EPIDEMIOLOGY OF HEPATITIS C IN GREECE: RESULTS OF THE NATIONWIDE *HEPNET.GREECE* COHORT STUDY

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BACKGROUND/AIMS

HEPNET.GREECE is an ongoing nationwide retrospective-prospective study initiated in 1997. The study is sponsored by the Greek government. The main aims of the study are to evaluate the epidemiology and the course of chronic Hepatitis C (HCV) infection in Greece and their longitudinal changes.
In this initial report, we describe the patients baseline demographic, clinical and virologic characteristics.

METHODS

30 Hepatology centers, spread throughout Greece, participate in the HEPNET.GREECE study. All anti-HCV (+) positive individuals followed in these centers during 1997-2004 who met the inclusion criteria were enrolled in the study.

INCLUSION CRITERIA:

- All anti-HCV (+) individuals with at least one of the following:
  - -transaminasaemia>1.5 times the upper normal values in at least two measurements per month
  - -HCV-RNA positive
  - -RIBA of second or third generation positive
  - -histologic findings of chronic HCV infection
- All patients who were under follow up, independently of treatment and final clinical outcome on 01/01/1997, or patients who initiated their follow-up at the participating centers during the period from 01/01/1997 till the end of 2004
- All patients must had been followed up at the same centers for at least 12 months or should be under follow up at the end of the afore-mentioned period.

EXCLUSION CRITERIA:

-coinfection with HIV or HBV co-infection
-children (i.e age at infection<14 years)

At study entry, we retrospectively collected detailed data on patients demographic characteristics (gender, race, BMI, birth place, residence place, occupation, educational level, marital status, number of children, smoking and alcohol drinking habits). We also collected information for clinical signs and other chronic diseases, as well as for therapy history. Biochemical, virological, histological and serological findings were also recorded.
We used a structured case record form (CRF) for data collection. Data were prospectively updated twice a year. The method of case record form lasted until 2004. CRFs have currently been replaced by a modern, up-to-date electronic data base in which quality control programs are built in.
Study entry was considered the date of patients first visit to the clinic or the date of first HCV diagnosis if that proceeded patients first visit.
Follow-up time was defined as the time interval between study entry and last available patients' clinical information.

RESULTS

In total 1626 patients were identified. Of them 86 were excluded because they were HBV coinfected and 22 because they were younger than 14 years old at study entry. The baseline characteristics of the 1518 individuals included in the study are presented in Table 1.
Over half of them (59.6%) were male. The median age (IQR) of patients at study entry was 40 (30.6-56.1) years while the median (IQR) follow up time was 1.72 (0.39-4.4) (Table 2).
The majority of the study population was born in urban areas (55%), whereas at study entry most of the patients were over-weighted (BMI=25-30: 42.2%) or obese (BMI>30: 10.6%).
The overwhelming majority of patients (92.2%) had no history of acute icteric hepatitis. A 93.5% had no family history of hepatitis neither.
Regarding education level 8.32% of the patients were illiterate, 25.72% had primary education, 42.92% secondary and 23.04% among them had higher/university education.
A 5% of the patients with HCV appertained in high risk avocations such as practitioners in health-related business.
28.7% of the patients presented at least one other chronic disease (22.7% presented diabetes mellitus, 38.69% had hypertension, 19.35% had cardiovascular disease and only 3.26% had neoplasia, while 47.55% presented various other chronic diseases).
Intravenous drug use and transfusion prior to 1992 were the leading reasons for infection.
The frequency of clinical signs of advanced liver disease at study entry is presented in Figure 1. The majority of subjects had hepatomegaly.
HCV genotype was available for 913 subjects. The distribution of the HCV genotype is presented in Figure 2. The majority of subjects (415 or 44%) had HCV genotype 1 followed by HCV genotype 3 (309 or 32.8%) and genotype 4 (144 or 15.3%). For 30 subjects HCV genotype was unidentifiable.

Table 1. Demographic characteristics of the study population

Characteristic	N	%
Gender		
Male	905	59.6
Female	613	40.4
Birth Place		
Rural	348	29.5
Semi-urban	184	15.6
Urban	648	54.9
Residence Place		
Rural	180	12.7
Semi-urban	126	8.9
Urban	1113	78.4
History of acute icteric hepatitis		
Yes	117	7.8
No	1375	92.2
Source of Infection		
Intravenous drug user	483	33.8
Blood/blood products transfusion (prior to 1992)	376	26.3
Other	571	39.9

