Prevalence of Hepatitis C Virus Infection among Egyptian Patients with Schizophrenia

Fawzi MH, Fawzi MM (Jr.), Fawzi M M, Said NS

Department of Psychiatry, Faculty of Medicine, Zagazig University, Sharkia, Egypt.

ABSTRACT

Background: Although the importance of identifying high-risk groups and individuals infected with hepatitis C virus (HCV) has been recognized, there is a dearth of published information on the prevalence of HCV among people with schizophrenia, a population which is probably at high risk, particularly in a country such as Egypt, where HCV infection is rampant and causing a huge public health crisis. **Objective:** Our aim is to determine the frequency of HCV infection in a sample of Egyptian schizophrenia patients. **Subjects and method:** A total of 413 patients with the diagnosis of schizophrenia according to ICD-10 were recruited. Both clinical and psychiatric evaluation was done followed by blood screening test for HCV antibodies using a third generation ELISA technique. **Results:** Of the 413 patients diagnosed of schizophrenia whom we studied, 131 (31.7%) were HCV positive compared to 86 (21.5%) HCV positive out of 400 control subjects (p=0.001). In all of the HCV positive individuals, the diagnosis of hepatitis C was a de-novo diagnosis. HCV infection was significantly higher among males than females in both patient (p=0.010) and control groups (p=0.002) and among older than younger patients (p=0.000) and controls (p=0.000). Correlations between history of injection for schistosomiasis and HCV infection in both patients and controls were highly significant (p=0.000) and also between intravenous drug addiction and HCV infection in patients (p=0.000) as well as in controls. **Conclusion:** We should like, therefore, to suggest that Egyptian patients with schizophrenia have to be offered screening for HCV infection. This may have to be more mandatory if patients are from Sharkia governorate, male and above the age of 40, and especially so if there is a history of injection for schistosomiasis or intravenous drug addiction.

Key words: Schizophrenia, Hepatitis C virus, Schistosomiasis, Egypt

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INTRODUCTION

Hepatitis C virus (HCV) infection is now a serious global health problem[1] with nearly 3% of the world's population, or 170 million individuals having chronic HCV[2] and with an associated high mortality that is expected to increase substantially in the next 20 years[3-4]. HCV in Egypt, however, has been particularly rampant for decades causing a huge public health crisis. Egypt probably has the highest prevalence of the virus in the world[5] and is approximately 10-fold greater than in the United States and Europe[6]. The overall prevalence of antibody to HCV in the Egyptian general population

is around 15-20%[7]. Though an intrafamilial spread of HCV in Egypt has been recently suggested[8-9], the very high prevalence of HCV infection has been traced back to the mass campaigns to treat schistosomiasis before 1980 with repeated intravenous injections of tartar emetic (potassium antimony tartarate) without following rigorous hygiene standards[7, 10]. Continued transmission in Egypt has been associated with transfusion of unscreened blood, invasive medical procedures including surgical operations, hemodialysis and injections by informal health care providers[11]. Infection with HCV becomes persistent in 85% or more of patients, and within 10- 20 years; at least 20 percent of patients with chronic hepatitis C develop cirrhosis[12]. After 20 to 40 years, a smaller percentage of patients with chronic disease progress to hepatocellular carcinoma[13]. The incidence of hepatocellular carcinoma, however, seems to be rising[14] and is progressively affecting younger persons with evidence indicating that HCV infection is responsible for the current trends[15].

The increasing number of cases of hepatocellular carcinoma is but one indicator of the importance of identifying high-risk groups and individuals infected with HCV. Although few studies have examined HCV infection among persons with serious mental illness, this population is probably at high risk. In a study of 931 patients with severe mental illness undergoing inpatient or outpatient treatment in Connecticut, Maryland, New Hampshire, or North Carolina, the HCV sero-prevalence rates (19.6%) was approximately 11 times the estimated US population rate[16]. In another large study in Japan for detection of anti-HCV antibody in 1193 hospitalized patients, the prevalence of the inpatients diagnosed in schizophrenia group accounted for 6.2% indicating significantly higher ratio than that of healthy controls[17]. It may be remarked, however, that rates provided by such non-Egyptian studies have not surpassed the overall prevalence of HCV infection reported for our general population. Yet, it is not known whether the prevalence of HCV infection among patients with schizophrenia could be even higher than of the general population in Egypt. Part of the reason that HCV infection rates is expected to be high in patients with schizophrenia is tied to behaviors that place them at increased risk for contracting the disease. Intravenous (IV) drug use, which is one of such risky behaviors that has been strongly tied with HCV infection[18-19] may be a frequent comorbid condition with schizophrenia[20].

