ejpmr, 2020,7(4), 89-93

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

PREVALENCE OF CYTOMEGALOVIRUS ANTIBODIES AMONG PATIENTS WITH TYPE1 DIABETES MELLITUS IN ADEN CITY-YEMEN

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Article Received on 29/01/2020 **Article Revised on 19/02/2020** **Article Accepted on 09/03/2020**

ABSTRACT

Cytomegalovirus (CMV) is an enveloped deoxyribonucleic acid (DNA) virus belongs to the herpes viruses family. It has been implicated as inducers Type1 diabetes mellitus (T1DM). The association between CMV and T1DM has been well described in the medical literatures. The study was a Case – Control and experimental combining the use of a structured questionnaire and analysis of serum samples obtained from 100 children (1- 19 years) who had history of TIDM as case group compared with 100 healthy children as control group in Al-madaen laboratories in Aden city, during the period from November 2016 to December 2017. The serum samples were analyzed for Immunoglobulin G (IgG) antibodies to CMV by Electro-Chemiluminescence Immunoassay (ECLIA). Sera of two hundred (200) of children were collected. The samples were tested for anti-cytomegalovirus IgG, 69 (34.5%) of the total children of study were sero-positive CMV IgG, 13 (13%) of sero-positive CMV IgG were non-diabetic children (control group), while most of them, 43 (21.5%) were diabetic children which represent the case group, the results indicate association (P-value 0.011) of CMV IgG antibody with TIDM in children. The seroprevalence of CMV antibodies among children (1- 19 years) in Aden City, Yemen is slightly high 69 (34.5%), and the study reveals significant relationship of CMV IgG antibodies with TIDM in children.

KEYWORDS: Prevalence, Cytomegalovirus (CMV), Type 1 diabetic mellitus (TIDM), Aden, Yemen.

INTRODUCTION

Cytomegalovirus (CMV) is a β-herpes virus that was first isolated in 1957.[1] The CMV virion is characterized by enveloped and double strand, linear DNA genome enclosed in an icosahedral capsid protein surrounded by a proteinaceous tegument. CMV belongs to the herpes viruses family, sub-family Beta herpesvirinae, genus Cytomegalovirus.[2,3]

The incidence of Type 1 diabetic mellitus (T1DM) may reach the status of an epidemic disease in this century. T1DM is the first non-infectious disease that causes death in the world after an infectious diseases, Acquired immunodeficiency syndrome (AIDS) as the most important single cause of death.[4] A defect in metabolism of insulin leads to enormous influencing of a number of metabolic processes. A tiny concentration of free, biologically active insulin can lead to the development of diabetes mellitus. Possible causes of this include destruction of the β-cells in pancreas.[5] Type I diabetes usually effects the people in childhood.[6] In early childhood, environmental factors might trigger or increase process of T1DM.[7]

The exact etiology of T1DM is unknown. However, it is suggested that it initiating persons who are susceptible genetically, who come in contact with certain environmental factors, which trigger immune mediated destruction of the ß-cell mass. The interplay between environmental triggers, genetics and immunological response involve a balance between protective factors and susceptibility in each category.[8,9]

Particular viruses, such as: Cytomegalovirus, Rubella virus, Measles virus or Mumps virus can infect human and may cause diabetes mellitus through different mechanism such as hepatitis or pancreatitis and their subsequent complications.[10,11] Molecular mimicry is one of the essential immunological mechanisms that lead to desolation of the B-cells in pancreas. This mimicry could be involved in CMV-included diabetes by triggering islet cell autoantibodies.[12] Some studies provide evidence for an important interplay between adaptive immune responses to CMV, T1DM and occurrence of certain autoimmune disorders and beta cells destruction.[13,14] New studies on the etiology of T1DM have concentrated on environmental factors in early childhood that might trigger or accelerate the disease process, and there is now confirmation that the process may initiate in early infancy or even in utero.[16] There is also a lot of evidence to manifest

that congenital CMV infection can be an important factor in development of T1DM after birth and in early childhood. CMV can infect many cell types of beta cell in the islets of Langerhans, although beta cells are strongly resistant to the effects of this virus.[15]

In Yemen, there is no information has been found in the literature on the association between CMV and T1DM among children. Only limited studies have investigated the prevalence of CMV infection among women carried out in Sana'a, Ibb city and Hodeida city Yemen, which found a seroprevalence of 100%, 68% and 98.7% respectively.[16,17,18] The aim of the study was to determine the prevalence of CMV infection and to clarify the possible correlation between CMV infections and T1DM.

