Original Article

PREVALENCE AND RISK FACTORS OF CYTOMEGALOVIRUS INFECTION AMONG HAEMODIALYSIS PATIENTS IN SOUTHERN GAZA STRIP, PALESTINE

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ABSTRACT

Introduction: End-Stage Renal Disease patients (ESRD) on maintenance Haemodialysis (HD) are at high risk of acquiring Cytomegalovirus (CMV). The aim of the study was to determine the prevalence and risk factors of CMV infection among HD patients from Nasser's medical complex and Abu Yousef Al Najjar Hospital Southern Gaza strip. **Methods**: This study was an analytical cross-sectional from March to September 2019. Serum samples were taken from 96 patients (51.1% of them from Nasser medical complex and 48.9% of them from Abu Yousef Al Najjar Hospital), analyzed for CMV-specific immunoglobulin G (IgG) by using the Chemiluminescence immunoassay (CLIA) techniques, questionnaire, and Virological identification. **Results**: CMV-IgG was detected in 80 patients (83.3%), were 16 patients (16.7%) were CMV IgG Negative. The prominent risk factors were HD duration time, Receiving Injection, and previous blood transfusion. **Conclusion**: The prevalence of CMV infection among HD patients in the Southern Gaza strip was very high. We recommend that HD patients should be vaccinated against CMV.

Keywords: Cytomegalovirus, Haemodialysis, Gaza Strip, Palestine.

Introduction

Cytomegalovirus (CMV), is an endemic herpes virus in all regions of the world, it is widespread and typically asymptomatic in otherwise healthy children and adults with CMV infections. The seroprevalence of the virus ranges from 45% to 100% in various countries in the general population (Landolfo et al., 2003; Cannon et al., 2010). When a human becomes infected, for the remainder of their life period, the CMV remains alive, but usually inactive, within the body of that person. Unless the person's immune system is suppressed due to medicinal medications or disease, it seldom causes recurrent illness. Therefore, CMV infection is not a serious concern for the vast majority of individuals (Gold & Nankervis, 1989; Rosenthal et al., 1997).

Renal failure is described as a kidney function deficiency that is acute or chronic. It happens when it is unable for the kidneys to eliminate waste products, monitor electrolytes in the blood, and maintain fluid balance. For certain forms of end-stage renal disease (ESRD), an alternative therapy is either dialysis or kidney transplantation. The most common renal replacement therapy treatment is Haemodialysis (HD), where the dialysis process is used to remove excess fluids and toxic substances from the body (Sepehrvand et al., 2010). CMV infections are a significant cause of disease and death in immunocompromised patients, including recipients of organ transplants, HD patients, cancer patients, patients receiving immunosuppressive agents, and patients infected with human immunodeficiency virus (HIV) (Greene et al., 2000; Mowatt et al., 2003; El Sanousi et al., 2016).

HD patients are at high risk of infection because the HD process involves long-term parenteral access in an environment where many patients undergo dialysis at the same time, so that the nosocomial transmission of infectious agents is repeatedly possible, directly or indirectly, through infected devices, equipment, hands or environmental surfaces (Horl & Williams, 1999). CMV infection is prevalent worldwide among HD patients, with a prevalence rate ranging from 55 percent to 90 percent (Gianella et al., 2013). The incidence rate varies between different populations, depending on several variables, including age, gender, ethnicity, population density, socio-economic conditions, modes of transmission, personal immunity, chronic diseases, chemotherapy, blood transfusion frequency, as well as dialysis time and length (Sepehrvand et al., 2010; Akter & Toods, 2011). CMV infection is an additional risk and health issue for HD patients at the local and national levels. The main objective of this research is to determine the prevalence of CMV infection and associated risk factors in the southern Gaza Strip of Palestine among HD patients.

Methods

This is an analytical cross-sectional study conducted on ninety-six dialysis patients in southern Gaza strip centers from March to September 2019. Multiple-choice questionnaires in the Arabic language were adapted from previous studies and completely achieved by the researcher via a direct meeting with patients to assure excellent data collection and prevent any mistake, the collected data was included personal and socio-economical information's, HD units services, and medical history of the

patients (El-Ottol et al., 2010). A pre-test was performed to ensure the construct validity of the questionnaire after its content validity was ensured by experts. The questionnaire was pre-tested among 30 ESRD patients attending the two HD units. In the key sample, the respondents who participated in the pre-test were omitted. The findings showed the internal consistency of the products evaluated with a Cronbach's α value of 0.78.