Despite the numerous studies that have been performed on HCV infection demonstrating alarmingly high prevalence rates in Egypt, and despite the expectation that patients with severe mental illness are at particularly high risk of HCV infection as depicted from reports from other countries, there is surprisingly a dearth of published information on the prevalence of HCV among people with schizophrenia in the Egyptian population.

Our aim in this cross-sectional study was to determine the frequency of HCV infection in a sample of Egyptian schizophrenia patients.

SUBJECT AND METHOD

Participants:

Patients: All consecutive attendees at the psychiatric out-patients clinic, Zagazig

University Hospitals, Zagazig, with a diagnosis of schizophrenia (F.20 of the ICD10) and aged ≥18 years, between January and December 2007, were included in the study. The only exclusion criteria were duration of <1 year of illness and failure to give consent or to provide blood for analysis.

Control subjects: A total number of 400 apparently healthy individuals were selected from blood donors presenting at the blood bank of Clinical Pathology Department, Zagazig University Hospital (327 donor), as well as from relatives of hospitalized patients for surgery (45 individual) and current or ex-Clinical Pathology department workers at the same hospital (28 worker) who agreed to participate in the study. They were frequency-matched to the patient group as much as possible by gender and 5-year age category.

Assessments:

Data evaluated from all patients and controls included a standardized medical history and a thorough physical examination. Patients were also subjected to a semi-structured psychiatric interview during which the socio-demographic and other data relevant to the study were collected and the ICD-10 diagnosis of schizophrenia was confirmed. On completion of the interview, a blood specimen was collected. There was no further follow-up with the study subjects. Screening for HCV antibodies was performed by a third generation ELISA technique (Abbott Diagnostics, Maidenhead, UK). HCV infection was verified by a reverse transcriptase-polymerase chain reaction (RT-PCR) assay using the HCV Amplicor Test (Amplicor PCR Diagnostics, Roche Diagnostic System, Lewes, UK). Nucleotide primers corresponding to sequences in the 5' noncoding region of the HCV genome were used for amplification in the nested reverse-transcription PCR. The amplified gene product was identified by staining with ethidium bromide after gel electrophoresis. All specimens were tested in duplicate. If the test results were discrepant, another duplicate PCR was performed, and a specimen was considered to be HCV-positive if at least two of the four tests were positive.

Statistical analysis:

Continuous data were expressed as mean ± standard deviation and were compared by use of Student's T-test. Categorical data were expressed as frequencies or proportions and were analyzed with the two-tailed chi-square test. A multivariate logistic regression analysis was conducted to identify factors associated with HCV infection.

Data were analyzed using SPSS version 11.0.1. Software[21]. Results were considered significant if *p* value was ≤0.05.

RESULTS

Table (1) shows the demographic characteristics of patients and controls. More patients than controls were unemployed (*p*=0.021) and unmarried (*p*=0.027).

Table (2) shows the frequency distribution of HCV positivity. More patients (31.7%) than controls (21.5%) were HCV positive (*p*=0.001). Of the 27 hospital workers 6 (22.2%) were HCV positive. None of the participants declared any attempt to test for the presence of, or received treatment for, HCV infection prior to his or her inclusion

in this study. In all of the HCV positive individuals, the diagnosis of hepatitis C was a de-novo diagnosis.

HCV positivity was further analyzed by gender (table 3). More patients than controls were HCV positive whether males (p=0.019) or females (p=0.038). Also, more males than females were HCV positive whether in the patient (p=0.010) or control group (p=0.002).