Figure 1. Distribution of clinical signs at study entry

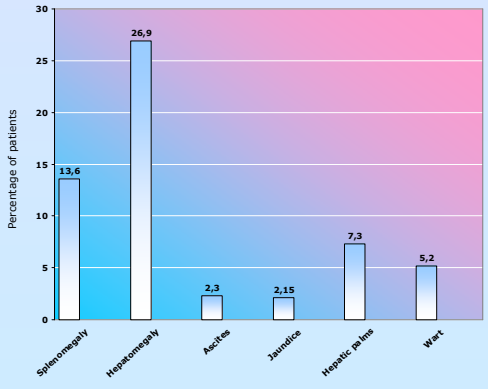
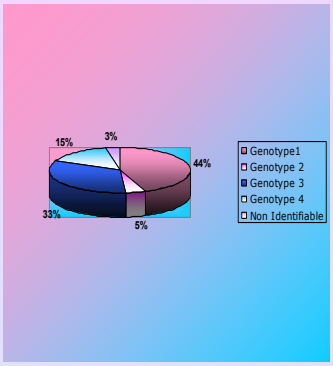


Table 2. Age at study entry and follow up time of the study population

Characteristic	N	Mean	S D	Median	Interquantile range	Range
Follow-up time (years)	1518	2.96	3.5	1.72	0.39-4.4	0-28.5
Age at study entry (years)	1516	43.5	15.8	40.5	30.6-56.12	14.1-85.8

Figure 2. Distribution of HCV genotypes



For 620 of the 913 patients with known HCV genotype the date of infection could be estimated. For those the date of infection was estimated based on the following assumptions:

-for IDUs the date of first intravenous drug use

-for individuals infected through transfusion prior to 1992 the date of first transfusion

In this subpopulation we examined the temporal trends in HCV genotype. Figure 3 presents the distribution of HCV genotypes by time of infection.

A reduction in the proportion of subjects with genotype 1 or 4 and an increase in the proportion of subjects with genotype 3 was observed over time. More specifically, among those infected prior to 1980, 54.1% of the subjects had genotype 1 and 22.1% had genotype 4 while 16% had genotype 3. The corresponding figures for those infected during 1980-1992 were 35.6%, 15.5% and 45% respectively, becoming 34.8%, 8.7% and 53.4% for those infected after 1992. The distribution of HCV genotypes by time of infection in IVDUS, transfused patients and patients with unknown source of infection is shown in Figures 4, 5 and 6.

As it can be seen from Figure 7, the source of infection also changed over time, with transfusion being the predominant source of infection prior to 1992 and IDU after 1992. Furthermore, figures 4, 5 and 6 present the distribution of HCV genotypes by time of infection in IVDUs, transfused patients and patients with unknown source of infection. Given that genotype 1 was the predominant genotype in transfusion related infections and genotype 3 in IDU ones, the change in the source of infection seems to parallel the change in the distribution of the HCV genotype over time.

Figure 3. Distribution of HCV genotypes by time of infection

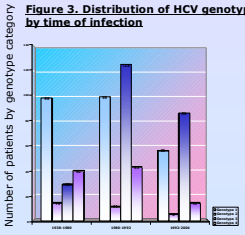


Figure 4. Distribution of HCV genotypes by time of infection in IVDUS

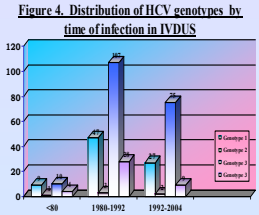


Figure 5.Distribution of HCV genotypes by time of infection in transfused patients

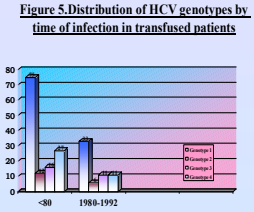


Figure 6. Distribution of HCV genotypes by time of infection in patients with unknown source of infection

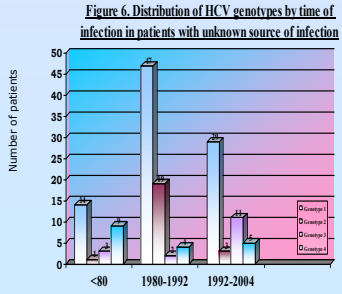
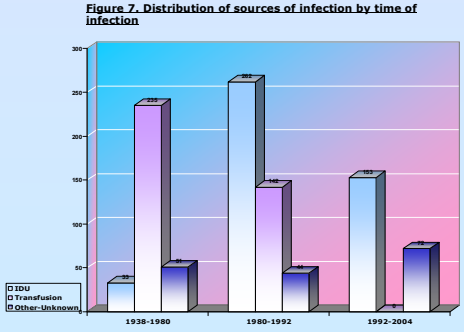


Figure 7. Distribution of sources of infection by time of infection



Conclusions

Our results showed that:
-the epidemiology of chronic HCV infection in Greece is changing over the last decades.
-there is a decrease in HCV genotype 1 accompanied with a possible decrease in HCV genotype4 and an obvious increase in HCV genotype3 infections. The decrease in the proportion of HCV genotype1 infections has started in 80s, before the institution of anti-HCV testing of blood products in 1992.
-This nationwide cohort study has provided important data contributing to further elucidation of the epidemiology and course of chronic HCV infection in Greece.