Journal of University of Babylon for Pure and Applied Sciences, Vol. (27), No. (6): 2019

Study of Association between Cytomegalovirus Infection and Multiple Sclerosis

Saaed Gulam Hussain

Immunity at Hawler Medical University , College of Medicine

Abdulrahman Aziz

(Neurology) University lecturer in Kurdistan Board for Medical Specialists **Center**
abdrania77@gmail.com
Sevan Hassan Bakir.
Erbil Polytechnic University/ Medical Technical Institutes / Erbil, in Medical Laboratory Technology Department
sevan.hasan@yahoo.com

ARTICLE INFO
Submission date: 26/8/ 2019
Acceptance date: 19 / 11/ 2019
Publication date: 31/ 12 / 2019

Abstract

Background: Multiple Sclerosis is chronic autoimmune inflammatory demylinative disease of the central nervous system that affects usually young ages. Cytomegalovirus still controversy and have either protective role in induction of multiple sclerosis disease via molecular mimicry. The current study was designed to assess the sero-prevalence of anti-Cytomegalovirus IgG in multiple sclerosis patients; its impacts if any association of Cytomegalovirus with either disease initiation and or disease activity.

Materials and methods: The study was conducted in Rizgary teaching hospital Erbil /Iraq. Patients group enrolled comprised of 50 multiple sclerosis patients. The controls group comprised of 30 healthy persons with age and gender match. Anti-Cytomegalovirus IgG titer using enzyme- linked immunosorbent assay test was assessed in Multiple Sclerosis patients.

Results: A total of 50 multiple sclerosis patients is enrolled in this study, 17 Patients (34 %) had Relapsing Remitting multiple sclerosis and 33 patients (66%) had secondary progressive pattern course. Common presenting symptoms were limb weakness, diplopia, visual obscuration, sensory impairment and ataxia. Results revealed a highly significant increase of anti-CMV IgG titer in MS patients compared with controls group; with higher titer in patients with more than 4-relapses that reflects disease activity.

Conclusions: Seropositivity of Cytomegalovirus was higher in Multiple Sclerosis patients than controls; therefore, it may have a possible role in Multiple Sclerosis pathogenesis but further studies are needed to prove this result.

Key words: Cytomegalovirus (CMV), Multiple Sclerosis (MS), Enzyme linked immunosorbent assay (ELIZA), Extended disability status scale(EDSS)and Central nervous system (CNS).

Introduction

Multiple Sclerosis (MS) is the most common autoimmune inflammatory disease of central nervous system that cause inflammatory demyelination a progression cell loss and axonal degeneration within the central nervous system [1].

Since long time role of an environmental factors discussed that has an important factor in Multiple Sclerosis pathogenes is among these environmental risk factors, numerous infectious agents both viral and bacterial agent is investigated some of them approved that have role in its pathogenesis [2].

Several viruses have already been implicated as triggers and there are several studies that implicate members of the *Herpesviridae* family in the pathogenesis of MS. The most important characteristic of these viruses is that they have periods of latency and exacerbations within their biological sanctuary the central nervous system. The Epstein-Barr, Cytomegalovirus, human *herpesvirus*6 and human herpesvirus7 viruses are the members that are most studied as being possible triggers of multiple sclerosis [3].

Cytomegalovirus (CMV) is a member of the *Herpesviridae* (beta herpes virus) with a double-stranded DNA (235kb) that infects more than 40- 60 % of the general population and up to 100% within some subpopulations and / or geographic areas [1].

Cytomegalovirus may have a detrimental or beneficial role in MS pathology; thus the role is dispute [4]. CMV has been implicated as a co-etiological agent in brain cancer and associated with a wide range of inflammatory diseases [5]. CMV uses a variety of strategies that target host defenses from the disruption of antigen-processing pathways to the modulation of cytokines [6] all of which may contribute to the success of CMV in establishing coexistence. During active infection CMV can be found in most tissues and organs as well as in most body fluids especially urine and saliva [7].

Other studies are indicative for a protective effect of CMV on autoimmune diseases. CMV infection is associated with anti-inflammatory activities which could lead to a less severe course of the disease [8]. It will establish lifelong latent infection in $\geq$ 70% of human population [4].

