Academic Journal of Research and Scientific Publishing | Vol 1 | Issue 11
Publishing Date: 5-3-2020 ISSN: 2706-6495

Relation between Epstein-Barr virus infection and Multiple Sclerosis

By: Dr. Aisha Yassin Abdul-Ghaffar[1], Dr. Dalia Youssef Samaha[2], Dr. Nancy Samir Wahba[3], and Ahmed Essam Ali Hussein[4]

Clinical Pathology Department, Faculty of Medicine, Ain Shams University

* Corresponding author: Ahmed Essam Ali

E-mail: ahmedessam175@gmail.com

Abstract:

Background: Multiple sclerosis (MS) is an immune mediated inflammatory disease that attacks myelinated axons in the central nervous system (CNS), destroying the myelin and the axon in variable degrees. The aetiology and pathogenesis of MS is complex and multifactorial, involving many interlacing mechanisms. Many theories had considered viral infections as a possible cause of MS. One of these viruses is Epstein-Barr virus (EBV), a herpes virus belonging to the family herpesviridae. There is obvious similarity between EBV and MS regarding their epidemiological pictures, and it was observed that most MS patients had a history of infectious mononucleosis (IM) a few years before onset.

[1] Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University – Egypt

[2] Assistant Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University - Egypt

[3] Lecturer of Clinical Pathology, Faculty of Medicine, Ain Shams University - Egypt

[4] M.B.B.C.h, Faculty of Medicine, Cairo University - Egypt

The relation between EBV and MS may give hope for development of biomarkers for prediction of disease development, early diagnosis, prediction of prognosis, curing or even preventing MS through an anti EBV vaccine or antiviral therapies.

Objectives: This study aims to analyze the association between EBV infection and multiple sclerosis.

Subjects and Methods: This is a case control study carried in the MS outpatient clinic at Ain Shams University Hospitals during the period from April 2019 till November 2019. Subjects included in this study were classified into two groups. The first group included 30 patients diagnosed as having MS, on the basis of their MRI finding, clinical presentation and according to revised Mc Donald criteria 2017. The patient group included 11 males and 19 females, their age ranged from 18 to 48 years. The second group included 30 age and sex matched healthy controls without any neurological or medical diseases. The control group included 11 males and 19 females, their age ranged from 18 to 48 years. Both groups were tested quantitatively for immunoglobulin G against Epstein Barr viral capsid antigen (VCA) using the enzyme linked immunosorbent assay technique (ELISA).

Results: All patients with MS (100%) were positive for EBV VCA IgG, whereas (93.33%) of controls were positive. In the MS group, the EBV VCA IgG mean level was (161± 66.32) U/ ml compared with (78.53±47.63) U/ ml in controls. The difference in serum level of EBV VCA IgG between both groups was statistically highly significant (P= < 0.001).

Conclusion: There were higher levels of EBV VCA IgG in the serum of MS patients compared to healthy controls. This finding postulates a relation between EBV infection and MS and its role in the pathogenesis of MS.

Keywords: Epstein Barr Virus, Multiple Sclerosis, Viral Capsid Antigen.

Introduction

Multiple sclerosis (MS) is an immune mediated inflammatory disease that attacks myelinated axons in the central nervous system (CNS), destroying the myelin and the axon in variable degrees. As true to most autoimmune diseases, it affects females more than males ***(Kamińska et al., 2017).***

Multiple sclerosis can affect the sensory, motor, cognitive, and even autonomic functions of the CNS, leading to a wide range of possible presentations. It takes several forms, with new symptoms either occurring in isolated attacks (relapsing forms) or building up over time (progressive forms). Between attacks, symptoms may disappear completely; however, permanent neurological problems often remain especially as the disease advances ***(Lublin et al., 2014)***.

The etiology and pathogenesis of MS is complex and multifactorial, involving many interlacing mechanisms: genetic factors, environmental agents, and autoimmune responses. The environmental factors may include smoking, vitamin D deficiency, lack of sunlight exposure, and infectious agents. Many theories had considered viral infections as a possible cause of MS, in support of which is the presence of clear examples of inflammatory demyelinating disease caused directly or indirectly by viral infections in both humans and animals. In addition, there is a beneficial role of interferon-β in MS treatment which is one of the most popular antiviral agents ***(Abdulrahman et al., 2014).***

Epstein-Barr virus, a herpes virus belonging to the family herpesviridae, is well known for its ability to induce lifelong latent infection. Many diseases are associated with EBV infection, for example, infectious mononucleosis (IM) and many types of malignancies, and it is thought to be related to some diseases of autoimmune origin ***(Chiu and Sugden, 2016)***.

