willing to participate. All study subjects completed a study questionnaire and had blood samples taken to determine HCV genotype and viral load.**

Results. **500 patients were recruited. Most of the study subjects were males (68%); 70% were 45 to 65 years old. The principal reported risk factors were: surgeries (75.5%), drug use (46.8%), sexual relationships with intravenous/intranasal drug users (30.3%), blood transfusions (30.2%), multiple sex partners (28.9%), tattoos (22.0%), needle accidents (12.7%), and sexual relationships with an HCV infected partner (9.0%). Most patients had multiple risks factors for infection, only 3.4% (17/500) reported a single risk factor whereas 2.0% (10/500) reported none. 33% of the patients were previously treated (non-responders or relapsers) while 67% were naïve. In general, 82% of the HCV patients had genotype 1, while 18% had non-1 genotypes. Among genotype 1 subtypes, genotype 1a (39.8 %) was more common than 1b (27%). The most common non-1 genotype was genotype 2 of which 2b represented 9.8% of the study population. Similar distribution was observed within the categories of the HCV risk factors, with the exception of those who reported sex with an infected partner (p=0.018), sex with multiple sexual partners (p=0.049) and IVDU (p=0.006). For patients in which the viral load was 2 million IU/ml or less, the genotype 1a (41%) predominates, followed by 1b (29%) and 1a/1b (9%); patients with viral load was greater than 2 million IU/ml, the genotypes distribution was 1a (38%), 1b (24%), and 2b (12%). After adjusting by type of patients (naïve and treated), age and gender, no significant association (p<0.05) were found between two-categories of genotype (1 vs. non-1) and HCV risk factors.**

***Conclusion*.** **This cross-sectional epidemiological study demonstrated that the most frequent genotype found in Puerto Rican HCV infected patients is genotype 1. The principal risk factors associated in our population were: surgeries, drug use, blood transfusions, sexual relationships with IVDU, and multiple sex partners. The statistical evidence showed that the genotype distribution is not affected by the HCV risk factor, after adjusting by type of patients (naïve and treated), age, gender or geographical area.**

Key words: HCV genotype, Viral load, HCV related risk factors, Hispanics.

Hepatitis C virus (HCV) constitutes an important public health problem around the world. It affects nearly 170 million people (3%) of the world population and is one of the main causes of chronic liver disease and commonest indication for liver transplantation (1,2). Prevalence of hepatitis C has been determined in many populations around the world demonstrating a higher prevalence in developing countries including Africa, Middle East and Southeast Asia (3-18). In developed

From †Graduate School of Public Health, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico and the *Gastroenterology Section, Department of Medicine, Veterans Affairs Medical Center, San Juan, Puerto Rico.

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Address correspondence to: Doris H. Toro, MD, Chief, Gastroenterology Section (111G- OPA),Veterans Affairs Medical Center, #10 Casia St., San Juan, P.R. 00921-3201, Email Doris.Toro@med.va.gov

nations, prevalence rates of HCV antibodies are generally less than 3%. In some highly endemic areas of the world, the prevalence rates range from 10% to 30% (19). It is estimated that in the United States 28,000 new infections occur each year and four million Americans (1.8%) are positive for HCV antibodies.

Approximately 85% of the individuals infected with HCV progress into chronic hepatitis C (CHC) infection (19,20). Of those with CHC, 20% to 50% may develop cirrhosis that can lead to decompensated liver disease and/or the development of hepatocellular carcinoma (19). In the United States 10,000 to 12,000 patients die each year due to complications of HCV infection and one of every three diagnosed hepatocellular carcinomas are related to HCV.

The HCV is characterized by its genetic heterogeneity and its high mutation rate (21). There are six major genotypes and at least 80 subtypes (22), with particular geographic distribution throughout the world. Analysis of the distribution of HCV genotypes in four geographic regions of the United States has revealed that HCV genotypes 1a (58%) and 1b (21%) predominate in patients with chronic hepatitis C (23). Genotype 1 predominance has also been reported in France, Spain, and South America (24-27. In countries such as Scandinavia, Far East, Pakistan, parts of India, and Australia genotype 3 is more common, while genotype 4 is found mainly in the Middle East and genotypes 5 and 6 are nearly always found in South Africa and Hong Kong, respectively (21).