It is mainly target cells of the myeloid lineage; can cross the blood brain barrier and has been detected in demyelinating plaques and the cerebrospinal fluid of MS patients [9,10]and causes demyelination mainly in the CNS of immune compromised host[11,12]. Based on CMV DNA and CMV- specific IgG antibody titers epidemiologic studies that support the role of CMV in MS pathology [1].

Accumulating evidence indicates that CMV contributes to MS pathophysiology via interplay of different mechanisms like molecular mimicry, bystander activation and epitope spreading [13].

The present study attempted to determine the sero-prevalnce of CMV in different specimens of Multiple Sclerosis patients to impact if any association of CMV with the disease.

Materials and Methods

The study is a case-control study, conducted in Rizgary teaching hospital Erbil /Iraq. The enrolled patient group comprised of 50 MS patients. The control group comprised of 30 healthy persons with a matched age and gender. The patients were treated with Beta- interferon. Verbal consent obtained from all patients and controls. According to criteria via clinical presentation and MRI the all patients was diagnosed and finding was supported by MS professional clinic team based on Revised McDonald criteria for diagnose of Multiple sclerosis [14].This study was approved by

the Ethic Committee at Erbil Medical Technical Institute/ Erbil Polytechnic University. The data was statistically analyzed by using the Graph pad prism software version 6 the applied tests are: ANOVA for single factor using Tukey's multiple comparison test and grouped t-test was used if the comparisons were between two variables. P value of ≤ 0.05 was considered statistically significant.

All patients had at least one attack of CNS inflammation. Expanded Disability Status Scale (EDSS)score for all patients at time of interview were below scale 5.0 except in cases with secondary progressive MS (SPMS).

The sera subjected to ELISA test for detection of anti- CMV IgG antibody in both MS patients and control group. According to anti-CMV IgG kit (Vircell) the sample with equivocal results must be retested and /or a new sample obtained for confirmation. Samples with indexes below 9 (U. /ml)were considered as not having IgG specific antibodies against cytomegalovirus. Samples with indexes above 11(U. /ml)were considered as having IgG specific antibodies against cytomegalovirus.

Results and Discussion

A total of 50 MS patients comprised of 38 females and 12 males with 30 controls (19) females and (11) males were enrolled. Included, 17 Patients (34 %) had Relapsing Remitting multiple sclerosis (RRMS) and 33 patients (66%) had secondary progressive pattern Multiple sclerosis (SPMS) and common presenting symptoms were limbs weakness, double vision, visual impairment, sensory signs and loss of balance (ataxia). The mean titer of CMVIgG in MS group was 23.29 ± 0.6079 vs16.27 ± 0.3804(U. /ml)in control group.

Figure (1) shows the mean titer of CMV IgG in M.S. patients and control group. The result revealed highly significant differences **P=0.0001**.

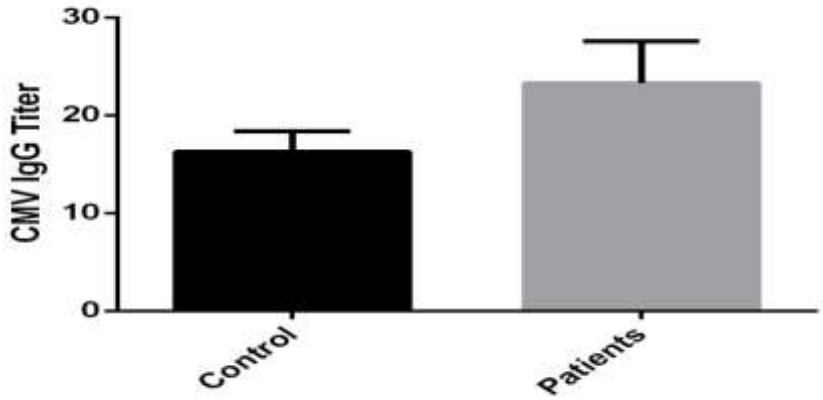

Figure (1): Mean titer of anti-CMVIgG in patients and control group

Figure (2) show the differences between CMV IgG titer among patients age groups. Statistically significan differences was recorded between different age groups **P=0.0326**.andhighest titer was recorded among ages (31-40).

