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Prevalence and Characterization of Hepatitis C infection and Determination of Liver Damage in Patients on Chronic Hemodialysis at the Largest Reference Center for Renal Health, EsSalud, Lima, Peru

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1. Abstract

1.1. Background: Hepatitis C (HCV) is a serious public health problem with approximately 3% of the world's population infected. Patients on chronic hemodialysis are known to be a population at risk of HCV infection worldwide.

1.2. Aims: This study aimed to estimate the serological prevalence of HCV and characterize the HCV viral load and genotype; as well as to determine the stage of liver fibrosis in patients on chronic hemodialysis at the largest Peruvian Social Security reference center for hemodialysis in Lima, Peru.

1.3. Materials and Methods: Observational case series study approved by the Ethics Committee of the Guillermo Almenara National Hospital (EsSalud). All patients who received chronic hemodialysis at the study center were invited to participate. Subjects who provided written consent were enrolled. Patients with HCV-positive serology determined with the Cobas® analyzer y and the immunoassay 601 from Roche Diagnostics, underwent determination of HCV viral load by means of RT-PCR (Abbott Realtime m2000 system / Xpert® HCV Viral Load). In subjects with detectable viral load, the HCV genotype was determined (Abbott HCV Real Time Genotype II / Roche Applied Science). Then subjects underwent determination of liver fibrosis using transitional elastography (Fibroscan 402 with E and XL probes): Metavir score: F0-F1: 2.5-7.5 kPa, F2: 7.6-9.5 Kpa, F3: 9.6-12 Kpa, F4 (Cirrhosis): 12,1-75 Kpa.

1.4. Results: Of all the subjects invited to participate (303 patients), 174 (57.4%) gave their written consent. Mean age was 52 years (range 22-91) and 116 (66.6%) were male. HCV serology was positive in 35.1% of patients (61/174), however, the prevalence of active HCV (positive serology and detectable viral load) was 20.11% (35/174). Genotype 1a was the most prevalent (85%). The majority (83.6%) of subjects with detectable viral load had values below 800.000 IU/ml. Twenty-nine of those 35 subjects underwent Fibroscan evaluation, and 13 (44.8%) had stage F2-F4 fibrosis.

1.4. Conclusion: The prevalence of HCV at the largest reference center for hemodialysis in Lima remains high, with GT1a predominance, viral load usually below 800,000 IU/ml and significant associated liver fibrosis. In the era of interferon-free HCV treatment regimens, interventions are urgently needed to reduce disease progression among HCV-infected patients on chronic hemodialysis.

2. Background

Hepatitis C (HCV) is a serious public health problem with approximately 3% of the world's population infected. Patients on chronic hemodialysis are known to be a population at risk of HCV infection worldwide. By 2015, chronic Hepatitis C virus (HCV) infection was estimated to affect approximately 71 million people globally [1,2,3]. HCV infection has surpassed HIV virus infection as the leading

