SEROPREVALENCE AND RISK FACTORS OF HCV IN DIALYSIS PATIENTS

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ABSTRACT

Nowadays, increased seroprevalence of hepatitis C virus (HCV) in hemodialysis (HD) patients is an important problem. In this study, it was aimed to investigate the seroprevalence and risk factors leading to spread of HCV in HD and continuous ambulatory peritoneal dialysis (CAPD) patients. 67 HD and 35 CAPD patients were enrolled in the study, 44 (43.1%) of them were female and 58 (56.9%) were male. Any risk factor for HCV infection was questioned. Third generation ELISA reagent was used in the study. In our HD Center, all precautions have been taken for the prevention of spreading of HCV. Rooms and dialysis machines of HCV patients were separated from others. Mean age of cases was 41.6±15.3 (range 19-75) year. All cases except two had blood transfusion and all cases had at least one surgical intervention (central venous catheter and/or arterio-venous shunting operation). Eight (7.8%) cases had dental interventions including conservative tooth treatment or tooth extractions. There was not relation between low socioeconomic status, duration time of dialysis and higher prevalence of HCV in dialysis patients (p>0.05). In general, anti HCV seropositivity in our center was 41% and these cases were generally asymptomatic, but had elevated liver enzyme levels and slightly decreased albumin levels and at least all cases had one risk factor. Seroconversion rate/year of our anti HCV (-) patients were 0.148/patients year in HD patients and 0.002/patients year in CAPD patients, respectively. The seroconversion rate/year and prevalence of HCV is higher in HD patients than CAPD patients. It should be necessary to take additional measures to universal precautions for the prevention of spreading of HCV such as separation of dialysis machines, education of nurses and to change gloves regularly when moving from patient to patient, etc.

Key Words: Hemodialysis, Hepatitis C, Risk factors, Blood Transfusion.

INTRODUCTION

Approximately 4 million persons in the United States and probably more than 100 million persons worldwide are infected with hepatitis C virus (HCV). The virus has the unique ability to cause persistent infection in susceptible hosts after parenteral or percutaneous transmission, and its underlying mechanisms are not well understood. Hepatitis C virus, which before its identification was labeled "non A, non B hepatitis" is a linear, single-stranded, (1,3,4,5,6) Department of Nephrology.
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positive-sense, 9500 nucleotide RNA virus, the genome of which is similar in organization to that of flaviviruses and pestiviruses; HCV constitutes its own genus in the family Flaviviridae. The HCV genome contains a single large open reading frame (gene) that codes for a virus polyprotein of approximately 3000 amino acids (1-3).

The 5' end of the genome consists of an untranslated region adjacent to the genes for structural proteins, the nucleocapsid core protein and two envelope glycoproteins, E1 and E2/NS1. Nucleotide sequencing has identified at least six distinct genotypes, as well as subtypes within genotypes, of HCV. The genotypic diversity of HCV results from its high mutation rate. There is no specific treatment for HCV and however there are new hopeful studies for that (2,4,5).

Essentially, it is determined that genotype 1, 2 and 3 are seen very often in all over the world, genotype 1b is the main genotype in Japan, Eastern and Southern Europe and Southeast Asia. It is suggested that the treatment and prognosis of that illness changes according to the type of genotypes. Especially in the patients with HCV genotype 1b, there is no correlation between the amount of viral load and response to interferon treatment. Type 1 is seen more often after blood transfusion and in sporadic hepatitis (6).

Initial studies reported on HCV antibody prevalence in hemodialysis (HD) patients ranging from 2 to 60%. A number of risk factors account for the increased risk of HCV infection in hemodialysis patients. These include blood transfusions, immune defects relating to viremia and extracorporeal hemocirculation that is repeated (7).

We aimed to determine the risk factors that are important for spreading of HCV and HCV seroprevalence in HD and CAPD patients in our HD center.