HCV constitutes an important public health problem in Puerto Rico. Few epidemiological studies regarding the magnitude and extension of this problem in the island have been performed. Serologic surveys have been limited to women attending prenatal clinics in San Juan and to allogeneic blood donors. In 1999, the prevalence of HCV in patients receiving hemodialysis at three units in the western region of Puerto Rico was reported as 2% (28). In 2001, a genotype analysis was carried out in patients co-infected with HIV and HCV, revealing that in this population genotype 1a is the more common genotype (29).

Several years ago, the Puerto Rico Gastroenterology Association (APG) performed a pilot study to determine the genotype distribution of HCV infected patients in which 231 patients participated. This pilot study found that 88% of the evaluated subjects were genotype 1. Based on this information the APG decided to sponsor an island-wide cross-sectional epidemiological study (34) with randomly selected patients and pre-defined inclusion and exclusion criteria. (Communication from the Puerto Rico Association of Gastroenterology). The main purpose of this study is to describe an epidemiological profile of the HCV virus genotype in chronically infected Puerto Rican patients aged 21-65 years.

Methods

Consecutive patients with chronic HCV diagnosed with ELISA, RIBA or PCR from 1990 to May 2002 who had visited a physician at least two times and referred by one of the members of the Puerto Rico Gastroenterological Association from November 2001 to May 2002 were eligible to participate. Inclusion criteria included an age range between 21 to 65 years old; no previous antiviral treatment or if previously treated but relapsed or failed to respond, therapy ended at least six months prior to participation in the study; no history of HIV or other hepatic viral infection; no history of organ transplant and legally competent to sign a consent form. Based on the prior pilot study results, and a desired precision of 4.5% in the prevalence estimation with a 95% confidence level (35), we established a required sample size of 500 patients.

Patients willing to participate were referred to the nearest Veterans Affairs Medical Center (VAMC) or Satellite Clinic either in Ponce, Mayagüez or San Juan where the study was conducted. The San Juan VAMC Institutional Review Board evaluated and approved the designed study. Informed consents were obtained from all participants.

All participating study subjects answered an epidemiological and risk assessment questionnaire. Blood samples were drawn to determine the HCV viral load and genotype.

The hepatitis C viral load (HCV PCR) and genotype tests were determined using the Roche Amplicor and LIPA methods respectively, at the Ponce School of Medicine Laboratory. A quality assurance plan was defined in order to ensure the data collection quality in the phases of patient's selection, questionnaires completion and data entry.

Descriptive statistics were used to identify the study group and to calculate the genotype prevalence (36). Chi-square distribution was used to assess the statistical association between genotype distribution and HCV risk factors. Also, a logistic regression model was used to evaluate this association after adjusting by type of patients (naïve and treated), age and gender (37-38). The magnitude of the statistical association was estimated by the Odds Ratio (OR) (38). The computer package Epi-Info (39) was used to create the database. STATA (40) and SAS (41) were the computer programs used for the statistical analysis.

Results

Demographic characteristics. Five hundred consecutive patients participated in this study. Results of the univariate analysis show that the study population

was composed primarily of men (70%). Sixty eight percent (351/500) were between 45 to 65 years old. 338 (68%) had never been treated (naïve) while 162 (32%) were patients that either failed to respond to treatment or relapsed. Almost half (49%) of the study population attained or completed high school ($10^{th} - 12^{th}$ grade), thirty-six percent (36%) obtained undergraduate studies or a higher educational level, while 16% only finished intermediate school ($7^{th} - 9^{th}$ grade). Half (49.8%) of the study population lived in the northeast (Metropolitan Area) of Puerto Rico, while the rest of the subjects were distributed in the south/southwest (21.2%) and west/northwest regions (29.0%). Nearly 25% (113/500) of the subjects were veterans of which 99.1% (112/113) were males. One-third of the subjects reported to have an income less than $500.00 per month, 46.5% between $500.00 and $1,999 and 18.8% above $2,000. (Table 1).

Table 1. Profile of Chronic HCV Infected Participants

Variables	Levels	n	%
Gender	Male	342	68.4
	Female	158	31.6
Age (years)	21-44	149	29.8
	45-65	351	70.2
Educational level			
(completed years)	≤ 9	78	15.6
	10-12	242	48.6
	> 12	178	35.7
Monthly income ($)	< 500.00	169	33.9
	500.00 - 999.99	106	21.2
	1000.00 - 1999.99	126	25.3
	≥ 2000.00	94	18.8
Type of patient	Naïve	338	67.6
	Treated	162	32.4
Veterans	Yes	113	22.6
	No	387	77.4
Geographic distribution	Northeast	249	49.8
	South/Southwest	106	21.2
	West/Northwest	145	29.0