cause of death from viral infection in multiple countries including the United States [4]. Complications of chronic HCV occur after several years and include cirrhosis, liver failure, need for liver transplantation, and hepatocellular carcinoma. Complications of cirrhosis include portal hypertension, spontaneous bacterial peritonitis, gastrointestinal bleeding, and hepatic encephalopathy, among others. [5]. There are also multiple extrahepatic manifestations of the disease such as uveitis, cryoglobulinemia, autoimmune thrombocytopenic purpura, membranoproliferative glomerulonephritis, porphyria cutanea tarda, among others [6]. Thus, HCV infection, its complications, and the medications employed for its treatment represent a major cause of health care expenditures for the health care systems. In the U.S., these expenses exceed $10 trillion annually [7]. In Peru, in a recent sero-epidemiological study of viral hepatitis (A, B, C, D and E), carried out in the 25 regions of the country; a low prevalence of hepatitis C was found, estimated at 0.1% in the general population [8]. It is also known that people who receive multiple blood transfusions and health care workers are known risk groups for HCV infection, but the highest prevalence (59%) has been reported in people receiving chronic hemodialysis. Until a few years ago, patients with stage V chronic kidney disease received blood transfusions for the treatment of anemia associated with this pathology, and so it was considered an important risk factor for HCV infection [9,10]. This practice has decreased significantly with the use of erythropoietin (EPO). The most important risk factor for HCV transmission in chronic dialysis patients is currently considered to be nosocomial transmission related to inadequate biosafety practices. Hepatitis C virus infection is common among patients on chronic hemodialysis, is higher than the general population, and is associated with increased morbidity and mortality. In a study to determine the prevalence, incidence and risk factors of HCV infection, a prevalence of 10% was found between 2012-2015, with ranges of 4% to 20% [11]. The Social Security (EsSalud) is the second largest public health system in the country and is the main provider of chronic hemodialysis in Peru. The National Center for Renal Health (Centro Nacional de Salud Renal, CNSR) of the Social Security system in Peru (EsSalud) is the largest provider of specialized health care, including hemodialysis, to people with advanced kidney disease from all districts of Lima. The CNSR provides specialized care for a population of HCV infected patients who have developed complications of the disease that will result in a high economic burden for EsSalud. On the other hand, Chronic Kidney Disease (CKD) is considered a public health problem, due to its tendency to increase the number of patients and the high associated care costs make it a "Catastrophic Disease" for our health care system. Likewise, chronic hemodialysis (CHD) is the most frequent renal replacement therapy with a rate of 363 persons per million population (pmp), followed by peritoneal dialysis (PD) with 51 pmp and kidney transplant with four pmp. 88% of the population is in the CHD program and 12% in the PD program [13]. Until 2014, the standard of treatment for HCV in the world has been with pegylated interferon with or without ribavirin, however, its use in hemodialysis patients has been limited due to its low efficacy and unfavorable safety and tolerability profile. There has been significant improvement in the drugs and drug combinations approved for HCV treatment. Current treatments are interferon-free oral regimens, combining 2 or more drugs called direct-acting agents (DAAs) including sofosbuvir-ledipasvir (SOF-LDV), sofosbuvir-velpatasvir (SOF-VPT), grazoprevir-elbasvir (GZV-ELBV), glecaprevir/pibrentasvir (GLP-PBV). DAAs are highly effective and well tolerated, with cure rates greater than 90%, even in patients who have traditionally been difficult to treat. In patients with chronic kidney disease including stages IV or V and patients in hemodialysis, no dose adjustments of DAAS are recommended and patients should be treated according to general recommendations [13]. The metabolism of DAAs varies between different classes, with only a few being indicated for use in people receiving hemodialysis. In Peru, there are currently several registered schemes of interferon-free HCV treatments, which are effective and safe in patients with hemodialysis, therefore, there is the potential of implementing therapeutic interventions that reduce or even eradicate HCV infection from hemodialysis programs, especially in the public sector [14,15].

3. Aim

The study aimed to estimate the serological prevalence of HCV infection, determination of HCV viral load and genotype; as well as to determine the stage of liver fibrosis in patients on chronic hemodialysis at the CNSR, the main reference center for hemodialysis in the Peruvian Social Security system in Lima, Peru.

4. Material and Methods

This is an observational case series study of adults on chronic hemodialysis cared for at the CNSR. The study protocol and informed consent were approved by the Ethics Committee of the Guillermo Almenara National Hospital (EsSalud). All patients who received chronic hemodialysis at the study center were invited to participate. Subjects who provided written consent were enrolled. Patients with HCV-positive serology determined with the Cobas® analyzer y and the immunoassay 601 from Roche Diagnostics, underwent determination of HCV viral load by means of RT-PCR (Abbott Realtime m2000 system / Xpert® HCV Viral Load). In subjects with detectable viral load, the HCV genotype was determined (Abbott HCV Real Time Genotype II / Roche Applied Science). Then, subjects underwent determination of liver fibrosis using transitional elastography (Fibroscan 402 with E and XL probes). The Metavir score was as follows: F0-F1: 2.5-7.5 kPa, F2: 7.6-9.5 Kpa, F3: 9.6-12 Kpa, F4 (Cirrhosis): 12,1-75 Kpa. Figure 1 displays the study scheme. A case report form (CRF) was prepared to collect information including: date of birth, sex, time since the first hemodialysis, date of the first positive local serology, frequency of dialysis, time since the first hemodialysis at the CNSR-EsSalud, number of centers where the volunteer received hemodialysis, history of surgery (yes / no, and type

of surgery) before HCV diagnosis, history of blood transfusions or derived products (yes/no, and number) before HCV diagnosis, type of venous access for hemodialysis (AV fistula/catheter), use of dedicated hemodialysis machines (yes/no), use of individual filters (yes/no), comorbidities (such as diabetes mellitus, HIV infection, and other immunosuppression conditions), history of transplantation, number and type of sexual partners, and history of intravenous drug use.