SUBJECTS AND METHODS

PATIENTS AND STUDY DESIGN

67 HD [38 Male (M), 29 Female (F)] and 35 CAPD [20 M, 15 F] patients undergoing dialysis program in HD center, Medical Faculty of Dicle University were evaluated according to prospective cohort study from January 1999 to December 1999. Our new renal dialysis center started its function since 1998. The rooms of HD patients, dialysis machines and personnel were divided in three sections such as HBV, HCV and normal groups. Any risk factor for HCV infection (blood or blood products transfusion, low socioeconomic status, surgical interventions, intrafamilial transmission and hospitalization) was questioned. The ethical committee of the university hospital approved the protocol of the study. All patients and controls gave written informed consent to the study.

Blood sampling

The collection of blood samples of controls was performed in early morning. In patients undergoing HD, blood samples were drawn just before the start of HD and immediately after its end from the arterial line. Freshly drawn blood (15 ml) samples obtained and immediately centrifuged at 200 g (20 min at
24°C). Then, centrifuged samples were investigated by Third generation ELISA reagent (Equipar, Sri. -Italy) and Tecan-Minilyser (Austria) apparatus. The results were supported immunoComb II HCV test (indirect solid phase enzyme immunoassay-EIA, Organics-Israel). Cut-off value: After finding mean values of both two positive controls and two negative controls, the results were divided by three. Cut off: positive control+negative control/3.

Hemodialysis

The patients received 5 hour and three times per week HD with a PS hollow fiber disposable dialyser (Fresenius Medical Care, Germany) and dialysers were never reused. HD was carried out using Braun-Dialog and Fresenius-4008S (Germany) dialysis machines and bicarbonate as dialysate. All patients were receiving heparin (low molecule weight heparin). Machines were heat disinfected between treatments and chemically every month. Screening of anti-HCV antibodies and monitoring of alanine aminotransferase (ALT) and albumin levels were part of HD center routine. Blood samples are collected every 2 weeks from anti-HCV negative patients and every 4 weeks from anti-HCV positive ones. Medical records were kept constantly for all patients, and these records included data such as symptoms of hepatitis, history of liver enzyme abnormalities, medication history, past medical history, history of transfusions, dialysis schedule, bleeding episodes, and demographic and risk factors.

Statistical Analysis

Statistical analyses were made in SPSS 7.5 PC program. Results were expressed as means±SD. Two different groups were compared by independent t test. The one-way ANOVA and post hoc Bonferroni tests were used to compare independent-unpaired parametric samples of different groups, chi-square test were used to compare categorical samples and the Spearman correlation tests were used to determine the correlations. Values of p<0.05 were considered statistically significant.

RESULTS

In table 1, age, duration of hemodialysis and laboratory data of patients in HD and CAPD group were reported, and in table 2 all of them were compared according to type of hepatitis. 44 of patients were female and 58 were male. Mean age of patients was 41.6±15.3. HCV patients (40.8±15.9) were younger than HBV (49.4±16.0) and normal (44.6±14.8) groups, but there was statistically no difference between them (p>0.05).

There was difference in ALT (p=0.03) and AST (p=0.01) levels between these groups. There was statistically significant difference in ALT levels between normal and HCV (+) groups (p=0.03) and that of AST levels between normal and HbsAg (+) groups (p=0.01). However, duration of hemodialysis, albumin concentrations and ages of HCV patients weren't statistically different from other groups (p>0.05). All of the patients had at least one risk factor. All patients except two had blood transfusion, all patients had at least one surgical intervention (central venous catheter and/or arterio-venous shunting operation).
Only eight (7.8%) patients had dental interventions including conservative tooth treatment or tooth extractions. All patients had a social guarantee. However, the socioeconomic status of patients those were insured by social guarantees and by government were lower than that of Western societies. There was no relation between low socioeconomic status, time of dialysis duration and prevalence of HCV in dialysis patients (p>0.05). In general, anti HCV seropositivity in our center was 41% and these patients were generally asymptomatic, but had elevated liver enzyme levels and decreased albumin levels (Figure 1 and 2).