Risk factors. The principal reported HCV-related risk factors were: surgeries (75.5%), body piercing (48.8%), drug use (46.8%), sexual relationships with intravenous/ nasal drug users (30.3%), blood transfusions (30.2%), and multiple sex partners (28.9%). Body piercing was reported by 48.8% of the study population: 92.4% (146/158) of the females and 28.6% (98/342) of males. Sixty percent of those who reported body piercing were females that described ear piercing when born. Among the participants who reported drug use (intravenous and/or nasal), 75% were intravenous drug users of which 80% reported sharing syringes or other paraphernalia (Table 2). Only 3.4% (17/ 500) of the patients reported having a single HCV-related risk factor prior to HCV diagnosis, while 2% (10/500) did not reported identifiable risk factors (Figure 1).

Table 2. HCV Related Risk Factors Reported Among Participants.

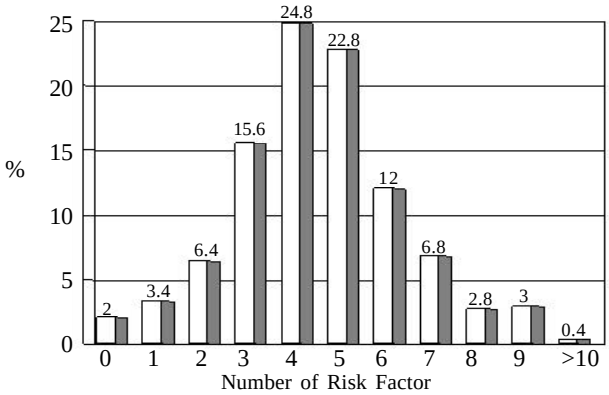
Risk Factors(*)	%	Proportion(†)
Surgeries	75.5	376/498
Body piercing	48.8	244/500
In females	92.4	146/158
In males	28.7	98/342
Drug users	46.8	234/500
Intravenous drug users	74.9	176/235
Syringes and equipment sharing	81.0	141/174
Sex with a drug user		
(i.e. cocaine, heroine)	30.3	143/472
Blood transfusions	30.2	146/483
Multiple sexual partners		
(≥10 partners)	28.9	137/474
Contact with blood	26.3	128/486
Colonoscopy/Endoscopy	25.6	127/496
Tattoos	22.0	110/500
Health workers	20.0	100/500
Syringes/needles accidents	12.7	62/490
Sex with an HCV infected partner	9.0	35/390
HCV infected relatives (1st degree)	8.4	41/489
Homosexual (men sex with males)	8.3	28/338
Sharing of hygiene objects		
(i.e. razor, toothbrush)	7.6	34/446
Blood products transfusion		
(i.e. platelets, plasma)	4.1	20/485
Hemodyalisis	1.0	5/500

(*)Risk factors are not mutually exclusive (one person could have more than one risk factor).

(†)Based on Yes/No responses (excluding Refuse and Don't know).

Genotype. When taking into consideration only those patients in whom a genotype determination was possible the predominant HCV genotype in our study subjects was the genotype 1. A genotype determination was not possible in 53 (11%) of the 500 patients, of which 46 had a non-detectable viral load. There were 7 patients with measurable viral load in which genotype could not be determined. (Please refer to page 13 paragraph 3 for further

Figure 1. Frequency of Reported Risk Factors



explanation.). Among genotype 1 subtypes, genotype 1a (39.8 %) was more common than 1b (27%). The most common non-1 genotype was genotype 2 of which 2b represented 9.8% of the study population. In general, 82% of the HCV patients had genotype 1, while 18% had non-1 genotypes (Figure 2). A similar distribution (p=0.794) of genotypes was observed after stratifying by gender and age groups. (Table 3).

Figure 2. Genotype Distribution

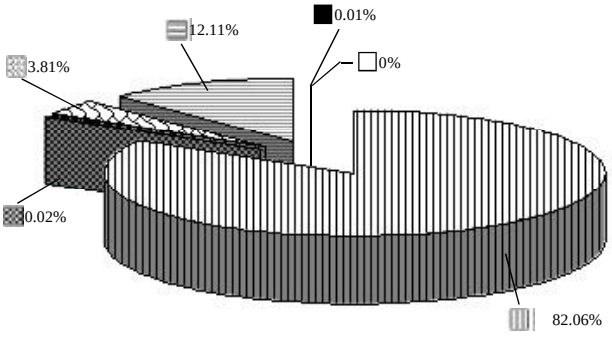


Table 2. Genotype Distribution Among Chronic HCV Patients.