METHODS

Aden is a port city, located in south of Yemen, 170 kilometers east of Bab-elMandeb and 300 kilometers south of Sana'a. Its population is approximately 800,000 people according to governorate census in 2004.[19] This study carried out in local modern lab in Aden City. Specimens were taken from children who attended to the laboratory or transported to the lab from different clinics and hospitals in Aden City. The type of this study: Observation study (Case – Control). This design was sufficient to determine diabetic and non-diabetic children as well as determining some risk factors that may trend to cause T1DM. The study was carried out during the period, from November 2016 to December 2017. All Children attended to Al-madaen laboratories and to other local laboratories whom diagnosed with type I diabetes mellitus of both genders males and females with age ranged from 1-19 years old (Cases) while Healthy children, non-diabetic, of both genders males and females whom conducted to Al-madaen laboratories, with age ranged from 1-19 years old, and from some schools with age ranged from 1-19 years old (Controls)

Data collection was designed as questionnaire for face to face interview with the child or his/her family was used. A meeting interview done with the children or the children's families, the information was collected in a standardized sheets.

Five-ml blood sample was collected from 200 children, 100 of them were diabetic (case group) and the last 100 children were non-diabetic (control group). The sample was collected in gel tube for serological tests which was centrifuged (6000 rpm, 10 min). Serum glucose was determined immediately by glucose oxidase producer[20], using an instrument (Mindray BS-200 Shenzhen Biomedical Electronic, China) while the last of serum was transferred into labeled eppendorf cuvette and stored at -20° C until required for use. The serum was tested for CMV-specific IgG antibodies using IgG Elecsys kit by Electro-Chemiluminescence Immunoassay (ECLIA) technique (Cobas e411 analyzer, Roche Diagnostic GmbH, Mannheim, Germany).

Statistical analysis

Analysis of the data was performed in the computer for statistically analysis using statistical package for social science (SPSS) program version 20.0 to obtain percentage and correlations. Differences and association between categorical variables were tested by chi-square test and considered statistically significant at (P-value < 0.05).

Ethical considerations

Permission to perform the study was taken from post Graduate Studies, Sana'a University. Concerning the current study, the discussion conducted by specialists were appropriate and valid, associated with the agreements. All subjects participated were informed before blood collection.

RESULTS

Two hundred (200) children were investigated seroprevalence of CMV infection in this study, 100 (50%) represented case group (diabetic children) and 100 (50%) were healthy children representing control group (non-diabetic). The total number of male/female was 92/108 respectively. The demographic characteristics are listed in Table 1.

Table 1: Socio-demographic variables of children in Aden city.

Variables	Study groups			
	Case (Diabetic)		Control (non diabetic)	
	No.	%	No.	%
Gender				
Male	42	42	50	50
Female	58	58	50	50
Age group (years)				
1-4	6	6	7	7
5-9	27	27	30	30
10-14	30	30	38	38
15-19	37	37	25	25
Resident				
Aden City	100	100	100	100
Other Governorates	0	0	0	0
Place of birth				
Aden City	85	85	76	76
Other Governorates	15	15	24	24
T1DM Family history				
Yes	79	79	36	36
No	21	21	64	64

Table (2) shows the relationship between seroprevalence of cytomegalovirus IgG antibody and diabetic children, gender and age groups. The positive rate of IgG against cytomegalovirus in the study group (diabetic children) was higher than in control group (non-diabetic children) this result indicated statistically significant correlation between IgG antibodies of cytomegalovirus and diabetes mellitus type 1 (P value = 0.011). The seropositive of cytomegalovirus was slightly higher in female than male but there was not statistically significant. In the same way age groups were not significantly associated with CMV seropositive for IgG and antibodies.

Table 2: The association between CMV IgG and study groups, their gender and age groups in Aden city, Yemen.