Approximately five Milliliter of blood were collected from each patient in a clean glass tube with no additives, serum was separated and tested within 2 hours and the remaining serum was frozen at -70 °C until reused if required (El-Ottol et al., 2010). CMV antibodies were detected by Chemiluminescence immunoassay CMV (CLIA) (ref 130212005M) according to the manufacture's instruction (Shenzhen New Industries Biomedical Engineering Co, Ltd).
Because there is no CMV IgG universal standard material, the various manufacturer has different traceability chains. Therefore, results from the test of other manufacturers cannot be used interchangeably. According to our kits result from less than 2 AU/ml were treated as negative, results greater than or equal to 2 AU/ treat as positive.

Statistical analysis: Collected data were analyzed by using statistical package for the social sciences (SPSS) version 22 (IBM Corp., Armonk, N.Y., USA), differences in proportions were been determined by a chi-square test, p-value ≤ 0.05 were been taken into consideration as statistically Significant (Altaher et al., 2020).

Ethical consideration: The study was been confirmed and approved by the university college of science and technology research (UCST) committee, and the Palestinian ministry of health (MOH). After Clarifies the goals of the study, oral agreements were obtained from all patients, and all personal information of the study subjects and result were been process in high exclusiveness.

Results

The study was conducted on HD patients attending HD units in South Gaza Strip. A total of forty-seven samples were collected from Abu Yousef Al-Najjar Hospital out of 96 attending patients, and a total of 49 samples were collected from Nasser medical complex out of 150 attending patients; two patents from Abu Yousef Al-Najjar Hospital and one patient of Nasser medical complex were not responded to the study and was neglected. A summary of the demography of respondents is seen in Table1.

Personal information.

Patient's Age: the ages of the patients ranged from fifteen to eighty years; The mean age for all patients was 52.75 years with standard deviation (SD) ±15.84 years, thirty-four patients were over sixty years, one patient was less than nineteen years old sixty-one patients between nineteen and sixty years old.

Table 1: Relationship between CMV infection and age, sex, education level, Residence, and Marital status among HD patients.

Variable		MCV Positive	MCV Negative	Total	P-Value
Age	Mean Age	53.7 ± 14.6	49.8 ± 17.8		**0.31**
Patient Sex	Male	44	6	50	**0.46**
	Female	37	9	46	
Education Level	unlettered	6	3	9	**0.16**
	elementary	15	6	21	
	preparatory	5	0	5	
	Secondary	36	5	41	
	University	18	2	20	
Marital status	Single	11	4	15	**0.6**0
	Married	69	12	81	
Khan Younis governorate residence	West	7	2	9	**0.22**
	East	23	2	25	
	Middle	10	4	14	
Rafah governorate residence	West	14	4	18	**0.52**
	East	14	3	17	
	Middle	12	1	13	

*significant level at $P < 0.05$

Patient's residence: patients of Nasser's medical complex were from three regions of Khan Younis governorate, fifteen patients were from the center of the Khan Younis governorate, twenty-five were from East Khan Younis governorate, and nine patients were from the West Khanyunis governorate. Al-Najar hospital patients were also from three regions of Rafah governorate, twelve patients from the center of Rafah governorate, seventeen patients from west Rafah governorate, and eighteen patients of East Rafah governorate.

Patient's education level: the degree of patient education was divided into five categories, unlettered, elementary, preparatory, secondary, and university. Forty-one patients (42.7%) were secondary, which was the highest proportion of HD patients. Patient's marital status**:** We found that 82 patients were married from all the study population, which made (85.4%), while the remainder were single (14.6%)**.**

HD units services

HD time and duration: Three shifts are served by HD centers; the first shift from 8 a.m. to 12 a.m., the second shift from 12 a.m. to 4 p.m., and the third shift are from 4 p.m. to 8 p.m. The study found that in the first shift there were 28 patients (29.2%), 60 patients, (62.5%) in the second shift, and 8 patients (8.3%) in the third shift. For each patient, doctors recommend the duration of HD sessions according to the health condition of the patient. Two to four sessions a week are sufficient for most patients. We found that 26 patients (27.09%) received two HD sessions a week, 66 patients (68.75%) followed three HD sessions, and the minimum number of sessions was 4 sessions per week for 4 patients (4.16%). The length of each HD session is dependent on many factors, including the patient's age, weight, and response to treatment. The total length of time per session varied from 3 to 4 hours. In most patients, 82 patients (85.4%) underwent HD for three hours per session, followed by 14 patients (14.6%) for four hours per session.