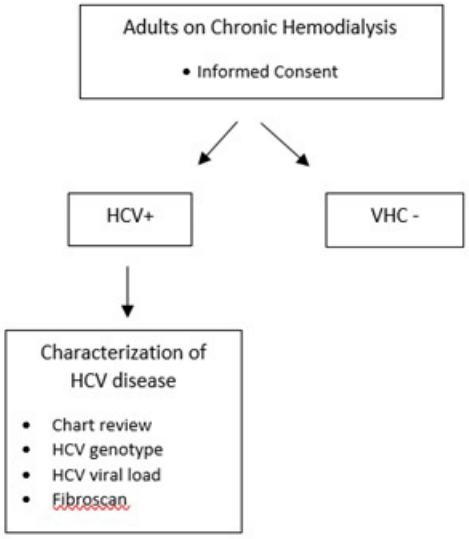

Figure 1: Decision Tree and Study Outline

5. Results

Of the 303 patients receiving chronic hemodialysis at the CNSR, 174 (57.4%) provided written informed consent and were enrolled in the study. Mean age was 52 years (range 22-91) and 116 (66,6%) were male. HCV serology was positive in 35.1% of study volunteers (61/174), however, the prevalence of active HCV (positive serology and detectable viral load) was 20.11% (35/174). Genotype 1a was the most prevalent (85%). The majority (83.6%) of subjects with detectable viral load had values below 800,000 IU/ml. There was a higher prevalence of anti-HCV cases in men (40/61) than in women (20/61) with no significant difference (p=2). Twenty-nine of the 35 subjects with active HCV underwent fibroscan evaluation, and 13 (44.8%) were found to have liver fibrosis in stage F2-F4. None of them had previous diagnosis of hepatic cirrhosis or manifestations of portal hypertension. No cases were found with hepatocellular carcinoma (HCC). See Table 1 for more details. Medical charts disclosed that primary glomerulonephritis (n=29) was the most frequent (16.7%) cause of chronic kidney disease were. Other causes were chronic arterial hypertension (n=06), type 2 diabetes mellitus (n=05), obstructive uropathy (n=03), eclampsia (n=2), lupus nephritis (n=01), polycystic kidney disease (n=01), and Alport syndrome (n=01). Importantly, the cause was unknown in 86 subjects (49%). See Table 1 for more details. None of the volunteers had tattoos, piercing, contact with relatives with hepatitis C, or sexual partners with hepatitis C. There was also no history of illicit drug use. Volunteers with positive HCV serology had an average of three hemodialysis sessions per week and were on hemodialysis for at least five years. Most volunteers (85) were dialyzed only at the CNSR. Sixteen volunteers were dialyzed in two other centers in the past, 35 in one, and three in three. Most subjects (94.2%) had alanine amino transferase (ALT) levels within normal range, and the rest (5.8%) had levels between 1-3 times the upper normal limit. Twenty-five volunteers had history of kidney transplant, five had nephrectomy, four had cholecystectomy, and 18 had history of other types of surgeries. Five volunteers had history of receiving five or more blood transfusions, three received three to five transfusions, and nine receive two or less transfusions. Access for hemodialysis was: arterial-venous fistula in 153 volunteers and placement of long-term hemodialysis catheter in 21 volunteers. Comorbidities were chronic arterial hypertension (n=26), type 2 diabetes mellitus (n=3), systemic lupus erythematosus (n=2), tuberculosis (n=2), and type 1 diabetes mellitus (n=1). Two volunteers were found to have coinfection with hepatitis B virus (HBV) surface antigen (one of them had detectable HCV detectable y F4 Fibrosis) and 28 volunteers had isolated HBV anticore. There were no cases of coinfection with the human immunodeficiency virus.

Table 1: Study volunteers and characterization of HCV burden (serostatus, viral load, genotype, and liver fibrosis) among adults on chronic hemodialysis at the CNSR.