Table 1. Sociodemographic and laboratory data of patients in HD and CAPD groups.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>HD (n=67)</th>
<th>CAPD (n=35)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Year)</td>
<td>44.6±16.4</td>
<td>40.3±13.8</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Duration time of Dialysis (Month)</td>
<td>15.9±9.0</td>
<td>43.8±34.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>3.4±0.6</td>
<td>3.0±0.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>58±63</td>
<td>42±73</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>36±33</td>
<td>31±44</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 2. Sociodemographic and laboratory data of patients according to type of hepatitis.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>NORMAL n=69</th>
<th>HCV n=39</th>
<th>HBV n=11</th>
<th>HCV+HBV n=3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Year)</td>
<td>44.6±14.8</td>
<td>40.8±15.9</td>
<td>49.4±16.0</td>
<td>33.7±7.6</td>
</tr>
<tr>
<td>Duration time of Dialysis (Mnh)</td>
<td>28.3±23.9</td>
<td>23.1±27.3</td>
<td>28.2±28.3</td>
<td>16.3±6.7</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>3.3±0.8</td>
<td>3.3±0.5</td>
<td>3.0±0.5</td>
<td>3.0±0.6</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>21±11</td>
<td>69±82</td>
<td>68±65</td>
<td>51±38</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>18±11</td>
<td>40±42</td>
<td>61±52</td>
<td>29±15</td>
</tr>
</tbody>
</table>
**Figure 1a.** Liver enzymes levels in patients undergoing HD.

**Figure 1b.** Liver enzymes levels in patients treated by CAPD.
Figure 2a. HCV and HBV Percents in patients undergoing HD.

Figure 2b. HCV and HBV Percents in patients treated by CAPD.
In HD group, in 28 of 67 cases HCV, in three of them HCV + HBV, and in seven HBV was positive. In CAPD group, in 11 cases HCV and in four cases HBV was positive. In HD group 28 cases and in CAPD group 20 cases had negative hepatitis marker. Seroconversion rate/year of our anti HCV (-) patients were 0.148/patients year in hemodialysis patients and 0.002/patients year in CAPD patients, respectively.

**DISCUSSION**

In patients with hepatitis C, an episodic pattern of aminotransferase elevation is common. A specific serologic diagnosis of hepatitis C can be made by demonstrating the presence in serum of anti HCV. Because nonspecificity can confound immunoassays for anti-HCV, a supplementary recombinant immunoblot assay (RIBA) should be done, especially in persons with low prior probability of infection, to establish the specific viral proteins to which anti-HCV is directed. Assays for HCV RNA are the most sensitive tests for HCV infection (8,9).

Elevation of ALT with anti-HCV seropositivity for at least 6 months are the laboratory features enough to define chronic hepatitis C. Chronic hepatitis follows acute hepatitis C in 50 to 70 percent of patients. Many patients of hepatitis C are identified in asymptomatic patients who have no history of acute hepatitis, e.g., those discovered while attempting to donate blood or as a result of routine laboratory screening tests. Among symptomatic persons with anti-HCV, even when aminotransferase levels are normal, between a third and a half have been reported to have chronic hepatitis on liver biopsy, although mild in most patients. In these asymptomatic persons with normal aminotransferase levels, the presence of detectable circulating HCV RNA appears to distinguish those with chronic hepatitis on biopsy from those with normal liver histology (10,11).

Among the patients with chronic hepatitis B, HCV seroprevalence was reported ranging from 10 to 20% in the Southern Europe and USA (11,12). HCV co-infection in patients with inactive chronic hepatitis B increases to 30-35% levels especially in the Mediterranean Countries (13). In our country, dual infection ratio was found 9% in a study that HCV co-infection was investigated among patients with chronic HBV infection (14).

HCV infection is investigated in two different groups according to the routes of transmission.

A-Parenteral: Occupational, Transfusion of blood and blood products, Nosocomial, Hemodialysis patients, Intravenous drug users,

B-Non-Parenteral: Perinatal transmission, Sexual transmission, Intrafamilial transmission. Routine screening of blood donors for anti-HCV reduced the frequency of transfusion-associated HCV infection. After the introduction of first generation anti-HCV immunoassays, the infection risk of transfusion-associated hepatitis reduced 80% in countries such as Japan, USA, and Spain that HCV genotype 1 is predominant. The introduction of second-generation of HCV assays has reduced the frequency of transfusion-associated hepatitis C to almost imperceptible levels. Rarely, when
donor is at window period during the blood transfusion, it can be transmitted (15,16). Solvent detergent treatment in screening of plasma for anti-HCV is the most effective method and is used commonly. Thus, transmission of HCV by immune globulins preparations and coagulation factor concentrates are eliminated by this way (17). The mechanism of HCV transmission as a hospital infection isn't well known. During surgical interventions, it should be necessary to take additional measures for the prevention of transmission of HCV (18). Although it is reported that HCV is the most common cause of post-transfusion or sporadic non A-non B hepatitis in USA, in 40% of the patients there was no risk factor for parenteral transmission (19).