There is obvious similarity between EBV and MS regarding their epidemiological pictures, and it was observed that most MS patients had a history of IM a few years before onset. The relation between EBV and MS may give hope for development of biomarkers for prediction of disease development, early diagnosis, prediction of prognosis, curing or even preventing MS through an anti EBV vaccine or antiviral therapies ***(Toepfner et al., 2012)***.

AIM OF THE WORK

This study aims to analyze the association between EBV infection and Multiple Sclerosis.

SUBJECTS AND METHODS

A. Subjects:

This is a case control study carried in the MS outpatient clinic at Ain Shams University Hospitals during the period from April 2019 till November 2019. Subjects included in this study were classified into two groups:

1. Patients with MS:

This group included 30 patients diagnosed as having MS, on the basis of their MRI finding, clinical presentation and according to revised Mc Donald criteria 2017. The group included 11 males and 19 females, their age ranged from 18 to 48 years.

Exclusion criteria of the patient group:

- Patients who had not yet fulfill diagnostic criteria of multiple sclerosis.
- Patients who had any other autoimmune disease.
- Patients with a history of blood transfusion within the last three months.
- Patients with immune-deficient diseases (AIDS, liver, kidney failure and Post transplantation patients).

2. The control group

This group included 30 age and sex matched healthy controls without any neurological or medical diseases. The control group included 11 males and 19 females, their age ranged from 18 to 48 years.

Sampling:

Five milliliters (5ml) of venous blood were withdrawn under complete aseptic conditions from each subject in a plain tube (Greiner VACCUETTE 4.5ml Z Serum Clot Activator, Greiner Bio-One GmbH, 4550 Kresmunster, Austria).

The samples were centrifuged at 3000 rpm for 5 minutes at room temperature in order to separate serum. Serum was stored at ≤ -20° C until measuring serum level of EBV VCA IgG.

B. Methods:

I. The study groups were subjected to the following:

1. **The MS group:** Detailed questionnaire and full medical history, general and local neurological examination including initial assessment of MS according to the Revised McDonald criteria 2017 for MS diagnosis, assessment of functional disability using Expanded Disability Status Scale (EDSS) at the time of sample withdrawal.
2. **The control group:** Complete medical history to confirm that they are free of any neurological and medical diseases,

Both groups were informed about the aim of our study, methodology and they had agreed to participate in the study. Both groups were assessed for EBV VCA IgG titre by the enzyme linked immunosorbent assay (ELISA) technique using an ELISA kit provided by Institut Virion\ Serion GmbH (Friedrich-Bergius-Ring19, D-97076 Wurzburg, Germany). The assay was done in the laboratories of Clinical Pathology Department of Ain Shams University Hospitals.

II. Assessment of EBV VCA IgG titre by ELISA technique:

1. **Principle:** The reaction is based on the specific interaction of antibodies with their corresponding antigen. Microtiter wells are coated with EBV capsid antigen (solid phase). Sample is added to the wells and any antibodies specific for the antigen present will bind to the solid phase. A secondary anti-human IgG antibody conjugated with the enzyme alkaline phosphatase is allowed to react with the immune complexes. The colourless substrate p-nitrophenylphosphate is added which reacts with the conjugated enzyme and converted into the coloured product p-nitrophenol. The colour intensity of the reaction product is proportional to the concentration of the specific antibody bound and can be quantified photometrically.

2. **Reagent and material provided:** Plate (12 strips x 8 wells), Standard serum (2x2ml), Negative control serum (2ml), Anti-human IgG conjugate (13ml), Washing solution concentrate (33.3ml), Dilution buffer (2x50ml), Substrate (13ml), Stopping solution (15ml), and Standard curve.
3. **Preparation of reagents:** Washing buffer was diluted with distilled water 1:30 before use.
4. **Interpretation of results:**

The substrate blank OD value was subtracted from all OD values prior to evaluation. All OD values of the samples were multiplied by a factor representing (OD reference value of STD / OD of measured STD). This procedure was done to adjust the level of the measured OD values of the samples with the kit specific standard curve. OD Values of the samples were plotted on the standard curve and EBV VCA IgG titres in IU/ml were obtained.