Characteristic	Subjects (%), [range]
Subjects enrolled	174
Mean age in years	52 [22-91]
Male	116 (66.6%)
Cause of end stage renal disease Unknown Glomerulonephritis Chronic arterial hypertension Type 2 diabetes mellitus Obstructive uropathy Eclampsia Lupus nephritis Alport´s syndrome	174 (100) 127 (72.9) 29 (16.7) 6 (3.4) 5 (2.9) 3 (1.7) 2 (1.2) 1 (0.5) 1 (0.5)
Subjects with positive serology	61 (35.1)
Subjects with positive serology and detectable viral load	35 (20.11)
HCV viral load <100,000 IU/mL ≥100,000 IU/mL	35 (100) 29 (83.6) 6 (16.4)
HCV genotype 1a 3 Unable to determine	35 (100) 30 (85.7) 1 (2.9) 4 (11.4)
Liver fibrosis on Elastography F0-F1 F2-F3 F4	29 (100) 16 (55.2) 7 (24.4) 6 (20.4)

6. Discussion

Patients with end-stage chronic kidney disease who receive supportive treatment with hemodialysis are a high-risk group for acquiring HCV infection. Previously, most studies showed a great influence of the time under hemodialysis and the number of blood transfusions received. [16] However, it is currently known that nosocomial is the main route of HCV transmission in patients undergoing hemodialysis and it can be prevented by strictly following the biosafety recommendations for hemodialysis centers [17]. The prevalence of HCV infection remains high among adults receiving chronic hemodialysis at the CNSR, the largest center providing specialized kidney health care services in Lima Peru. Genotype 1a predominates, with the viral load usually falling below 800,000 IU/ml, and with significant associated liver fibrosis. As a reference, in 2005, the prevalence of HCV infection in hemodialyzed patients was reported as 59% with HBV confection in 4.5% [18]. Our study provides more current data from a cohort of patients on chronic hemodialysis at the CNSR, showing HCV seroprevalence of 35.1% and co-infection with HVB of 1.13%. The prevalence of active HCV (positive serology and viral load) was 20.11%. These differences probably reflect the positive effect of the biosafety measures implemented across hemodialysis units in our country. However, the prevalence of HCV remains high. High seroprevalences have also been reported in other countries in the region. The prevalence of HCV among patients on hemodialysis was 71% in a hemodialysis center in Caracas-Venezuela [20], 90% in a study performed in Cuba [20], and 33.4% in the Santa Catarina state in Brazil [20]. The prevalence of HCV varies within regions of a given country, as reported in Argentina (23.8% in the Northeast, 45.5% in the North, 46.7% in the Midwest and 35.3% in the Southeast) [20], In Peru, HCV prevalence varied between 90% and 4,65%, and in Uruguay varied between 16 and 3% [20]. Interestingly, in studies conducted in hemodialysis units in Cali and Bogotá-Colombia, the seroprevalence of HCV was very low (2.9 and 2.7% respectively) [20], however, it was high in Medellín (42,2%) [20]. Possibly, the low

prevalence found in Cali and Bogotá reflect the impact of the strict biosecurity measures that have been implemented for more than a decade [20]. As for the HCV genotypes among adults on hemodialysis, our study found that genotype 1a was the most frequent (85%) followed by genotype 3, in contrast to what has been reported in other countries. The predominant genotypes are 1b and 3 in Colombia; 1b, 3a and 1a in Brazil and Venezuela [20]. In other areas of the world predominate 1a and 1b in Indonesia and Jordan; and 1b, 2a y 2b in Japan [20]. In contrast, genotype 4 predominates (84%) in Egypt, followed by genotype 1. Genotype 1b predominates in Germany and France and 1b, 3a and 2a-b in Italy [20]. On the other hand, while isolation is not recommended for hemodialyzed patients infected with HCV, the monthly determination of ALT and semi-annual HCV serology screening are important to detect transmissions within a center and to ensure that precautions are being applied correctly and continuously [20]. In our study, the ALT levels remained normal in the majority of study volunteers, similar to the findings of other studies in this type of patient population. Study imitations include the fact that this is a single center study and that only 57% of adults receiving chronic hemodialysis at the study center accept to participate in the study. We did not collect information about the reasons for not accepting to participate, so there is a potential for bias from an unknown variable. It should be noted that the study was conducted during the COVID-19 pandemic facing significant restrictions from the impact of the disease and from the strict measures that the Peruvian government implemented to control the pandemic.

7. Conclusion

The prevalence of HCV at the largest reference center for hemodialysis in Lima remains high, with GT1a predominance, viral load usually below 800,000 IU/ml and significant associated liver fibrosis. In the era of interferon-free HCV treatment regimens, interventions are urgently needed to reduce disease progression among HCV-infected patients on chronic hemodialysis.

8. Acknowledgement

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