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Multiple Sclerosis: Possible Role of Epstein-Barr virus in the Etiology and Relapses

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Abstract

Background and objectives: Multiple Sclerosis is the most common inflammatory demyelinating and degenerative autoimmune disease of the central nervous system. The cause of multiple sclerosis is unknown but several viruses have been proposed as a trigger for multiple sclerosis and lately Epstein- Barr virus has been recently associated with the onset of multiple sclerosis we assess the relation between Epstein-Barr virus infection and multiple sclero-sis. We assess the relation between Epstein-Barr virus infection and multiple sclerosis. **Methods:** In present study we assess the Epstein-Barr virus nuclear antigen IgG antibody titer level by ELISA technique in both Multiple Sclerosis patients (n= 50) and healthy controls (n= 30). **Results:** The results of the present study demonstrated increasing mean titer of EBNA IgG antibodies in patients (21.32) comparing with healthy control (15.37) (P value= 0.003) with neither effect of gender nor age. This study demonstrates the statistically significant relation between new relapses and clinical presentations of multiple sclerosis relapses (P value 0.05) also demonstrated a significant difference be-tween different types of symptoms (P=0.0362) and EBNA IgG antibodies concentration while the EDSS and number of relapses had no significant differences.**Conclusions:** This study revealed the possible role of EBV during the course of multiple sclerosis an autoimmune disease via anti-EBNA IgG seropositivity that correlated with type of attack or relapse.

Keywords: Multiple Sclerosis; Epstein-Barr virus; autoimmune; Erbil; Iraq.

Introduction

Multiple sclerosis is an autoimmune inflammatory disorder of CNS of unknown etiology characterized by demyeliza- tion and variable degrees of axonal loss. The disease affects mostly young women (between ages 20 and 40 years)and is one of leading causes of disability in young adults[1-2]. The etiology although unknown; presumably involves interaction between genetic, environmental, and other factors triggering an aberrant autoimmune attack resulting in damage to myelin and axons[3]. Although MS is not an inherited disease there is a strong genetic component to its etiology as evidenced by clustering of MS cases within families, The risk of MS among first degree relatives of MS patients is 10-50 times higher than the general population (absolute risk 2-5%) the concordance rate in monozygotic twins is about one-third[4-5]. Linkage analysis studies have revealed several gene loci as risk factors with the major histocompatibility complex (MHC) specifically HLA DR/ DQ6 allele being the strongest one[6-7]. More recently, alleles of interleukin-2 receptor alpha gene (IL2 RA) and interleukin-7 receptor alpha gene (IL7RA) have also been identified as inherit-able risk factors[7-8].Among environmental factors EBV infection and vitamin D deficiency have been extensively studied and linked to MS risk[9-10]. Several studies have compared the seroprevalence for common EBV antibodies between MS patients and healthy individuals. A systematic review studies demonstrated that nearly all MS patients are infected with EBV com- pared with only about 90% of controls[11]. Uniquely EBV chronic infection is established within immortalized B-lymphocytes that are transformed by an array of viral proteins that functionally mimic host proteins to create long-lived memory cells[12]. Viral persistence is then promoted through mechanisms that reduce antigen presentation to the adap-tive immune system[13]. Among EBV antigens EBNA-1 is not immunologically silent as once thought but is an

antigenic target for both CD4 and CD8 T-cell responses as well as antibodies[14]. Several lines of evidence link EBV specific immunity to MS risk. Both serological[15-16], and CD4 T cell responses directed against EBNA-1 have been associ ated with MS, with further evidence that EBNA-1 specific antibodies differentiate disease- discordant identical twins[17]. Several groups have demonstrated higher EBV seroprevalence in MS patients compared to controls and it has further been demonstrated that EBV infection late in life in particular if manifested as infectious mononucleosis increases a person s MS risk[18-19]. Epstein-Barr virus nuclear antigen-1 (EBNA1) is the most consistently recognized EBV-specific antigen which stimulates CD4 T-cell responses in healthy virus carriers. Selective expansion of T cells specific for EBNA1 was observed in MS patients[20]. Moreover a small subset of them have been shown to cross-react with myelin antigens supporting the hypothesis that clonally expanded EBNA1-specific T cells could be actively involved in MS immune pathology by stimulating cross-recognition through molecular mimicry[16].