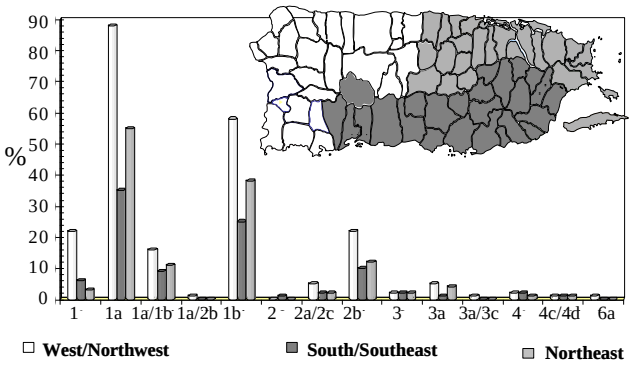
		Gender		Age Range	
Genotype	**n (%)**	**Male**	**Female**	**21-44**	**45-65**
1	31 (6.94)	21 (6.8)	10 (7.25)	5 (4.03)	26 (8.07)
1a	**178 (39.82)**	**126 (40.9)**	**51 (36.96)**	**53 (42.74)**	**124 (38.51)**
1a/1b	36 (8.05)	23 (7.47)	13 (9.42)	9 (7.26)	27 (8.39)
1a/2b	1 (0.22)	1 (0.32)	—-	—-	1 (0.31)
1b	**121 (27.06)**	**83 (26.95)**	**38 (27.54)**	**33 (26.61)**	**88 (27.33)**
2	1 (0.22)	—-	1 (0.72)	—-	1 (0.31)
2a/2c	9 (2.01)	6 (1.95)	3 (2.17)	1 (0.81)	8 (2.48)
2b	**44 (9.84)**	**29 (9.42)**	**15 (10.87)**	**13 (10.48)**	**31 (9.63)**
3	6 (1.34)	4 (1.30)	2 (1.45)	1 (0.81)	5 (1.55)
3a	10 (2.24)	9 (2.92)	1 (0.72)	7 (5.65)	3 (0.93)
3a/3c	1 (0.22)	—-	1 (0.72)	—-	1 (0.31)
4	5 (1.12)	3 (0.97)	2 (1.45)	1 (0.81)	4 (1.24)
4c/4d	3 (0.67)	2 (0.65)	0.72	—-	3 (0.93)
6a	1 (0.22)	1 (0.32)	—-	1 (0.81)	—-
Total*	447	308	138	124	322
		$P^{chi2} = 0.794$		$P^{chi2} = 0.371$	

*Excluding N/A results.

When comparing by type of patient, naïve vs. previously treated or veteran vs. non-veteran, there was no statistically significance differences observed in the proportion of genotypes 1a and b subtypes and 2b in each group (p=0.32 and p=0.291, respectively).

When stratified into three main geographical areas, northeast, south/southeast and west/northwest, no association between the geographic region and distribution of genotypes could be identified (p=0.861). However, samples obtained from the west/northwest region of Puerto Rico contained a slightly higher proportion of genotypes 1a and 1b as compared with the other two regions (Figure 3)

Figure 3. Genotype Distribution by Geographic Areas



Genotype 1a, followed by genotypes 1b and 2b predominate when analyzing for each reported risk factor. Nevertheless, genotype 2b predominated over genotype 1b in subjects that reported to have had sex with an HCV infected partner and in those who reported to have shared hygiene objects with an HCV infected person. Of those subjects that reported hemodialysis as a risk factor, 80% had genotype 1b while 20% were genotype 3.

When the genotypes were grouped into two categories, 1 and non-1, no difference in distribution was observed after analyzing by gender, age groups, veterans, geographic distribution and most risk factors. A different distribution of 1 and non-1 genotypes was observed for those who reported blood product transfusion (95% vs. 5%), sex with an infected partner (70% vs. 30%) and HCV infected first-degree relatives (94% vs. 6%) prior to HCV diagnosis (Table 4). A significant difference (p = 0.014) was found between naïve HCV patients and those previously treated when taking into consideration only two genotype groups: 1 and non-1. The naïve patient's genotypes distribution was 79% vs. 21% (1 vs. non-1), while for patients who received treatment was 89% vs. 11%. This is an expected finding due to the fact that a significant percentage of non-responders are genotype 1 (29-32) (Table 5).