Age related prevalence of HCV positivity was also assessed. Table (4) shows the frequency distribution of HCV positivity among patients and controls assorted into two groups, group (A) included those aged forty or younger and group (B) included those above the age of forty. Significantly more patients than controls were HCV positive in both groups. However, the prevalence of HCV infection was significantly higher among older than younger patients (p=0.000) and controls (p=0.000).

Table (1): Demographic characteristics of participants

		Patients (N=413)	Controls (N=400)	Analysis
Gender:	Male: N Female: N	293 120	259 141	χ^2=3.577; df=1; p=0.060
Age (years):	Male: Mean (± SD) Female: Mean (± SD) Total: Mean (± SD)	37.5 (±13.499) 35.6 (±13.786) 36.8 (±13.669)	36.9 (±12.814) 35.1 (±12.677) 35.7 (±12.734)	t=1.101; df= 811; p=0.271
Residency:	Urban: N Rural: N	215 198	207 193	χ^2 =0.008; df=1; p=0.930
Education	Intermediate or below: N Above intermediate: N	249 164	219 181	χ^2 =2.554; df=1; p=0.110
Employment:	Employed: N Unemployed/Retired: N	139 274	166 234	χ^2=5.333; df=1; p=0.021
Marital status:	Married: N Unmarried*: N	189 224	214 186	χ^2=4.866; df=1; p=0.027

Unmarried= Never married, divorced, separated and widowed.

Table (2): Frequency distribution of HCV-positivity

	Patients		**Controls**		**Analysis**
	N	**(%)**	**N**	**(%)**	
HCV-Positive HCV-Negative	131 282	(31.7) (68.3)	86 314	(21.5) (78.5)	χ^2 =10.845; df=1; p=0.001
Total	413	(100)	400	(100)	

Table (3): Frequency distribution of HCV-positivity, by gender

	Gender	Patients	Controls	Total	Analysis
Male	HCV-Positive HCV-Negative Total	104 189 293	68 191 259	172 380 552	χ^2 =5.472; df=1; *p*=0.019
Female	HCV-Positive HCV-Negative Total	27 93 120	18 123 141	45 216 261	χ^2 =4.305; df=1; *p*=0.038
		χ^2 =6.638; df=1; *p*=0.010	χ^2 =9.842; df=1; *p*=0.002		

Table (4): Frequency distribution of HCV-positivity, by age group

	Age group	Patients	Controls	Total	Analysis
Forty or younger	HCV-Positive HCV-Negative Total	46 190 236	26 188 214	72 378 450	χ^2 =4.501; df=1; *p*=0.034
Above forty	HCV-Positive HCV-Negative Total	85 92 177	60 126 186	145 218 363	χ^2 =9.396; df=1; *p*=0.002
		χ^2 =38.015; df=1; *p*=0.000	χ^2 =23.841; df=1; *p*=0.000		

Risk factors of HCV transmission were assessed. Table (5) shows the number of patients exposed to these risk factors and those found to be HCV positive. Of 150 patients (36.3% of patient group) who had a history of injection treatment for schistosomiasis 37 (24.7% of those who received treatment) were HCV positive. A majority of these patients who received injection treatment for schistosomiasis (121 patients; 80.7%) were above the age of forty. Of 81 patients (19.6%) who admitted intravenous drug use 19 (23.5%) were HCV positive. Of 212 patients (51.3%) who used folk medicine and cultural practices, e.g., 'hegama' (blood letting) and tattooing, 14 patients (6.6%) were HCV positive. Of 78 patients (18.9% of patient group) who reported blood transfusions with or without surgical intervention 5 (6.4% of the blood transfused) were HCV positive. Of 69 patients (16.7%) who reported household contact with hepatitis 3 (4.3%) were HCV positive. On univariate analysis, injection for schistosomiasis (*p*=0.001) and intravenous drug addiction (*p*=0.001) were the only two variables with a statistically significant correlation with the presence of HCV infection. There were no other statistically significant differences between the HCV positive and HCV negative patients in terms of demographic characteristics or topic areas associated with HCV infection/transmission such as the use of folk medicine and cultural practices, blood transfusions with or without surgical or dental intervention and history of household contact with hepatitis. Results of the control subjects, compared with those of patients, showed similar figures as regard history of injection for

schistosomiasis, but significantly lower figures (p=0.000) as regard intravenous drug addiction, with only 3 individuals (0.75%) admitting intravenous drug use. None of whom was HCV positive. The use of folk medicine and cultural practices among control subjects was also significantly lower (13 individuals; 1 HCV positive) than among patients (p=0.000). However, comparison between HCV positivity of patients and controls exposed to other risk factors did not show significant differences. Results of the univariate analysis for control subjects showed that injection for schistosomiasis to be the only variable which significantly correlated with HCV infection (p=0.001).

