ORIGINAL PAPERS

Prevalence of hepatitis C in patients with non-affective psychotic disorders

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ABSTRACT

Introduction: the goal of this study was to determine the prevalence of hepatitis C virus (HCV) infection in patients with non-affective psychotic disorders and to compare it with population-based data.

Material and methods: an observational study was performed that measured anti-HCV antibodies (HCV-RNA in case of seropositivity) in 425 serum samples from patients with non-affective psychosis. Eight patients were positive for anti-HCV (1.9 %) and five had detectable HCV-RNA (1.2 %). The prevalence of viremia was significantly higher than in the general population (OR: 5.4; 95 % CI: 1.9-14.6).

Conclusions: patients with non-affective psychotic disorder have a higher prevalence of active infection than that of the general population and should undergo systematic screening.

Keywords: Hepatitis C. Prevalence. Severe mental disorder. Non-affective psychotic disorder.

INTRODUCTION

Infection with the hepatitis C virus (HCV) represents a heavy burden for health systems, with a global prevalence of 1 % (1). The potential for cure with the newer antiviral drugs has encouraged the establishment of goals for its elimination by 2030 (2). In Spain, various lines of action were established in 2015 and epidemiological surveillance is a key aspect (3). Consequently, over 130,000 patients have been treated and cured. Several epidemiological studies have been performed in the population, obtaining seroprevalence (an-HCV) levels of 0.9 % to 1.3 % and viral load levels of 0.2 % to 0.6 % (4-6). Furthermore, the identification of risk groups in these studies has encouraged a number of elimination strategies, including the one implemented in Cantabria in the general population and risk groups (6-8).

A higher prevalence of infection with parenteral transmission viruses has been reported in patients with severe mental disorders (SMDs), usually in association with risk behaviors (mainly the use of parenteral substances and risky sexual practices) (9). However, most studies rely on seroprevalence levels. Hence, disease burden may be overestimated. Besides, these studies consider SMDs (schizophrenia, bipolar disorder, major depressive disorder, etc.) as a whole and do not differentiate one from another. Finally, we found no studies assessing this association in Spain.

The goal of this study was to determine the prevalence of hepatitis C in a cohort of patients with non-affective psychotic disorders and to compare it with population-derived data.

METHODS

A cross-sectional study was performed using samples from 425 adult patients in the retrospective PAFIP (Programa Asistencial de las Fases Iniciales de Psicosis) cohort, who presented with a non-affective psychotic episode. The samples were collected between 2001 and November 2018. PAFIP is a healthcare program developed in Cantabria that has been previously described (10). Patients are referred to the Psychiatry Department, Hospital Universitario Marqués de Valdecilla, from Primary Care or mental health centers or other hospitals. Referral occurred following an initial episode of non-affective psychosis according to DSM-IV criteria, six months after inclusion for a primary diagnosis with schizophrenia, schizophreniform disorder, schizoaffective disorder, brief reactive psychosis or other specified psycho-

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Table 1. *General characteristics of the study population by serology and viral load status*