Medical history of the patients

History of Blood Transfusion: fifty-three patients (55.2%) received at least one blood unit transfusion out of the total study population. A positive history of blood transfusion was divided into three classes by the number of blood units received. The first group consisted of patients receiving fewer than 5 units of blood (83.02%), the second group consisted of 5 to 10 units of blood (15.09%), and the third group consisted of more than 10 units of blood (1.89%) as shown in table 2.

History of Surgical Operation: One of the known risk factors for the transmission of CMV viruses are surgical operations. Every patient underwent surgery to establish a fistula (shunting blood from an artery to a vein) as a requirement for the HD procedure. Of the total study population, 23 (23.95%) of subjects had surgery before beginning HD, while the remaining 73 (76.05%) had just a fistula.

History of treatment, surgical operation, and blood transfusion abroad: The data shows that 40 patients (41.67%) were treated abroad among the 96 patients tested. From them 24 patients (60%) had surgery abroad only, 8 patients (20%) had blood transfusions abroad only, and 1 patient (2.5%) had surgery and received blood abroad, 7 patients (17.5%) did not have an operation or received blood abroad (Table2).

History of receiving Injection: From the total study population, 43 patients (44.8%) were injected prior to HD, while the remaining 53 patients (55.2%) were not injected prior to HD (Table2).

Prevalence of CMV IgG in the southern Gaza Strip: The overall prevalence of CMV among HD patients was found to be 83.33% (83.7% at the Nasser medical complex and 83.0% at the Abu-Yousef Al-Najar Hospital) (Table2).

Table2: Relationship between CMV infection with HD centers, time duration on HD, blood transfusion, treatment abroad, and receiving an injection.

Variable		CMV positive	CMV negative	P-value
HD centers	Nasser medical complex	41	8	**0.57**
	Abu Yousef Al Najjar Hospital	39	8	
Blood transfusion	0	35	8	**0.04**
	1-5	40	6	
	5-10	5	1	
	>10	1	0	
Duration time (month)	Meantime	61.25 ± 58.74	48.8 ± 42.21	**0.5**0
No of the patients treated abroad	Yes	35	9	**0.4**0
	No	45	7	
Receiving injection	Yes	48	5	**0.03**
	No	32	11	

*significant level at $P < 0.05$

Relationship between the prevalence of CMV-IgG antibodies and some personal and clinical characteristics.

The mean age was 53.7 ± 14.6 years for CMV-positive patients, while the mean age was 49.8 ± 17.8 years for CMV negative patients, and there was no statistically relevant association between CMV and patient age (p=0.31) as shown in table 1. Of the 96 patients tested, there are 50 (52.08%) male and 46 (47.92%) female, also no statistically significant association was found between the patient's sex and CMV infection (p=0.46). Patients on HD have varying levels of learning. There was no statistically significant association between CMV infection and the level of education (p=0.16), with the majority of CMV patients at the secondary level (42.7%) followed by the universal level (20.8%).

No statistically significant association was found between CMV infection and patient residence (p=0.22 and 0.5) for both Khanyounis and Rafah regions respectively, most CMV patients were found in the city of East Khanyounis (26%) followed by the city of West Rafah (17.7%). On the other hand, no important association between CMV infection and marital status has been identified (p=0.6) while married patients tend to be more exposed than single patients to CMV infection. There was also no statistically significant association between CMV infection and HD centers (p=0.57), with the highest positive prevalence of CMV in the Nasser complex (83.7%) followed by (83.0%) in the Al-Najar region as shown in table 2.

The varying amount of time spent on HD is between one month to 240 months. A slightly statistically significant relationship between CMV infection and HD duration time (p=0.5) was found, the probability risk of infection increases with the increased duration time. The mean period was 48.84± 42.21 months for negative CMV patients and 61.25±58.74 months for CMV-positive patients.

Before or during HD, forty-four patients on HD were treated abroad. The bulk of treatments have been performed in neighboring Arab countries, mainly in Egypt. In countries such as occupied Palestine and Jordan, some patients have a history of a kidney transplant. It is also important to remember that certain cases have been handled in more than one country. A non-statistically significant relationship was found with treatment abroad (p=0.4). On the other hand, the study found a significant association between blood transfusion and MCV infection (p=0.04). The risk of infection increased with the increase in the number of blood units received. There is a statistically significant association between CMV infection and injection receiving, we found that patients receiving injection were more susceptible to CMV infection than non-injection receiving patients (p=0.03).