Table (5): Risk factors of HCV transmission in the schizophrenia patients

Risk factor	Patients exposed to risk F.	HCV +ve patients	
	N	N	%
Injection for schistosomiasis	150	37	24.7
Intravenous drug addiction	81	19	23.5
Folk medicine and cultural practices (e.g., hegama' and tattooing)	212	14	6.6
Blood transfusions with or without surgical intervention	78	5	6.4
Household contact with Hepatitis	69	3	4.3

DISCUSSION

HCV infection, which poses a serious health threat around the world, has a unique high prevalence in Egypt attracting the attention of investigators and becoming a source of concern. However, psychiatric aspects of HCV though may prove important, have received the least attention. Themes of the available few psychiatric studies were mainly related to the impact of HCV on issues such as 'quality of life'. These studies, however, could tell nothing about the magnitude of the problem as they tended to utilize small convenient samples of patients with HCV infection, drawn from services such as tropical[22] or obesity clinics[23]. The presence of psychiatric symptoms in HCV infected patients was the exclusion, rather than the inclusion, criterion in these studies which tended also not to involve control groups. Current study, to the best of our knowledge, is the first to estimate the frequency of HCV infection in patients with schizophrenia in Sharkia governorate. We also failed to find studies from other parts of Egypt that could be compared with.

In this study, the prevalence of HCV positivity was determined using a sensitive third-generation HCV ELISA and results were further verified by an RT-PCR.

Our control group consisted largely of blood donors who were supposed to be healthy and probably not adopting risk practices. In fact, only three control subjects (0.75%) were reported to use illegal intravenous drugs. Nevertheless, the prevalence of HCV positivity among controls was high (21.5%) though not higher than that reported for the general population in Sharkia governorate, which may have the highest prevalence in Egypt with estimates as high as 25.8%[24]. Although hospital workers included in the control group have or had frequent exposure to blood and blood products, as they worked at the Clinical Pathology Department, they did not show significantly higher prevalence rate of HCV positivity than other controls in our study. This may be because of the small sample size of this

subgroup. Should it have included other high risk medical personnel like surgeons, dentists, nursing staff and Physicians, a higher prevalence rate might have been obtained?

Male preponderance in HCV-infected individuals which we found among patients and controls was also reported by many others[24-27]. However, we are wondering whether this gender preference would simply be a reflection of a difference in risk practices or would females be endowed with some intrinsic characteristics that protect them from contracting HCV infection and from developing schizophrenia as well?! Previous literature was not of much help but interestingly, it was noted in a recent study that female blood donors, compared with male blood donors, had higher prevalence of spontaneous viral clearance as well as biochemical and histological evidence of less advanced liver disease[28]. Indeed, relating such differences to intrinsic characteristics of female gender could prove to be an intriguing idea! Nevertheless, the lower prevalence of HCV among females could also be secondary to associated factors such as younger age which may denote less exposure. On the other hand, there are studies which do not support this gender difference[11, 29] and even slightly higher prevalence of HCV infection in females has been also claimed[30].

The prevalence of HCV infection was reported to vary by age[31]. In USA, HCV seroprevalence among blood donors ranged from 0.5 per 1000 in donors younger than 20 years, to 6.9 per 1000 in donors of ages 30 to 39 years[32]. In one community-based study at Zagazig, Egypt, the seropositivity of HCV was observed to increase sharply from 3.6 % in those below 20 years of age to 30.9 % in individuals above 40[33]. Our study also confirms this observation showing that in patients as well as in control subjects, there was a higher prevalence of HCV infection among older than younger individuals. These results may reinforce the probable influence of the long-term exposure to HCV, but they may also reflect the higher risk of transmission in the distant past, probably through parenteral anti-schistosoma injections. Indeed, we noted that a history of receiving injection treatment for schistosomiasis to be significantly more frequent among patients and controls above the age of forty than younger participants.