C. Statistical analysis of data:

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science. Data was presented and suitable analysis was done according to the type of data obtained for each parameter. P- value: level of significance: P>0.05: Non significant (NS), P< 0.05: Significant (S), P<0.01: Highly significant (HS).

RESULTS

Table 1: Demographic data of the control group:

		Min.	Max.	Mean	SD
Age		18.00	48.00	28.67	8.13
		N		**%**	
Sex	**Male**	11		36.7%	
	Female	19		63.3%	

The control group included 11 males (36.7%) and 19 females (63.3%), and their age ranged from 18 to 48 years with a mean of 28.67 ±8.13 years.

Table 2: Demographic data of the MS group:

		Min.	Max.	Mean	SD
Age		18.00	48.00	31.10	9.34
		N		**%**	
Sex	**Male**	11		36.7%	
	Female	19		63.3%	

The MS group included 11 males (36.7%) and 19 females (63.3%). Their age ranged from 18 to 48 years with a mean 31.1 ± 9.34 years.

Table 3: Medical history and clinical status of the MS group:

		Min.	Max.	Mean	SD
Age at onset		15.00	44.00	24.83	7.53
Duration of illness		1.00	20.00	6.27	5.00
Total number of relapses in Relapsing Remitting Multiple Sclerosis (RRMS) patients		.00	10.00	3.37	2.22
EDSS score		1.00	7.00	3.65	1.98
		N		**%**	
Family History	**negative**	29		96.7%	
	positive	1		3.3%	
Smoking	**no**	27		90.0%	
	yes	3		10.0%	
Type of MS	**RRMS in relapse**	16		53.4%	
	RRMS in remission	10		33.3%	

	Secondary Progressive Multiple Sclerosis (SPMS)	3	10.0%
	Primary Progressive Multiple Sclerosis (PPMS)	1	3.3%

Regarding the cases group, it was found that 1 patient (3.3%) had a positive family history (FH) of MS and 3 patients (10%) were current smokers. The age of the patients at the onset of the disease ranged from 15 to 44 years with a mean of 24.83 ± 7.53 years. The duration of illness ranged from 1 to 20 years with a mean of 6.27 ± 5.00 years. Regarding the clinical status of MS in our patients, there were 26 patients in RRMS (with 16 patients in relapse (53.4%), 10 patients were in remission (33.3%)), 3 patients were in SPMS (10.0%) and 1 patient was in PPMS (3.3%) as shown in**.** The total number of relapses in RRMS patients ranged from 0 to 10 with mean of 3.37 ± 2.22. The EDSS score at the time of sample withdrawal ranged from 1 to 7 with a mean of 3.65 ± 1.98.

Table 4: Serum EBV VCA IgG antibodies among the study groups:

Variable	**Measure**	**Cases (N=30)**	**Controls (N=30)**
EBV VCA IgG seropositivity	**Positive**	30 (100.0%)	28 (93.3%)
	Negative	0 (0.00%)	2 (6.7%)
EBV VCA IgG titres	**Mean±SD**	161±66.32	78.53±47.63
	Range	50-280	15-200

Assay for EBV VCA IgG was done for both groups in the study. Results of the control group showed that 28 individuals (93.3%) had positive serum EBV VCA IgG titres while 2 individuals (6.7%) had negative serum EBV VCA IgG titres. The antibodies titres ranged from 15 to 200 IU/ml with a mean of 78.53±47.63 IU/ml. Assay results in the MS group showed that all 30 patients (100.0%) had positive serum EBV IgG. The antibodies titres ranged from 50 to 280 IU/ml with a mean of 161±66.32 IU/ml.

The comparison between both groups regarding prevalence of EBV VCA IgG seropositivity showed no significant difference (P= 0.49).

Table 5: Comparison between cases and controls regarding EBV VCA IgG titres:

	Cases		Controls		t*	P value
	Mean	SD	Mean	SD		
EBV VCA IgG titres	161.00	66.32	78.53	47.63	5.53	<0.001 HS

*Student t test

On the other hand, the comparison between both groups regarding the EBV VCA IgG titres showed that the MS group had higher EBV VCA IgG titres than the control group (P= < 0.001) and the difference was statistically highly significant.