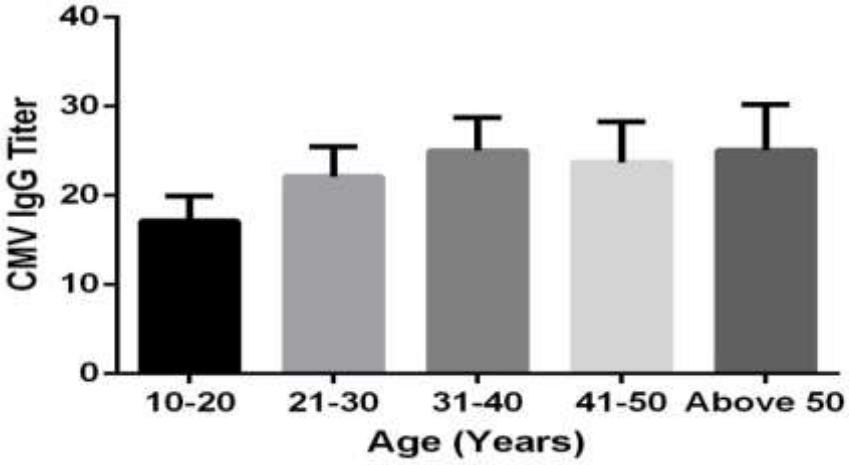

Figure (2): Mean anti-CMVIgG titer according to age groups in MS patients.

Figure (3) shows the titer was higher in female than male but with no significant value**. P=0.0811**

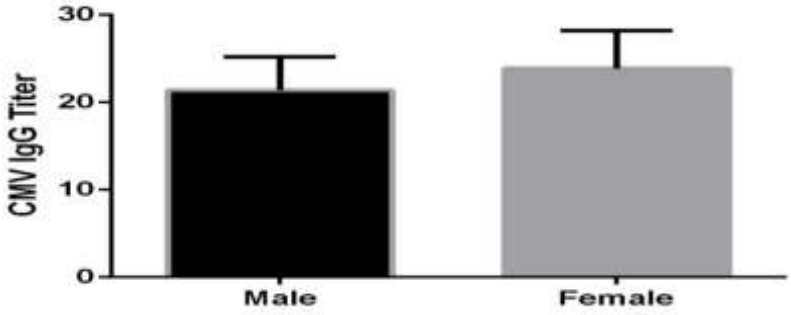

Figure (3): Mean anti-CMVIgG titer according to gender

Figure (4) delineate anti-CMV IgG titer in relation with symptomatic presentation. IgG titer has no significant differences between the different symptomatic presentation of MS.**P=5.93**.

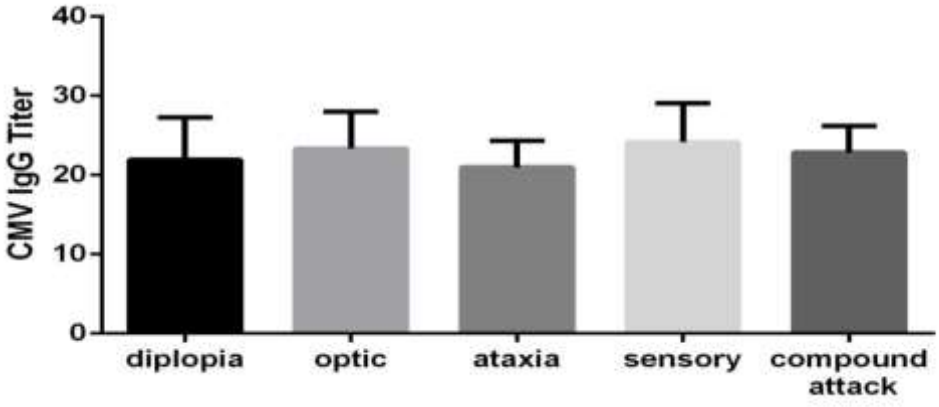

Figure (4): Mean anti-CMV IgG titer in relation to symptomatic presentation in MS patients

Figure (5) clarifies association between EDSS score and anti-CMV IgGtiter, this figure shows that despite the disease progression the titer is not significantly changed. **P=0.2812**.