Similarly, also in our country, only 44% of patients whose anti-HCV was positive had a transfusion story (20). Since 1989, the prevalence of HCV infection in different risk groups and blood donors was investigated by using specific tests for HCV. First prevalence study of HCV infection was made in volunteer blood donors (21). Anti-HCV prevalence in volunteer blood donors is lower than 2% in Northern Europe and larger part of USA, 0.5-0.8% in Australia and other parts of USA, 1-1.5% in the Southern Europe and Japan, 5% in Chine, higher than 10% in the Northern Africa (22-24). In our country, the prevalence of anti-HCV in blood donors is about 1% (25,26).

The seroprevalence of anti-HCV in intravenous drug users is high in all over the world (57-86%) and there is a significant parallelism between the seropositivity and duration of drug using (27,28). The importance of sexual transmission in the epidemiology of HCV infection is not clear. It ranges from 0 to 27% (29). The hospitalization story is an epidemiological risk in patients with HCV infection (30). Transmission from a patient to another one can be seen. It is reported that this type of transmission can cause outbreak of HCV infection in hematology and pediatric oncology clinics (31).

The risk of HCV infection is increased in organ transplant recipients and in hemodialysis patients (7,27,32-37). The HCV prevalence changes from country to country. In our country, according to European Dialysis and Transplant Association (EDTA) data, HCV prevalence was 17.7% in 1993. However, according to Turkish Nephrology Associations' (TNA) data, HCV seroprevalence was reported as 38% in 1996, it increased to 52.6% in 1997 and finally to 63.2% in 1998 (32,33).

In these studies, the relationship between HCV seropositivity and blood transfusion and duration of hemodialysis were demonstrated. Previous HD story is an important risk factor for HCV seropositivity of CAPD patients. Some of these studies were tests that made by using first generation ELISA and had significant risk of false negativism (34-36). A number of factors account for the risk of HCV infection in hemodialysis patients. These include blood transfusions and duration of hemodialysis. Moreover, the presence of anti-HCV has been often documented in non-transfused hemodialysis patients suggesting nosocomial transmission of HCV. Seroconversion rate/year of 129 anti-HCV (-) patients undergoing HD was reported as 0.15/year (9,37).

The patients that are enrolled in our study had a hospitalization story at least one time. At the beginning of 1999 (first six months), when there was 16
patients in HCV room, liver enzymes of 16 patients that undergoing dialysis in normal room began to increase. All these patients had blood transfusions or/and surgical intervention during 1999. In 11 of these patients anti-HCV antibody became detectable in 6-12th months. On the other hand, in CAPD group, only one anti-HCV seropositivity was demonstrated. In only one case, intrafamilial transmission was identified. Only eight (7.8%) patients had dental interventions including conservative tooth treatment or tooth extractions.

It is reported that in France anti-HCV seroprevalence was 23.6% in renal transplant recipients (35). When 27 patients were followed prospectively, it was seen that ten (37%) patients were seropositive during the transplantation and other patients became seropositive in following days, in 11 (41%) patients antibodies become detectable after 95 months and in 6 (22.2%) patients who were seropositive at the beginnings, antibodies became undetectable after 111 months (35).

Hemodialysis patients are at high risk of infection by hepatitis C virus and this is also an important problem that is met in our country’s hemodialysis units. It is suggested the separation of the hemodialysis machines and rooms of anti-HCV positive patients, couldn’t prevent the outbreak of HCV infection in a HD Unit. However, in a recent study of Katsoulidou and his colleagues (37), molecular and epidemiological analysis suggested that horizontal nosocomial patient to patient transmission was the most likely explanation for the virus spread within the HD Unit and other recognized rates had less importance.