Category	Participants		CMV IgG Reactive		P-value	Odds Ratio	95 % Confidence Interval	
	No.	%	No.	%			Lower	Upper
Study group								
Diabetics (case) T1DM: Type 1 diabetic mellitus.	100	50.0	43	21.5	0.011	2.147	1.182	3.900
Non-diabetics (control)	100	50.0	26	13.0				
Gender								
Male	92	46.0	29	14.5	0.413	1.134	0.820	1.596
Female	108	54.0	40	20.0				
Age group (years)								
1-4	13	6.5	3	1.5	0.733	1.168	0.644	2.117
5-9	57	28.5	19	9.5				
10-14	68	34.0	23	11.5				
15-19	62	31.0	24	12.0				
Category	**Participants**		**CMV IgG Reactive**		**P-value**	**Odds Ratio**	**95 % Confidence Interval**	
	No.	**%**	**No.**	**%**			**Lower**	**Upper**
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5-9	57	28.5	19	9.5				
10-14	68	34.0	23	11.5				
15-19	62	31.0	24	12.0				

Correlation of TIDM with Gender and age groups

There were no significant correlations between T1DM and Gender or age groups (Table 3). Both distributions show a slightly difference. In other words, diabetic females a somewhat higher than diabetic males, while the age group (15-19 Years) was the most diabetic group.

Table 3: The association between T1DM and Gender / age groups in Aden city, Yemen.

Category	TIDM		P-value	Odds Ratio	95% Confidence Interval	
	No.	%			Lower	Upper
Gender						
Male	42	21.0	0.256	2.413	0.790	1.381
Female	58	29.0				
Age group (years)						
1-4	6	3.0	0.321	0.608	0.294	1.257
5-9	27	13.5				
10-14	30	15.0				
15-19	37	18.5				

CMV: cytomegalovirus, IgG: Immunoglobulin G, P- value: probability value, T1DM: Type 1 diabetes mellitus.

DISCUSSION

This is the first published data on the epidemiology of CMV infections among children in Aden city, Yemen. Cytomegalovirus was chosen to examine seroprevalence of IgG antibodies and to find the relationship between infectivity and T1DM in children. Using a sensitive quantitative method, we demonstrated that TIDM correlate with presence or absent of CMV infection. The results in this study revealed that cytomegalovirus IgG antibodies were present in diabetic children with slightly high specific IgG response rates and statistically significant variation, these were similar to that previously reported in different area.[21,22,23] A contrary report, there is no correlation between T1 DM and virus infectivity, and there is not differences in serological responses to the virus between the diabetic and non-diabetic children.[24] Another contrary, there is no significantly association between perinatal CMV infection and progression to T1DM.[3] The results in current study also contrast with other study which concluded no correlation between CMV and TIDM disease.[25] CMV early children may reactivate in adolescent age and subsequently infect pancreatic islet cells led to T1DM. In this present study, we found that females had more seropositivity than males children. This is similar to previous study revealed, increase of IgG anti-cytomegalovirus in females.[26] CMV seroprevalence differed by gender and was higher in females than in males.[27] The females were more infected by the virus because the females spent more time together than males so the virus had more time to transport between the females children. Seropositivity of CMV IgG in groups (10-14 years) and (15-19 years) were higher than in other groups while the children from 1 to 4 years old showed the lowest CMV-IgG responses. This because of the children are known to shed the CMV and this may explain why most infected individuals had high infection at age 10-19 as they may have had exposure to children of their own, neighboring . household, school, or work place. This is in line with findings reported by.[26,28] These finding disagree with previous study reported that study reported that, prevalence of CMV antibodies increase in age between 1- 9 years.[29] There were limitations of this study. One limitation was that failure to enroll absent patients into the study lead to loss of potential cases to have larger sample size. The other limitation was Unavailability with high cost of serology kits for CMV lead to lost more time. More studies should be performed in other parts of Yemen to find the correlation between CMV infectivity and T1DM in children and used more sensitive and accurate molecular techniques.

ACKNOWLEDGEMENTS

This study supported by Al-madaen Medical Laboratories, Aden city, Yemen.

Conflict of interest

The authors state they have no conflicts of interest in this study.

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