Table 6: Correlation between EBV VCA IgG titres in the MS group and age:

	Mean	SD	Pearson correlation r*	P value
Age	31.10	9.34	0.12	0.53 NS
EBV VCA IgG titres	161.00	66.32		

There was no significant correlation between EBV VCA IgG titres in the MS group and age (P= 0.53).

Table 7: Comparison of EBV IgG titres in the MS group according to sex, smoking and family history of MS:

		EBV VCA IgG titres		Test value	P value
		Mean	SD		
Sex	male	161.36	66.49	0.02*	0.98 NS
	female	160.79	68.05		
Family History of MS	negative	156.90	63.50	1.91*	0.07 NS
	positive	280.00	.		
Smoking	no	156.48	66.43	1.13*	0.27 NS
	yes	201.67	60.48		

*Student t test

Among the MS group, the EBV VCA IgG titres did not show a statistically significant difference between males and females (P= 0.98), smokers and nonsmokers (P= 0.27), or between patients with negative versus positive family history for MS disease (P= 0.07).

Table 8: Comparison of EBV VCA IgG titres in different clinical types of MS in the MS group:

		EBV VCA IgG		Test value	P value
		Mean	SD		
Type of MS	RRMS in remission	140.50	72.28	0.64*	0.60 NS
	RRMS in relapse	167.50	63.53		
	PPMS	155.00	.		
	SPMS	196.67	75.06		

*One Way ANOVA test

Table 9: Correlation between EBV VCA IgG titres and clinical characteristics of the disease:

	EBV IgG conc.	
	r*	**P value**
Age at onset	0.23	0.22 NS
Duration of illness	-0.08	0.69 NS
Total number of relapses in RRMS patients	-0.31	0.10 NS
EDSS score	0.23	0.23 NS

***Pearson's correlation**

Regarding the clinical characteristics of the disease, there was no significant association between the EBV VCA IgG titres and different clinical types of MS (P= 0.60)**.** Also, there was no significant correlation between the EBV VCA IgG titres and the age of the patient at the onset of the disease (P=0.22), the duration of illness (P=0.69), total number of relapses in RRMS patients (P=0.10), or EDSS score (P=0.23).

DISCUSSION

Multiple sclerosis is a demyelinating autoimmune disease with different clinical forms and uncertain etiology. Many studies suggest that it is likely caused by infections triggering a systemic immune response resulting in autoimmune disease in CNS. There is a largely divergent body of literature regarding the relationship between EBV infection and development of MS ***(Tao et al., 2017).***

In this study, we aimed to investigate the possible association between EBV infection and MS disease. The study was carried out on 30 MS patients according to Revised McDonald criteria 2017 and 30 matched age and sex healthy controls. Assay for EBV VCA IgG was done for both groups.

Most of MS patients (93.3%) in this study were between 18 and 45 years of age; this finding is in accordance with those of many other studies dealing with age groups of MS. In a previous study conducted by ***Etemadifar and Maghzi 2011*** on 3345 MS patients,

(88.85%) were aged 20–45 years. Also, ***Abdulrahman et al. 2014*** conducted a study with (84%) of patients aged between18-45. This is consistent with the epidemiological fact denoting that MS mostly affects age groups of late adolescence and early adulthood.

In our study, males represented 36.6% of MS patients and females represented 63.4% of MS patients with a male to female ratio nearly 1:2.This finding is in accordance with many studies dealing with sex groups of MS as ***Dooley et al., 2016 and Abdulrahman et al. 2014.*** This is consistent with the fact denoting that MS mostly affects females than males with a male to female ratio 1:2 ***(Leray et al., 2016).***

Regarding prevalence of seropositivity of EBV infection, the results showed no significant difference between cases and controls (P= 0.49) and this finding agrees with a study done by ***Honarmand et al., 2015*** who studied 46 MS patients using the ELISA technique and found no significant difference between cases and controls (P= 0.98). ***Schlemm et al., 2016*** studied 29 MS patients using the ELISA technique and stated that no significant difference was found in prevalence of EBV seropositivity between cases and controls (P= 0.49). Also, ***Hon et al., 2012*** studied 31 MS patients using the ELISA technique and found no significant difference in prevalence of EBV seropositivity between cases and controls (P= 0.99). On contrary ***Abdulrahman et al., 2014*** studied 75 MS patients using the ELISA technique and found that 100% of MS patients were positive for EBV VCA IgG compared with 80% of controls (P= < 0.001). Similarly, ***Deeba et al., 2019*** studied 133 MS patients using the ELISA technique and found that EBV seropositivty among MS patients was 100% which was significantly higher than healthy controls (P= 0.0025).