Patients and Methods

The study was a case control study conducted at Rizgary teaching hospital Erbil /Iraq. Criteria for diagnosed via clinical presentation and MRI finding was supported by MS professional clinic team based on Revised McDonalds's criteria of diagnose MS. Verbal consent obtained from all patients and controls and this study approved by the Ethic Committee at Erbil Medical Technical Institute/ Erbil Polytechnic University. The data statistical analyzed were done by using the software is Graph pad prism 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. Expanded Disability Status Scale (EDSS) score for all patients at the time of inclusion were below scale 5.0 except of in cases with secondary progressive MS (SPMS). All patients had at least one clinical relapse proved that it is inflammatory in origin. 50 MS patients enrolled in this study beside 30 people healthy aged and gender matched control group. The sera subjected to ELISA test for detection of anti-EBNA IgG in patients with MS and control.

Results

A total of 50 MS patients comprised of 38 females and 12 males and 30 controls females and males were enrolled and common clinical presentation were motor, diplopia, optic, sensory and ataxia. The mean titer of EBNA IgG in MS group was 21.32 versus 15.37 in control group ($P < 0.05$).

Figure 1 shows the mean titer of EBNA IgG in M.S. patients and control group. The result revealed highly significant differences (21.32 vs 15.37; P 0.05). P value = 0.0003 (there is a significant differences).

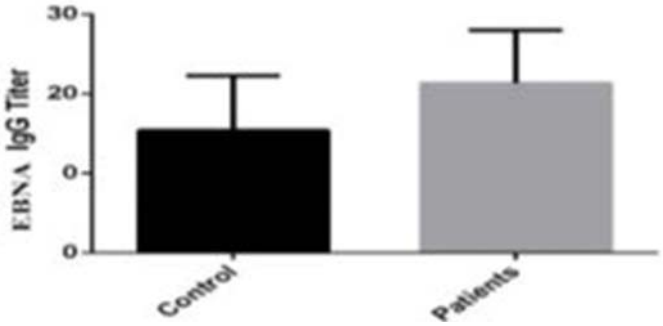

Figure (1): Mean titer of EBNA IgG in patients and control group.

Table 1 shows the difference between mean EBNA IgG titer of patients in relapse with those on remission stage; which the mean titer of patients on relapse was higher than the mean titer of patients on remission stage.

Table (1): Mean EBNA IgG titer according to the activity of MS.

Time of diagnosis	No.of patients	Mean titer of EBNA
Relapsing	15	25.52
Remitting	35	19.5

Figure 2 clarify the differences between EBNA IgG titer among age groups statistically no significant differences (P= 0.05) was seen although age groups 10-20 showed a higher mean titer. differences (21.32 vs 15.37; P 0.05). P value = 0.0003 (there is a significant differences).

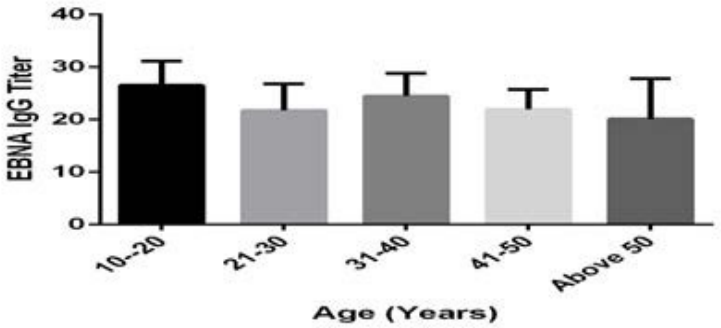

Figure (2): Mean EBNA IgG titer according to age in MS patients.