The unconditional logistic regression model was used to evaluate the grouped genotypes (1 vs. non-1) and each HCV related risk factor, adjusting by potential confounding variables. The confounding variables were: type of patients

Table 4. Categories of Genotypes by Risk Factors

Risk factors	Genotype 1 %	Non-1 Genotype %
Surgeries	83.33	16.67
Blood transfusions	85.82	14.18
Tattoo	83	17
Drug users	81.99	18.01
IVDU	82.61	17.39
Syringes sharing	84.5	14.5
Health worker	85.39	14.61
Syringes/needle accidents	81.82	18.18
Contact w/ blood	83	17
Body piercing	81.36	18.64
BP: in males	80.72	19.7
BP: in females	82.17	17.83
Sex w/ infected partner	70	30
Sharing hygiene object*	80	20
HCV infected relatives	93.94	6.06
Sex w/ drug users	84.73	15.27
Multiple sexual partners	78.86	21.14
Homosexual	83.33	16.67
Colonoscopy/Endoscopy	79.28	20.72
Blood product transfusion	94.74	5.26
Hemodyalisis	80	20

Note: Genotypes distribution excluding N/A results

Table 5. Two Categories of Genotypes by Type of Patient.

Genotype	Naïve patients		Treated patients	
	n	%	n	%
1	236	78.93	1308	8.44
Non-1	63	21.07	17	11.56
Total	299	100.00	147	100.00

$p_{chi2} = 0.014$

Note: Genotypes distribution excluding N/A results.

(naïve and treated), age and gender. The results showed that no significant ($p>0.05$) association was found between grouped genotype and the risk factors, even after adjusting by confounding variables.

Viral load. When excluding the non-detectable results, the median viral load was 764,641 IU/ml (Table 6). Sixty three percent (63%) of the patients had a viral load less than 2.0 million IU/ml. For those patients in which the viral load was 2.0 million IU/ml or less, the genotype 1a (41%) predominated followed by 1b (29%), 1a/1b (9%), and 2b (8%); while for those with viral load greater than 2.0 million IU/ml was 1a (38%), 1b (24%), 2b (12%), and 1 (10%). In general, 84% of the patients with less than 2.0 million IU/ml had genotype 1 as compared to 79% of those with higher viral load.

Table 6. Chronic HCV Patients by Viral Load Level.

Viral load	n	%
Not detected	46	9.22
600 - 350,000	115	23.04
350,001 - 850,000	134	26.85
850,001 – 2,000,000	17	3.41
2,000,001 – 6,850,000	77	15.43
6,850,001 – 95,000,000	109	21.84
≥ 95,000,001	1	0.20
Total	500	100.00

Discussion

An important strength of this study is the diversity of patients it included and the 100% response rate of the administered questionnaire. Even though this study was dependent on referrals of patients with hepatitis C by physicians who are members of the Gastroenterology Association of Puerto Rico, the geographic distribution of the patients was diverse, providing a balance between patients living in or near the metropolitan area (49.8%) and those residing in the rest of the Island (50.2%). Also included were patients with different socio-economical and educational backgrounds providing a good spectrum of the Puerto Rican society. The present study reveals that the genotype distribution of HCV infected Puerto Rican patients is essentially uniform throughout the island with a predominance of genotype 1 (82%).

The principal risk factors associated with HCV infection in our study population were: drug use (intravenous/nasal), blood transfusions, sexual relationships with IVDU, and multiple sex partners. These results are consistent with those previously reported in the literature, reaffirming that the principal routes of transmission are parenteral and high-risk sexual exposures (19). A large percentage of our study subjects also reported a clinical history of surgeries, endoscopic procedures and body (ear) piercing prior to HCV diagnosis. Since most of the patients studied have more than one risk factor for HCV infection, a direct relationship between ear piercing, multiple surgeries, endoscopic procedures and HCV infection cannot be established. Even though a direct correlation could not be demonstrated in our study, an association between nosocomial HCV infection and surgeries (41), hemodialysis (42), and usage of multidose vials among others (43) has been previously reported.

The category of HCV risk factor did not affect the genotype distribution in our population, after adjusting by type of patients (naïve or previously treated), age and gender. These results differ from previous studies that have reported an association between HCV genotypes 1a and 3 with intravenous drug use (46-47).

The genotype distribution in our study did not differ between low and high viral loads groups, although a higher proportion of genotype 1 patients had a viral load of 2 million IU/ml or less. This finding also contrasts with prior studies that have reported an association between higher levels of viremia and genotypes 1a and 1b when compared with other genotypes (23).