However, our results showed that the MS group had statistically significant EBV VCA IgG higher titres when compared to the control group (P= <0.001) which indicates that EBV infection may be a strong risk factor for MS. These results have been demonstrated in previous studies which showed that EBV VCA IgG titres were higher in MS patients compared to controls as ***Mouhieddine et al., 2015*** who studied 249 MS patients using the quantitative chemiluminescent assay and found higher titres in MS patients compared to controls (P= <0.05). ***Abdulrahman et al., 2014*** studied 75 MS patients using the ELISA technique and found higher titres in MS patients compared to controls (P= <0.001).

Schlemm et al., 2016 studied 29 patients of MS using ELISA technique and found higher titres in MS patients compared to controls (P= <0.01).

Among the MS group there was no significant correlation found between the EBV VCA IgG titres and the age of patient (P=0.53). This finding is going with a study done by ***Hon et al., 2012*** who studied 31 MS female patients with age ranged between 28-51 years for EBV VCA IgG using ELISA technique and found no correlation between EBV VCA IgG and age of MS patients.

In addition, our results in the MS group showed no significant difference in the EBV VCA IgG titres between males and females (P=0.98), smokers and non-smokers (P=0.27) or negative and positive family history of MS (P=0.07). On contrary, ***Mouhieddine et al., 2015*** who studied 249 MS patients with age ranged between 25-49 years using the quantitative chemiluminescent assay reported that older age and female gender were associated with a higher EBV VCA IgG titre. Also, he reported that EBV VCA IgG levels were positively correlated with current smoking and cumulative tobacco consumption.

We compared the EBV VCA IgG levels in the different clinical types of MS (RRMS in remission, RRMS in relapse, SPMS, PPMS) and the difference was not statistically significant (P= 0.60). This finding is going with a study done by ***Abdulrahman et al., 2014*** as they did not find any statistical difference in the EBV VCA IgG titres of different clinical types of MS. ***Buljevac et al., 2005*** found no correlation between whether patient in relapse or remission and titre of EBV VCA IgG.

Regarding the relation between EBV VCA IgG levels and the clinical characteristics of the disease, results revealed that there was no significant correlation between the EBV VCA antibody titre and the age of onset of the disease (P=0.22), duration of illness (P=0.69), total number of relapses (P=0.10) or EDSS score (P=0.23) which indicate that the increased levels of EBV VCA IgG is not associated with MS activity or progression regarding relapse rate, age of onset of the disease, duration of the disease or EDSS score. This agrees with previous studies showing that there was no association between levels of EBV VCA IgG and these parameters. For examples, ***Munger et al., 2015, Castillazi et al., 2014 and Gieß et al., 2017*** found no convincing evidence that serological parameters of EBV were associated with age of onset, MS relapse hazard or progression in disability.

The discrepancy in the results of different research work and studies in assessing prevalence of seropositivity of EBV VCA IgG and titres in MS patients may be due to many possible causes. It could be due to a small sample size, patient or control selection, and methodological differences in determination techniques as using the quantitative chemiluminescent assay to measure EBV VCA IgG levels.

We acknowledge that the sample size in this study is relatively small and findings should be validated in larger patient populations, a longitudinal study of antibody responses to EBV antigens in MS patients for suitable period with different methodologies must have been used for different correlations and the using of well-designed antiviral clinical trials with safe, efficient and CNS-penetrable antiviral drugs. All are necessary to determine whether antibody responses to EBV change during the course of disease progression and its effect on disease relapses. Collectively, our data together with earlier reports still strengthens the hypothesis that EBV may be associated with MS disease pathogenesis.

CONCLUSION

From this study we concluded that: there were higher levels of EBV VCA IgG in the serum of MS patients compared to healthy controls. This finding postulates a relation between EBV infection and MS and its role in the pathogenesis of MS. There was no correlation between EBV VCA IgG titres and MS patients' age, sex, smoking and positive family history of MS. There was no correlation between EBV VCA IgG titres and MS clinical characteristics of MS disease as age of onset of the disease, duration of illness, different clinical types of MS, total number of relapses and EDSS.

REFERENCES

Abdulrahman HS, Selim HS, Hashish MH and Sultan LI (2014): Epstein-Barr virus in multiple sclerosis. J Egy Pub Heal Assoc; 89: 90 - 95.