Variable	All (n = 425)	Anti-HCV + (n = 8)	HCV-RNA + (n = 5)	p*
Gender (male)	226 (53.2)	3 (37.5)	3 (60 %)	0.56
Age (years)	36.5 (18.5-67.3)	42.6 (29.9-55.8)	45.5 (33.3-55.8)	0.05
Spanish nationality	394 (92.7)	8 (100)	5 (100)	0.68
Low socioeconomic level	209 (49.2)	1 (12.5)	1 (20)	0.18
Low education level	184 (43.3)	4 (50)	3 (60)	0.38
Days from diagnosis	1131 (342-5,601)	2,395 (1,102-4,445)	3,670 (1,102-4,257)	0.55
Smoker	225 (52.9)	5 (62.5)	4 (80)	0.24
Alcohol consumption	93 (21.9)	3 (37.5)	3 (60)	0.07
History of sporadic heroin use	3 (0.7 %)	1 (12.5)	1 (20)	0.04
BMI	26.9 (16.5-56.3)	23.4 (18.9-34.6)	22.6 (19-34.6)	0.28
Abdominal obesity†	207 (48.7)	2 (25)	1 (20)	0.20
HBP‡	127 (29.9)	1 (12.5)	1 (20)	0.50
IFG§	74 (17.4)	1 (12.5)	1 (20)	0.62
Insulin resistance‖	180 (42.4)	5 (62.5)	4 (80)	0.11
Hypertriglyceridemia¶	99 (23.3)	1 (12.5)	1 (20)	0.66
Low HDL-C**	135 (31.8)	2 (25)	2 (40)	0.50
Metabolic syndrome ††	96 (22.6)	0 (0)	0 (0)	0.25
Hemoglobin (g/dl)	14.5 (9.9-17.6)	13.4 (12.3-16.8)	13.9 (12.9-16.8)	0.27
Platelets (x 1000/mm^3)	222.5 (48-421)	223 (153-250)	226 (164-249)	0.76
GOT (U/l)	21 (10-602)	33 (14-77)	35 (32-77)	0,00
GPT (U/l)	21 (6-164)	32 (10-90)	43 (26-90)	0,01
GGT (U/l)	20 (1-650)	24 (7-650)	141 (12-650)	0.03
AP (U/l)	70 (31-150)	68.5 (38-150)	109 (48-150)	0.08
Bilirubin (mg/dl)	0.5 (0.1-2.6)	0.4 (0.2-0.6)	0.6 (0.2-0.8)	0.89
Hypertransaminasemia‡‡	84 (19.8)	5 (62.5)	5 (100)	0.01
Albumin (g/dl)	4.5 (3.7-5.4)	4.4 (4-5)	4.6 (4-5)	0.71
VL (HCV-RNA PCR; IU/ml)	-	-	3,882,184 (291,976-7.8 x 10^6)	
VL (HCV-RNA PCR; log)	-	-	6.6 (5.5-6.9)	

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HBP: high blood pressure; IFG: impaired fasting glycemia; HDL-C: high-density lipoprotein cholesterol; GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; GGT: gamma-glutamyltransferase and AP: alkaline phosphatase. Qualitative variables are expressed as a number and percentage (n; %) whereas quantitative ones are expressed as the median and range (median; range). *Statistical significance for the comparison of positive and negative HCV-RNA patients using the Fisher's exact test for proportions and the Mann-Whitney U-test for mean values. †Defined as an abdominal waist circumference ≥ 94 in males and ≥ 88 in females. ‡Defined as SBP ≥ 135 or DBP ≥ 85 mmHg. §Defined as basal glycemia ≥ 100 mg/dl or diagnosis with/treatment for diabetes mellitus type 2. ‖Defined as HOMA-IR ≥ 2.6. ¶Defined as triglycerides ≥ 150 mg/dl. **Defined as < 40 mg/dl in males and < 50 mg/dl in females. ††Defined as meeting three or more of the above criteria (HBP, IFG, hypertriglyceridemia, low HDL, abdominal obesity). ‡‡Defined as GPT > 40 U/l and/or GOT > 30 U/l.

sis. They were subsequently followed up on an outpatient basis. All had at least moderate psychotic symptoms on inclusion. Patients with mental retardation, other SMDs, neurological disorders, or substance dependence according to DSM-IV criteria were excluded.

Variables associated with the samples stored at the Biobanco Valdecilla (Table 1) were recorded, including: demography, toxic habits, psychiatric disorder-related variables, anthropometry, clinical and lab parameters and risk factors for hepatitis C. Anti-HCV antibodies were measured with the enzyme-linked immunosorbent assay (ELISA) and then INNO-LIA if the ELISA results were inconclusive. HCV-RNA levels were measured in positive samples (COBAS® TaqMan, 2.0; Roche, Pleasanton, CA, USA), with a lower limit of quantitation and detection of 25 IU/ml and 10 IU/ml, respectively.