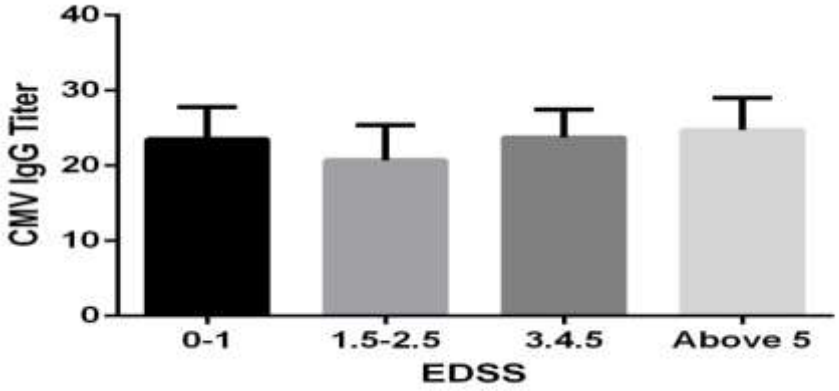

Figure (5): Relation between expanded disability status scale score and anti-

CMVIgG titer in MS patients

Figure(6) the relation between anti-CMVIgG titers and number of relapses, it reveals no statistically significant differences **P= 0.7307**; although the titers was higher in patients with more than 4- relapses of CNS inflammation.

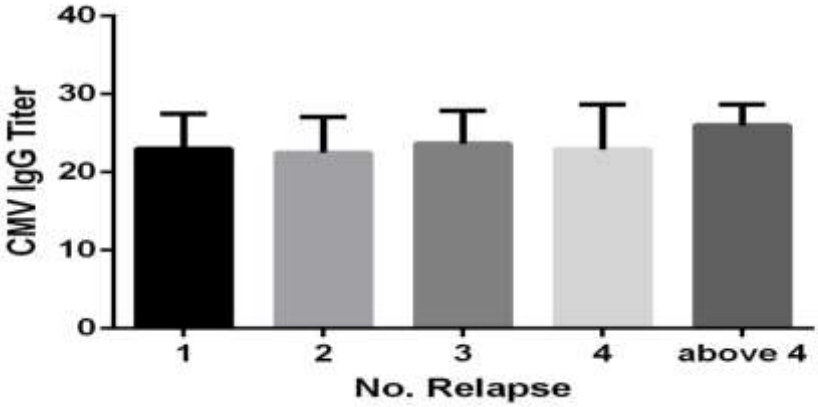

Figure (6): Relation between number of relapse and anti-CMVIgG titer in MS patients

There is a different idea on the role of CMV in MS disease. Some supports a detrimental role of CMV, as whereas others believe that CMV is disease- limiting. Various studies have focused on CMV as a potential trigger of MS [15, 16].

In this study, the mean titer of anti-CMV in MS patients was significantly more than control with gradual increases of titer with progressing of the disease. Though the anti-CMV IgG titer were more than higher in patients with more than 4-relapse. The results of the present study agree with Sanndgol *et al*.,2011 [1] who reported significant difference in anti-CMV IgG titer beside increased frequency of CMV-DNA in MS patients compared with control. Another study that produced by Horakovn *et al*., 2013 [17]found that the time to relapse decreased and the number of relapses increased with anti-CMV IgG positivity. Earlier study delineates a correlation between CMV Seropositivity titers and an increased MS disease risk [13]

in spite of Sundqvist *et al*., 2014 [18]that found CMV seropositivity was decreased risk of MS disease.

In this study, symptomatic presentation in association with anti-CMV IgG titer revealed no significant difference although when MS present in sensory symptom the titer was higher than present in any other symptoms. The same finding hold true for relation between EDSS score and anti-CMV IgG titer in MS patients although titer was higher in patients with EDSS score above 5. Our results disagree with study of Zivadinov *et al*., 2006 [19]who refers that association exists between anti-CMV seropositivity, a higher titer and better clinical and MRI outcomes this is could be our study has small sample size.