The technique used to determine HCV genotype sometimes expresses inexact genotype or subtypes resulting in reports with more than one genotype (e.g. 1a/1b). When this happens, LIPA does not have the potential to distinguish coinfection from infection with one genotype (e.g. 1a) or the other (e.g. 1b). Rarely incomplete results of genotypes (without its subtype) may be obtained (e.g. 1_) as well. In this study, 18.6% (n=93) of the genotype results were imprecise measurements. In order to correct for these measurements, genotypes were grouped into four categories (1, 2, 3, all other) and then in two categories (1 and non-1) for bivariate and multivariate analyses. When the genotypes were grouped into these categories, once more, no difference in genotype distribution was observed after analyzing by gender, age groups, veterans, geographic distribution and most risk factors.

The information obtained in this study is the first of its kind in Puerto Rico. It provides the clinicians, regardless of the geographical location, with a good epidemiological profile of our patient population and will help in the management of patients infected with hepatitis C throughout the island. Furthermore, it is an important tool for the allocation of health resources for our population since chronic HCV infection constitutes a very important public health problem in Puerto Rico.

Resumen

Este es el primer estudio hecho en Puerto Rico con el propósito de estimar la prevalencia de los genotipos en pacientes infectados crónicamente con el virus de Hepatitis C y determinar si existe alguna asociación entre el tipo de genotipo y variables tales como edad, sexo, factores de riesgo de contraer hepatitis C y la carga viral.

Se invitaron a participar a aquellos pacientes con hepatitis C crónica diagnosticados entre 1990 al 2002 y que estaban bajo seguimiento con los médicos miembros de la Asociación Puertorriqueña de Gastroenterología en todo Puerto Rico. Eran elegibles todos aquellos pacientes que no tuvieran infección con VIH o alguna otra infección viral hepática, que no hubieran sido tratados o de haberlo sido que hubieran terminado el tratamiento por lo menos con 6 meses de antelación, no tuvieran transplante de órganos y que estuvieran interesados en participar. Todos los sujetos completaron un cuestionario y se les tomó muestras de sangre para determinar el genotipo y la carga viral. Se reclutaron 500 pacientes, la mayoría de los cuales eran varones (68%); 70% de éstos tenían entre 45 a 65 años.

Los principales factores de riesgo fueron: cirugías (75.5%), uso de drogas (46.8%), relaciones sexuales con usuarios de drogas intravenosas /intranasales (30.3%), transfusiones de sangre (30.2%), múltiples parejas sexuales (28.9%), tatuajes (22.0%), accidentes con jeringuillas (12.7%), y relaciones sexuales con una pareja infectada con hepatitis C (9.0%). La mayoría de los pacientes tenía múltiples factores de riesgo para la infección, sólo 3.4% (17/500) reportó un solo factor mientras que 2.0% (10/500) no tenia factores de riesgo. 33% de los pacientes habían sido tratados en algún momento (no respondieron al tratamiento o recurrieron), mientras que el 67% nunca había sido tratado. En general el 82% de los pacientes tenía genotipo 1, mientras que el 18% tenía genotipos no-1. Entre los subtipos de genotipo 1 el 1a (39.8%) era más común que el 1b (27%). El genotipo no-1 mas común lo es el 2, del cual 2b representa el 9.8% de la población del estudio. Se observó una distribución similar cuando se compararon por factores de riesgo excepto para aquellos que reportaron sexo con una pareja infectada ($p = 0.018$), sexo con múltiples parejas ($p = 0.049$) y usuarios de drogas ($p = 0.006$). Para aquellos pacientes con carga viral igual o menor de 2 millones IU/ml, el genotipo 1a (41%) predominaba seguido por 1b (29%) y 1a/1b (9%); Aquellos con carga viral mayor de 2 millones la distribución de genotipos era: 1a (38%) 1b (24%) y 2b (12%). Luego de ajustar por tipo de pacientes (tratados previamente o no), edad y sexo no se encontró relación estadística significativa entre las categorías de genotipo 1 o no-1 y los factores de riesgo.

Este estudio epidemiológico de corte cruzado demuestra que el genotipo 1 es el genotipo mas frecuente en pacientes infectados crónicamente con hepatitis C en Puerto Rico. Los factores principales de riesgo en nuestra población son: las cirugías, el uso de drogas, las transfusiones de sangre, las relaciones sexuales con usuarios de drogas y múltiples parejas sexuales, entre otros. La evidencia estadística demuestra que el genotipo no está afectado por los factores de riesgo, por haber sido tratado anteriormente, por la edad, sexo o región geográfica.

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