Figure 3 shows no significant difference of mean EBNA IgG titer according to gender (P=0.3580).

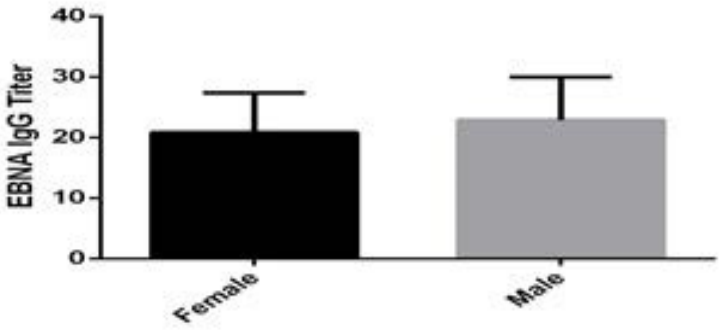

Figure (3): Mean EBNA IgG titer according to gender.

Figure 4 delineate EBNA IgG titer in relation with symptomatic clinical presentation; it shows highest in patients with brain stem signs and lowest in patients with optic neurites thusdifferent EBNA IgG titer between the different types of symptoms showed significant difference (P = 0.0362)

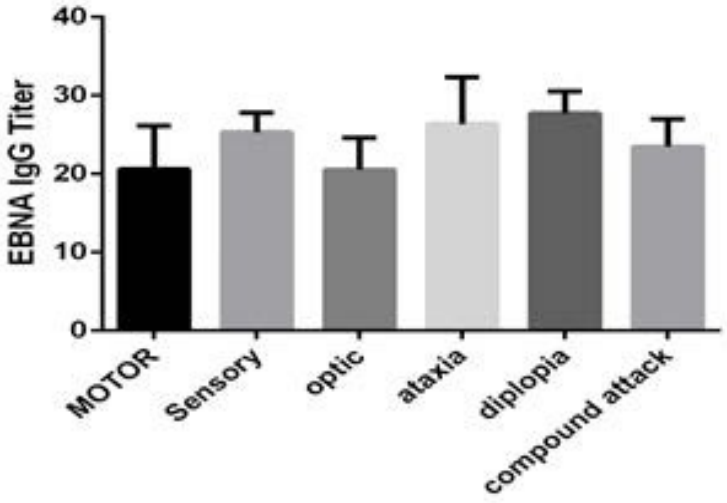

Figure (4): Mean EBNA IgG titer in relation to symptomatic clinical presentation in MS patients.tion to symptomatic clinical presentation in MS patients.

Figure 5 according to EDSS score and EBNA IgG titer showed no significant difference, it means how much the disease is progress the titer is not changed (P= 0.8346).

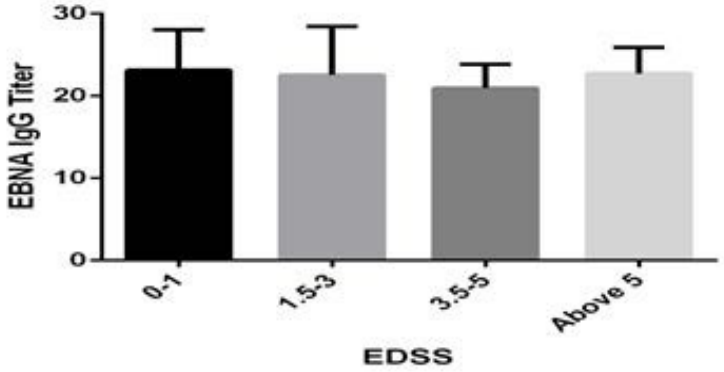

Figure (5): Relation between EDSS score and EBNA IgG titer in MS patients.

The relation between EBNA IgG titers and number of clinical relapses (Figure 6) revealed statistically no significant differences (P= 0.8725).