On the other hand, Wunsch *et al*., 2016 [14] show that the higher disease activity due to the elevating B-cell response to CM in MS patients experiencing an acute relapse according to the correlation between the frequencies of CMV and brain specific B-cells in MS patients[14].

Cytomegalovirus infection thus can lead to cell death and could therefore enhance autoimmunity as a result of the release of self-antigen from degenerating tissue [8].

Reactivation of CMV during ongoing MS could trigger the release of free virus in interstitial and cerebral fluids of the CNS [13].

Conclusions

Seropositivity of Cytomegalovirus in Erbil City/ Iraq MS patients is higher than controls so it may suggest a possible association between CMV and development of MS disease and further investigations with large number of patients are needed to confirm this finding.

Conflict of Interests.
There are non-conflicts of interest

References

1. N. Sanadgol, N. Ramroodi., GA. Ahmadi., M. Komijani., A. Moghtaderi, M. Bouzari, et al. Prevalence of Cytomegalovirus infection and its role in total immunoglobulin pattern in Iranian patients with different sub types of Multiple Sclerosis. New Microbiologica. 34, 263-274,2011.
2. S. Pawate, and S. Sriram. The role of infections in the pathogenesis and course of Multiple Sclerosis. Ann Indian A cad Neurol. 13 (2): 80-86,2010.
3. S.O. Guilherme, M.L. Bruna, M. S. Laura, S. Vitor, C. F. Maria, H. N. Luis, et al. Multiple sclerosis and herpesvirus interaction. Arq Neuropsiquiatr. 71(9-B):727-730,2013. DOI: 10.1590/0004-282X20130160.
4. P.J. Hanley and C.M. Bollard. Controlling cytomegalovirus: helping the immune system take the lead. Viruses 6. 2242–58,2014.
5. N.C. Söderberg. CMV microinfections in inflammatory diseases and cancer. J. Clin. Virol. 41, 218-223,2008.
6. D. Tortorlla, B.E. Gewurz, M.H. Furman, D.J. Schust and H.L. Ploegh. Viral subversion of the immune system. Annu. Rev. Immunol. 18, 861- 926, 2000.
7. C.M. Long, L. , R. Miner, D. Jekik-McMullen, C. Impraim and S.X. Kao. Detection of Cytomegalovirus in plasma and Cerebrospinal fluid specimens from human immunodeficiency virus infected patients by the Amplicor CMV test. J. Clin. Microbiol. 36, 2434-2438,1998.