The principles embodied in the Declaration of Helsinki and subsequent updates were complied with and approval was obtained from the Cantabrian Research Ethics Committee.

A descriptive analysis was performed of patient characteristics and the prevalence was determined together with the 95 % confidence interval (95 % CI). Comparisons between groups for categorical variables were performed using the

Table 2. *Comparison of anti-HCV and HCV-RNA prevalence in the PAFIP cohort* versus *the ETHON cohort and National Survey findings (second seroprevalence study in Spain, 2017-2018)*

	PAFIP (n = 425)	ETHON (n = 12,246)			Survey (n = 7,675)		
	% (95 % CI)	% (95 % CI)	OR (95 % CI)	p	% (95 % CI)	OR (95 % CI)	p
Anti-HCV	1.9 (0.9-3.7)	1.2 (1.0-1.4)	1.6 (0.8-3.2)	0.30	0.9 (0.6-1.1)	2.2 (1.1-4.6)	< 0.05
HCV-RNA	1.2 (0.5-2.7)	0.3 (0.2-0.4)	3.8 (1.5-9.8)	< 0.01	0.2 (0.1-0.3)	5.4 (1.9-14.6)	< 0.01

PAFIP: Protocolo de atención clínica e investigación de los primeros episodios psicóticos de Cantabria; ETHON: Epidemiological Study of Hepatic Infections; Survey: National Survey (second seroprevalence study in Spain, 2017-2018). *Odds ratio and statistical significance resulting from the comparisons between each population cohort and the PAFIP cohort.

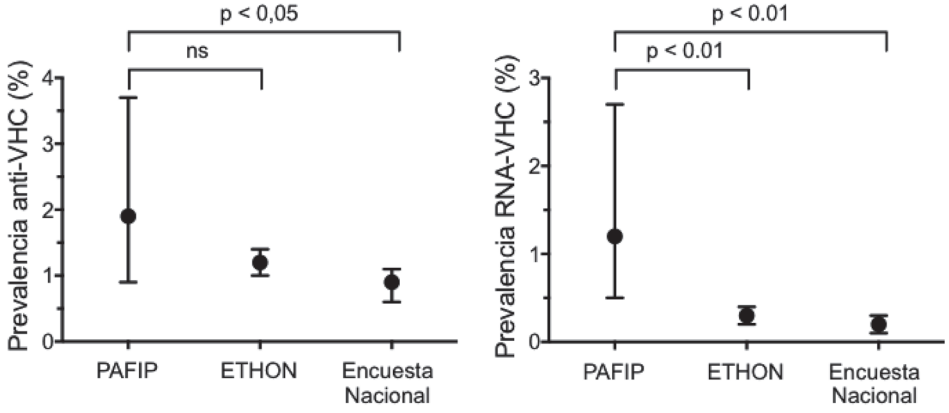

Fig. 1. *Comparison of anti-HCV and HCV-RNA prevalence between the PAFIP, ETHON and National Survey populations (second seroprevalence study in Spain, 2017-2018). Error bars correspond to 95 % CI for prevalence.*

Fisher's exact test and the Mann-Whitney U-test was used for quantitative variables. Comparisons with proportions in population cohorts (Epidemiological Study of Hepatic Infections [ETHON] and second seroprevalence study in Spain, 2017-2018 [National Survey henceforth]) (4,6) were performed using the !CI2IP macro (11). The SPSS (Version 21.0; IBM, USA) software package was used.

RESULTS

The characteristics of the study population are shown in table 1. Samples were analyzed from 425 patients (53.2 %, men) with a median age of 36.5 years (18.5-67.3); 62 % were younger than 40 years. Most (92.7 %) were of Spanish nationality and almost half were of a low socioeconomic (50.1 %) and education level (43.7 %). Only hypertransaminasemia (GPT > 40 U/l and/or GOT > 30 U/l) and a history of sporadic heroin use were significantly higher among viremic subjects (Table 1).