In our country, there are many studies that HCV seroprevalence in HD units was investigated (38). In the study of Özdemir et al. (39) anti-HCV seropositivity was found in 145 (34.7%) patients by using 2nd generation ELISA reagent. Yücel et al. (40) found anti-HCV seropositivity in 33 (32.6%) of 101 patients by using 2nd generation ELISA reagent in Bursa Hospital HD Unit. Olmez et al. (41) found anti-HCV seropositivity in 36 (24.6%) patients, HbsAg seropositivity in 20 (%13) patients and anti-HCV plus HbsAg seropositivity in six (%4.1) patients in Dicle University HD Center by using 2nd generation ELISA reagent (In 1996, dialysis machines, rooms and personnel weren’t yet separated).

Nowadays, in our center, the rooms, dialysis machines and personnel of HD patients are separated according to HCV, HBV and HCV plus HBV and normal patients groups. When 67 HD and 35 CAPD patients that are undergoing dialysis program at presently in our HD center as from 1999, are evaluated by using 3rd generation ELISA reagent, it is seen that anti-HCV seropositivity is 41%. In general, these patients were generally asymptomatic, but had elevated liver enzyme levels and decreased albumin levels. In our study, total 102 patients were enrolled. In 39 of them, anti-HCV seropositivity and in 11 of them, HbsAg seropositivity was demonstrated.

CONCLUSION

In conclusion, our observation that seroconversion rate/year of our anti-HCV patients were 0.148/patients years in HD patients and 0.002/patients years in CAPD patients, respectively. The seroconversion rate/year and
prevalence of HCV is higher in HD patients than CAPD patients. In HD patients, it should be necessary to take additional measures to universal precautions for the prevention of outbreak of HCV such as separation of dialysis machines, education of nurses and changing gloves regularly when moving from patients to patient, etc.

ÖZET

DIYALİZ HASTALARINDA HEPATİT C SEROPREVALENSİ VE RİSK FAKTÖRLERİ


Çalışmaya 67 HO ve 35 SAPO hastalıak alındı. Hastaların 44 (43.1%) kadın, 58 (56.9%) erkekti. Hastalar, HCV infeksiyonu için risk sayılan herhangi bir faktöre sahip olma (kan veya kan ürünleri transfüzyonu, doktor sosyoekonomik statü, cerrahi müdahale ve hastanede yatma) açısından sorgulandı. Çalışmada 3. kuşak ELİSA kiti kullanıldı. Merkezimizde HCV yayılması engelleyici tüm önlemler alınmıştır. HCV'li hastaların oda ve diyaliz makinaları diğerlerinden ayrılmıştır.

Olguların ortalama yaşı 41.6±15.3 (19-75) yıldır. Olguların ikisi dışında hepsine kan transfüzyonu ve tümüne en az bir cerrahi girişim (santral venöz katater ve/veyaarteriyo-venöz şant operasyonu) yapılmıştır. Yalnız sekiz olgu (%7.8) diş çekimi veya konserve diş tedavisi görmüştür. Diyaliz hastalarında düşük sosyoekonomik statü ve diyaliz süresi ile HCV seropozitifliği % 41'dir ve bu olguların tümü genelde asemptomatik olmakla birlikte, karaciğer enzim seviyelerinde yükselme, albumin seviyelerinde yükselme, albumin seviyesinde ise hafifçe düşme bulunuyordu ve hastaların hepsi en az bir risk faktörüne sahipti. Anti-HCV(-) hastalarımızda yıllık serokonversiyon oranı, HD hastalarında 0.148/hasta yılda iken; SAPD hastalarında bu oran 0.002/hasta yılda

HD merkezimizde, HD hastalarında HCV prevalansı ve yıllık serokonversiyon oranı SAPD hastalarından daha yüksektir. HD hastalarında, HCV yayılmasını önlemek için, diyaliz makinalarının ayırımı, hemşire eğitimi ve bir hastadan başka bir hastaya geçildiğinde eldiven değiştirilmesi vb. genel önlemlerin alınması gereklidir.

REFERENCES