8. A. Halenius and H. Hengel. Human Cytomegalovirus and autoimmune disease. Biomed. Res. Int. 47- 2978,2014.
9. D. S. Smyk, A. K. Alexander and M. Walker. A cute disseminated encephalomyelitis progressing to multiple sclerosis: are infectious triggers involved? Immunol. Res. 60:16–22,2014.
10. J. Djelilovic-Vranic, and A. Alajbegovic. Role of early viral infections in development of multiple sclerosis. Med. Arch. 66: 37–40,2012.
11. B. A.Hart, R. Q.Hintzen and J. D. Laman. Multiple sclerosis – a response-to-damage model. Trends Mol. Med.15: 235–44,2009.
12. C. Cermelli and S. Jacobson. Viruses and multiple sclerosis. Viral Immunol. 13, 255–67, 2000.
13. M. Vanheusden, P. Stinissen, A. Bert,T. Hart and N. Hellings.Cytomegalovirus: a culprit or protector in multiple sclerosis? Trends in molecular Medicine. 21: 1 16-23,2015.
14. M. Wunsch, C. Hohmann, B. Milles,C. Rostermund, P. V. Lehmann, M. Schroeter a, et al. The Correlation between the virus- and brain antigen- specific B cell response in the blood of patients with Multiple Sclerosis. J. Viruses. 8:105. doi: 10.3390./v8040105,2016.
15. M. M. Zheng and X. H. Zhang. Cross-reactivity between human cytomegalovirus peptide 981–1003 and myelin oligodendroglia glycoprotein peptide 35–55 in experimental autoimmune encephalomyelitis in Lewis rats. Biochem. Biophys. Res. Commun. 443: 1118–23,2014.
16. O. Barzilai, Y. Sherer,M. Ram, D. Izhaky,J. M. Anaya and Y. Shoenfeld. Epstein-Barr virus and cytomegalovirus in autoimmune diseases: Are they truly notorious? A preliminary report. Ann. N. Y. Acad. Sci. 1108: 567–77,2007.
17. D.Horakova, R. Zivadinov, B. Weinstock-Guttmann, E. Havrdova, J.Qu, . Tamano-Blanco and et al. Environmental factors associated with disease progression after the first demyelinating event: Results from the multi-center SET study. PLoS ONE. 8: e53996,2013.
18. E. Sundqvist, T. Bergström, H. Daialhosein, M. Nyström,P. Sundström, J. Hillert, et al . Cytomegalovirus seropositivity is negatively associated with multiple sclerosis. Mult. Scler. 20: 165–73,2014.
19. R. Zivadinov, D. Nasuelli,M. A. Tommasi, M. Serafin, A. Bratina, M. Ukmar, et al. Positivity of cytomegalovirus antibodies predicts a better clinical and radiological outcome in multiple sclerosis patients. Neurol. Res. 28: 262–69,2006.

دراسة العلاقة بين اصابات الفيروس المضخم للخلايا ومرض التصلب العصبي المتعدد

الخلاصة

الخلفية: يعد مرض التصلب العصبي المتعدد مرض مزمن من امراض الجهاز المناعي التي تصيب الجهاز العصبي المركزي حيث ان البحوث والدراسات السابقة تشير الى ادلة على ان الفايروس المضخم للخلايا قد يكون له دور ضار او مفيد في مرض التصلب العصبي المتعدد من الناحية الباثولوجية المناعية وقد تم اجراء هذه الدراسة لتقييم مدى انتشار الفيروس المضخم للخلايا في مصل مرضى متعددة التصلب ومدى تاثيره على المرضى التصلب العصبي المتعدد .

الاساليب: لقد تم اجراء الدراسة في مستشفى رزكاري التعليميفي أربيل/ العراق. حيث تم اخذ مجموعة من المرضى والتى تتألف من 50 مرضى التصلب العصبي المتعدد. و تم اخذ 30 شخصا صحيحا كعينة سيطرة مع اخذ بالاعتبار التقارب في الاعمار بين الفئتين و نوع بين الجنسين و قد تم دراسة نسبة انتشار الفايروس Cytmegalovirus Anti-IgGفي كلا الفئتين.

النتائج: من بين 50 من مرضى التصلب العصبي المتعدد في هذه الدراسة، كان 17 (34 ٪) مريضا يعانون من الانتكاس التصلب المتعدد التصلب و 33 مريضا (66 ٪) كان لها دورة نمط التقدم التدريجي من الدرجة ثانية . وكانت العامة الظاهرة على المرضى هي ضعف أطرافهم، شفع، التعمية البصرية، نقص الحسي والترنح. كشفت النتائج زيادة كبيرة جدا من عيار مضاد IgG لفايروس المضخم للخلايا لدى مرضى التصلب العصبي المتعدد مقارنة مع مجموعة السيطرة. مع ارتفاع عيار الفايروس في المرضى الذين يعانون من أكثر من 4 الانتكاسات او الاعراض المرضية في الجهاز العصبي التي تعكس مدى النشاط المرضي لديهم.

الاستنتاج: من خلال هذا البحث لقد كانت نسبة انتشار الفايروس المضخم للخلايا أعلى في المرضى الذين يعانون من التصلب العصبي المتعدد مقارنة بعينة السيطرة اي الاشخاص الصحيين وقد يكون لها دور ايجابي في ازدياد نسبة المرض في المرضى التصلب العصبي المتعدد ولكن هناك حاجة لدراسات اخرى ابعد من ذلك لإثبات هذه النتيجة.