Samples were provided by patients during different stages of their disease; 16.5 % at a median of 383.5 days after diagnosis (range, 342-517), 44.7 % at 1,107 days (1,048-1,262) and 38.8 % at 4,294 days (3,128-5,601). Most (90.1 %) had some antipsychotic medication recorded at sample collection and aripiprazole was the most common one (35.3 %).

Eight patients (1.9 %; 95 % CI: 0.9-3.7) were positive for anti-HCV and five had detectable HCV-RNA (1.2 %; 0.5-2.7). An increase in seroprevalence was observed compared to population-based studies (ETHON and National Survey), which was statistically significant *versus* the National Survey (OR = 2.2; 1.1-4.6). In both cases, a significant increase was found in the prevalence of viremia; OR = 3.8 (1.5-9.8) *versus* the ETHON cohort and OR = 5.4 (1.9-14.6) *versus* the National Survey (Table 2 and Fig. 1) (4,6). Among those cases younger than 40 years, the differences were even higher but statistical significance was only observed when comparing anti-HCV prevalence with the National Survey (Table 3). The influence of time from diagnosis/treatment onset on viral load was not statistically significant.

DISCUSSION

This study showed a prevalence of active HCV infection of 1.2 %, which is four to almost six times higher than among the general population. This was the first study that was exclusively focused on a population with non-af-

Table 3. *Comparison of anti-HCV and HCV-RNA prevalence in the PAFIP cohort in subjects younger than 40 years versus the ETHON cohort and National Survey findings (second seroprevalence study in Spain, 2017-2018)*

	PAFIP (n = 267)	ETHON (n = 2,682)			Survey (n = 2,409)		
	% (95 % CI)	% (95 % CI)	OR (95 % CI)	p	% (95 % CI)	OR (95 % CI)	p
Anti-HCV	1.1 (0.4-3.3)	0.4 (0.3-0.8)	2.5 (0.7-9.0)	0.3	0.1 (0.0-0.3)	13.7 (2.3-82.2)	0.04
HCV-RNA	0.4 (0.1-2.1)	0.2 (0.1-0.4)	2.0 (0.2-17.3)	0.9	0.1 (0.0-0.2)	9.1 (0.6-145.1)	0.5

PAFIP: Protocolo de atención clínica e investigación de los primeros episodios psicóticos de Cantabria; ETHON: Epidemiological Study of Hepatic Infections; Survey: National Survey (second seroprevalence study in Spain, 2017-2018). *Odds ratio and statistical significance resulting from the comparisons between each population cohort and the PAFIP cohort.

fective psychosis, as a condition independent from SMDs. In fact, all reported meta-analyses included studies where several SMDs (schizophrenia, schizoaffective disorder, bipolar disorder, psychosis, major depression, etc.) were represented in varying proportions, without differentiation (9,12). Furthermore, a higher prevalence of HCV infection among patients with SMDs was confirmed, as revealed by a recent meta-analysis of six European studies with a mean prevalence of 4.9 % (range, 0.1-10.7 %) (12). Similar results were obtained by other studies and meta-analyses (9,13). Seroprevalence in our study was lower but represented an increase of 50-100 % over the general population (4,6). More relevant still is the fact that viral load prevalence is 4-6 fold higher than that of the general population (4,6). In fact, there were very few isolated viral load estimates in this population. Specifically, viremia was in 4 % of a cohort of patients with schizophrenia treated with clozapine, although this population was different with long-standing schizophrenia, refractory to treatment, frequent admissions and addictive behaviors (14). Finally, there were greater differences among subjects younger than 40, a notable finding when considering that the prevalence of HCV infection is virtually anecdotal in this population cohort. All the above would justify systematic screening and treatment for patients with non-affective psychotic disorders and other SMDs, as has previously been suggested (15).

This study has the limitation inherent to its design and sample size. However, the results are consistent with previous reports.

To conclude, the prevalence of active HCV infection is four to six times higher in the population with non-affective psychotic disorders. Proactive case searches and treatment strategies should be implemented in this population.

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