Discussion

In patients with significant immune suppression, such as cancer, HIV, and renal failure, CMV disease may occur as an opportunistic infection (Ljungman et al., 2016). In general, HD patients have an impaired immune system due to multiple transfusions and a reduced number of lymphocytes. There were numerous defects identified that could be attributed to intrinsic T cell abnormality rather than HD abnormality (Mahmood et al., 2016).

Since HD was first carried out in 1956, the possibility of acquiring CMV infection has been apparent. A broad survey of the United States of America HD centers (1971) showed that CMV incidence rates among HD patients were 61.2% (Agha, 2001). The prevalence of CMV among patients on HD was not previously examined in the Gaza Strip and its associated risk factors were not assessed. This research shows the prevalence of CMV using serological techniques among HD patients. It also attempts to establish risk factors currently involved in transmitting CMV to patients on HD. In this study, the overall prevalence of CMV in patients receiving HD in the Southern Gaza Strip was 83.3% (83.7% at the Nasser Medical Complex and 83.0% at the Abu Yousef Al Najjar Hospital).

This prevalence was higher than that in Iran (71%), Sudan (45.2%), and Germany (56.7%) (Sepehrvand et al., 2010; Abd Alla et al., 2015; Lachmann et al., 2018) **but** lower than Egypt (98%), Iraq (95.6%) and Croatia (90.7%) (El-Sadek & Morsy, 2008; Salman et al., 2014; Vilibic-Cavlek et al., 2015). The two evaluated HD centers were diverse when comparing, the use of a disposable needle, dialysis equipment, type of machine for dialysis, sterilization and disinfectant process, type of dialysis rooms regarding infected patients, and so on. No statistically significant variations in prevalence between the two HD centers are evident (p<0.57), this was seen in the previous study reported in Turkey (OCAK et al., 2006). This small disparity in prevalence may be due to improvements in the degree to which universal precautions are applied to prevent the incidence of nosocomial transmissions, such as avoidance of exchanging multidose vials or blood contact equipment.

A statistically significant relationship between CMV and the period on HD was found in our study, this finding was consistent with a previous report in Turkey, Egypt and Iran (OCAK et al., 2006; El-Sadek & Morsy, 2008; Sepehrvand & Khameneh, 2010). A statistically significant relationship between CMV and Receiving Injection (p=0.03) was found in our research and this finding was consistent with a previous report in Egypt. (El-Sadek & Morsy, 2008).

In our study a statistically significant relationship was found between CMV and blood transfusion, this observation was in agreement with a previous report in Turkey, Egypt, and Iran (OCAK et al., 2006; El-Sadek & Morsy, 2008; Sepehrvand& Khameneh, 2010). Gaza Strip was occupied by (Israel) from 1967 to 1993 and the siege imposed on Gaza by the Israeli occupation since the year 2000, hampering the growth of health services in the Strip. The majority of patients with chronic illnesses or in need of major surgery have been treated outside the strip, often in neighboring countries. Some of them were treated in countries such as Jordan and Egypt (e.g., kidney transplantation patients). Some patients have also undergone HD during their treatment, a non-statistically relevant association between outside treatment and infection with CMV (p=0.4) was found.

In accordance with previous research among the general population in Iraq, our findings also found no statistically significant association between the prevalence of CMV in HD patients and the sex of patients (Salman et al., 2014). The study did not find any statistically significant correlation between the prevalence of CMV among HD patients and the level of education, residency, and marital status. A previous study in Germany among the general population found that CMV is more popular among married and educated people (Lachmann et al., 2018).

Limitations of the study

The study was limited to two HD units in the southern of Gaza Strip, we hope that future work includes samples from a greater geographic area or be expanded to a multi-units analysis among all Gaza strip.

Conclusion

A high proportion of HD patients (83.3%) are seropositive to CMV, the results of this study indicate that For CMV infection risk factors including, duration of HD, Receiving Injection, and blood transfusion to be the major risk factors, other risk factors may including, treatment abroad countries which are associated with acquisition by nosocomial transmission, CMV prevalence was found lower among female patients, and higher among the secondary and highest level of education, and married patients. The study ultimately demonstrated the role of HD centers, Receiving Injection and blood transfusion in CMV transmission, and the urgent need for a rigorous infection management program to be implemented.

Recommendation

Implementation of a comprehensive infection control program, the components of such program include infection control practices specially designed for HD setting, including routine serological testing and immunization, surveillance, training, and education. These practices should be carried out routinely for all patients in the HD centers.

Acknowledgments

The authors of this study gratefully acknowledge the University College of Science and Technology-Khan Yunis, Palestine for providing instruments, and chemicals for this research.

Conflicts of Interest:

The authors declare no conflicts of interest.

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