Buljevac D, Van Doornum GJ, Flach HZ, Groen J, Osterhaus AD, Hop W, van Doorn PA, Van der Meché FG and Hintzen RQ (2005): EBV and disease activity in multiple sclerosis. J Neurol Neurosurg Psych; 76(10): 1377-1381.

Castellazi M, Contini C, Tamborino C, Fasolo F, Roversi G, Seraceni S, Rizzo R, Baldi E, Tola MR, Bellini T, Granieri E and Fainardi E (2014): EBV specific intrathecal oligoclonal IgG production RRMS is limited to a subset of patients and is composed of low affinity antibodies. J Neuroinflamm; 11: 188-215.

Chiu YF and Sugden B (2016): EBV: The path from latent to productive infection. Ann Rev Virol; 3(1): 359-372.

Deeba E, Koptides D, Gaglia E, Constantinou A, Lambrianides A, Pantzaris M, Krashias G and Christodoulou C (2019): Evaluation of EBV specific antibodies in Cypriot MS patients. Mol Immunol; 105: 270-275.

Dooley J, Pauwels I, Franckaert D, Smets I, Garcia-Perez JE, Hilven K, Danso-Abeam D, Terbeek J, Nguyen AT, De Muynck L, Decallonne B, Dubois B, Liston A and Goris A (2016): Immunologic profiles of multiple sclerosis treatments reveal shared early B cell alterations. Neurol Neuroimmunol Neuroinflamm; 3(4): e240.

Etemadifar M and Maghzi AH (2011): Sharp increase in the incidence and prevalence of MS in Isfahan, Iran. Mult Scler; 17(8): 1022-1027.

Gieß RM, Pfuhl C, Behrens JR, Rasche L, Freitag E, Khalighy N, Otto C, Wuerfel J, Brandt AU, Hofmann J, Eberspächer B, Bellmann-Strobl J, Paul F, Ruprecht K (2017): EBV antibodies in serum and DNA load in saliva are not associated with radiological and clinical disease activity in patients with early multiple sclerosis. PLoS ONE; 12(4): e0175279.

Honarmand H, Moghadam MAJ, Hatamian H and Roudbary A (2015): Possible relations between Epstein - Barr virus past infection and classic multiple sclerosis in Guilan, Iran. Jundishapur J Microbiol; 8(6): 15985-15990.

Hon GM, Hassan MS, van Rensburg SJ, Erasmus RT and Matsha TE (2012): Assessment of Epstein-Barr virus in blood from patients with multiple sclerosis. Metab Brain Dis; 27(3): 311-318.

Kamińska J, Koper OM, Piechal K and Kemona H (2017): MS: Etiology and diagnostic potential. Postepy Hig Med Dosw (Online); 71(0): 551-563.

Leray E, Moreau T, Fromont A and Edan G (2016): Epidemiology of multiple sclerosis. Rev Neurol; 172(1): 3 – 13.

Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sorensen PS, Thompson AJ, Wolinsky JS, Balcer LJ and Banwell B (2014): Defining the clinical course of multiple sclerosis. Neurol; 83(3): 278-286.

Mouhieddine TH, Darwish H, Fawaz L, Yamout B, Tamim H and Khoury SJ (2015): Risk factors for multiple sclerosis and associations with anti-EBV antibody titers. Clin Immunol; 158(1): 59-66.

Munger KL, Fitzgerald KC, Freedman MS, Hartung HP, Miller DH, Montalbán X and Edan G (2015): No association of MS and progression with EBV or tobacco use in benefit. Neurol; 85(19): 1694-1701.

Schlemm L, Geiß RM, Rasche L, Pfuhl C and Wakonig K (2016): Fine specificity of the antibody response to Epstein-Barr nuclear antigen-2 and other Epstein-Barr virus proteins in patients with clinically isolated syndrome: A peptide microarray-based casecontrol study. J Neuroimmunol; 297: 56-62.

Tao C, Simpson S, Taylor BV and van der Mei I (2017): Association between human herpesvirus, human endogenous retrovirus and MS onset & progression. J neurol sci; 372: 239-249.

Toepfner N, Cepok S, Grummel V and Hemmer B (2012): The role of Epstein-Barr virus receptor CD21 in multiple sclerosis. J Neuroimmunol; 242(1):47-51.