The main aim of this study, however, was to determine the frequency of HCV infection in patients with schizophrenia. The main outcome was that rates of HCV positivity are much higher among these patients than among controls representative of the general population. The reason for this alarming result is not far fetched. The literature shows that injection drug use is currently the primary transmission route for HCV, and that a majority of injection drug users are currently infected with HCV[34-36] and that although people with schizophrenia might comprise a small percentage of the population who misuse drugs, there is an extraordinarily high rate of drug misuse among people with schizophrenia[37-40]. Here we found that 81 patients (19.6%) were illicit injection drug users, 19 (23.5%) of them were HCV positive, whereas in the control group we found only 3 (0.75%) illicit injection drug users, none of whom was HCV positive. Our data suggest that the drug use as a risk factor for HCV positivity in patients with schizophrenia is no less grave than the worldwide signalized Egyptian anti-schistosoma treatment.

Although a history of blood transfusion, use of folk medicine and cultural practices and household contact with hepatitis have all been reported to be associated with HCV infection[41-46,] none of them succeeded to show itself in this study as an independent risk factor for HCV infection. Our study does have several limitations. First, its cross-sectional design allowed for the determination of prevalent, rather than incident, cases of HCV. Analysis of prevalent cases does not allow for the inference of a causal relation between a characteristic and infection. Second, there is a possibility of a sampling bias. This study was conducted in a sample from a single center in Zagazig city. One could argue that being a tertiary-care center and an academic institution, psychiatric patients evaluated at Zagazig University Hospitals may be more likely to have increased medical complications, thus affecting HCV prevalence. We believe, however, that our large outpatient sample represents a population that would normally be seen in general outpatient psychiatric practice in Lower Egypt. It is also possible that the selection of the control group in this study as representative of the population of Sharkia governorate may be questioned. Other limitations of the study are linked to the difficulties inherent in self-reporting of behaviors such as sexual activity and drug use. Finally, the self-report of risk behaviors, especially those of a sensitive or illegal nature, is vulnerable to reporting bias. This might have lead to an underestimate of the association between these variables and being HCV positive.

Despite these limitations, we believe that our study has important implications. The recognition that patients with schizophrenia, who are coming from Sharkia, especially if male and above the age of 40, are representing an increased risk group for HCV implies that the psychiatrists and other medical practitioners who come across these patients should offer them testing for HCV. Since no vaccine is yet available for HCV infection, the most effective control measure would be to prevent this potentially life-threatening viral disease. Among important preventive measures are the identification, counseling and testing of persons at risk[47]. Our observation that the diagnosis of hepatitis C was a de-novo diagnosis in all of the HCV positive individuals should raise particular concern that HCV which was not suspected on clinical grounds may frequently remain undetected unless specifically sought for. Individuals with HCV infection, therefore, commonly fail to receive appropriate treatment to limit liver damage and unknowingly may be a source of infection to others[16].

Finally, having known that more than 30% of our patients with schizophrenia are harboring HCV it may be an implication for further research to know whether this sizeable proportion of population can be treated effectively and safely for HCV infection or are they ineligible for treatment? Clinical experience treating HCV in patients with schizophrenia is limited and to date, little is known whether such patients, compared with HCV patients without schizophrenia, are for example less compliant to antiviral therapy, whether they are more prone to psychosis exacerbation, mood disturbances and/or other neuropsychiatric complications, whether they can be treated with interferon monotherapy or can tolerate the currently recommended combination therapy including pegylated or nonpegylated interferon alpha (IFN) and ribavirin[48] and whether a comanagement with the

hepatologist and psychiatrist or psychotropic medications is cost-benefit and what are the barriers to receiving HCV care in this population? Studies so far have been few and samples have been small although we have plenty of patients as demonstrated by this study. Further research is worthwhile.

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Address of Correspondence:
Fawzi M. Department of Psychiatry**,** Faculty of Medicine, Zagazig University.
e-mail: *mfawzi40@yahoo.co.uk*