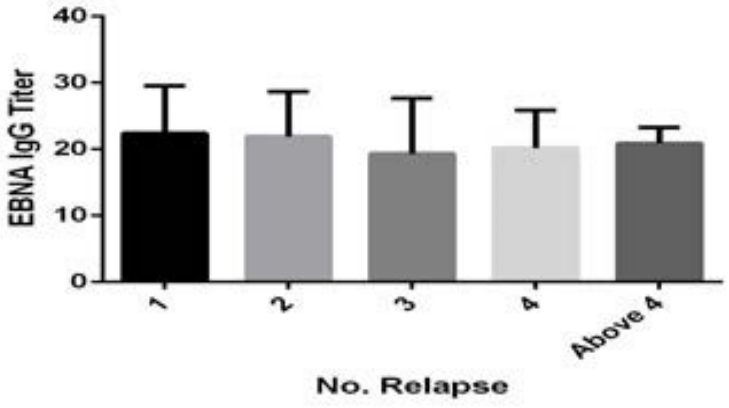

Figure (5): Relation between number of relapse and EBNA IgG titer in MS patients.

Discussion

Among factors determine susceptibility to MS jointly genetic and environmental factors[21]. The environmental risk factors proposed for MS the infectious etiology which fits with a number of epidemiological observations as well as immune pathological features of MS; of these EBV has become the leading candidate in recent years[22]. The results of the present study revealed increased mean titer of anti-EBNA IgG antibodies in MS patients compared with control with neither effect of gender nor age. Of interesting finding in this study the presence of significant differences (P 0.05) between mean EBNA IgG titer in relation to symptomatic clinical presentation; although EDSS score, number of clinical relapse with EBNA IgG titers revealed no significant relation. The impact of EBV reflected as anti EBNA IgG revealed a significant elevation in titer in those patients in relapse state in compare with those patients on remission state. With higher mean titer in patients with clinical presentations was ataxia, diplopia (Brain stem signs) which reflects aggressiveness of the disease. There are many evidence indicate an association between EBV reactivation with clinical disease activity in MS when these reactivation is defined as a pattern of increased IgM and IgA levels against EBV[23]. The result of the present study agree with several studies in which serum IgG levels and associated EBV nuclear antigen-1 (EBNA-1) are elevated before onset of MS and correlates with disease activity and prognosis in contrast IgG and lytic EBV proteins named viral capsid antigen (VCA) are not changed suggesting that EBV abnormalities in MS are associated with B-cell receptors to latent EBV antigen[24].Lünemann et al[25] refers that elevated immune response towards EBNA-1 are selectively increased in clinically isolated syndrome (CIS) patients and suggest that EBNA-1 specific IgG titers could be used as prognostic marker for disease conversion to MS and disability progression the another refer that only EBNA-1 specific antibody response correlated with neurological disability i.e EDSS at 1 and 5 years after disease onset. Epstein-Barr virus has a number of properties that make the virus as a potential causal factor for MS development including its ubiquitous expression, its ability to cause latent infection and its ability to undergo periodic reactivation[18]. Evidence supporting the role of EBV in MS includes, the statistically EBV seropositivity rate in MS patients relative to controls despite the ubiquitous nature of EBV infection in adults[9-18]. Studies have reported an increased risk of developing MS following infectious mononucleosis[19-26,27]. In addition several reports have shown reactivity of the immunoglobul in presents that cross react with EBV derived protein in CSF of MS patients to EBV antigens. Further recognizing an immunodominant epitope of myelin basic protein from patients with MS[28-29]. Despite these observations EBV could contributed to MS pathogenesis via an in direct effect on immune function[30]. The absence of sera-negativity and the increase in EBV specific IgG responses are universally present across patients with various and phenotypically different autoimmune disease, it will be interesting to directly compare finding on the regulation of EBV infection in patients with MS[31].

Conclusions

This study revealed the possible role of EBV during the course of MS autoimmune disease via antibody EBNA IgG seropositivity and correlated with type of attack or relapse.

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