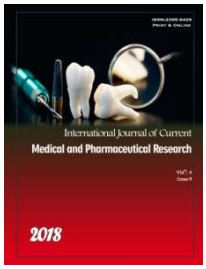
Review Article

INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH

ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 4; Issue 9(A); September 2018; Page No. 3674-3682
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr20180538



EPSTEIN-BARR VIRUS IS THE CAUSE OF MULTIPLE SCLEROSIS

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ARTICLE INFO

Article History:
Received 12th June, 2018
Received in revised form 23rd July, 2018
Accepted 7th August, 2018
Published online 28th September, 2018

Key words:
Epstein-Barr virus, multiple sclerosis, causal relationship

ABSTRACT

Aim: This systematic review assesses once again the causal relationship between Epstein-Barr virus (EBV) and multiple sclerosis (MS) for gaining a better understanding of the pathogenesis of this disease.
Methods: A systematic review and meat-analysis of some studies is provided aimed to answer among other questions the following question. Is there a cause effect relationship between Epstein-Barr virus and multiple sclerosis? The method of the conditio sine qua non relationship was used to proof the hypothesis without Epstein-Barr virus no multiple sclerosis. In other words, if multiple sclerosis is present, then Epstein-Barr virus is present too. The mathematical formula of the causal relationship k was used to proof the hypothesis, whether there is a cause effect relationship between Epstein-Barr virus and multiple sclerosis. Significance was indicated by a p-value of less than 0.05.
Results: The studies analysed were able to provide evidence that Epstein-Barr virus is a necessary condition (a conditio sine qua non) of multiple sclerosis. Furthermore, the studies analyzed provide impressive evidence of a cause-effect relationship between Epstein-Barr virus and multiple sclerosis.
Conclusion: Epstein-Barr virus the cause of multiple sclerosis.

INTRODUCTION

Multiple sclerosis is one of the most common inflammatory demyelinating diseases of the central nervous system, affecting people of almost all ages in many parts of the world. MS affects more than 2 million[1] people worldwide and is driven by a pathological inflammation. The first description of multiple sclerosis (MS) dates back to the 14th century[2], but it was Jean-Martin Charcot (1825-1893), the father of neurology[2] who provided the first detailed description of MS in 1868 (described as "*la sclérose en plaques*"[3]). The aetiology of Multiple sclerosis is still not well understood even if MS is not directly inherited. Some environmental factors such as latitude, vitamin D, or cigarette smoking[4]and other are unlikely to explain the cause of multiple sclerosis. Epidemiological studies[5-7] reported some evidence that EBV might be involved in the pathogenesis of MS. EBV itself is a member of the herpes family of viruses and persists after a primary infection latently in resting memory B cells[8-9]during the lifetime of the host. The prevalence of IgG antibodies to varicella zoster virus (VZV), herpes simplex virus (HSV), and cytomegalovirus (CMV) did not differ between multiple sclerosis cases and controls[10]. Numerous studies investigated the relationship between Epstein-Barr virus (EBV) and multiple sclerosis (MS) and provided some evidence that the titres of EBV antibodies are significantly lower among sero-positive controls when compared with sero-positive MS cases[11-12].

In line with observations like these, recent systematic reviews[13-14]provided evidence of an association between MS and sero-positivity for different EBV antibodies but failed to provide any etiological link between EBV and the pathogenesis of MS. Only one study was able to provide evidence of a causal relationship[15] between Epstein-Barr virus and multiple sclerosis. Still, the relationship between Epstein-Barr virus and multiple sclerosis remains a matter of controversy.

MATERIAL AND METHODS

Multiple sclerosis is very heterogeneous in nature and symptomatology and severity is varying greatly from patient to patient. Patient may present with a wide variety of clinical symptomatology including sensory, visual, motor, cerebellar and brainstem dysfunction. MS can restrict the individual's income-earning ability, resulting in a major financial burden on the society, the health system, the family and the patient. Considering the costs associated with MS disease severity, non-pharmaceutical or pharmaceutical interventions aimed at delaying the progression of disease may help to reduce the burden of MS.

Search strategy

For the questions addressed in this paper, Pubmed was searched for case-control studies conducted in any country which investigated the relationship between Epstein-Barr virus and MS. The search in PubMed was performed while using medical key words like "case control study" and "Epstein-

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Barr virus" and "multiple sclerosis" and "PCR DNA" et cetera. More than 600 articles were identified from which from which more than 30 published studies were selected for a re-analysis. The abstracts of the articles found where saved as a *.txt file while using PubMed's support (Menu: Send to, Choose Radio Button: File, Choose Format: Abstract (text). Click bottom "create file"). The created *.txt file was converted into a *.pdf file. If necessary, the original article was studied. The abstracts where studied within the *.pdf file. Those articles were considered for a review which provided access to data without any data access barrier; no data access restrictions were accepted. Additionally, references from relevant publications and review articles were checked. Studies were excluded if insufficient data were provided to calculate the measures of relationship or if there were data access barriers.

Statistical analysis

All statistical analyses were performed with Microsoft Excel version 14.0.7166.5000 (32-Bit) software (Microsoft GmbH, Munich, Germany). In order to simplify the understanding of this article, to increase the transparency for the reader and to correct some of the misprints of former publications, several of the following lines are repeated word by word and taken from former publications.

The 2x2 Table

The meaning of the abbreviations a_t, b_t, c_t, d_t, N_t of the data table used are explained by a 2 by 2-table Table 1.

Table 1 The sample space of a contingency table.

		Conditioned B_t (Outcome)		
		Yes = 1	Not = +0	Total
Condition A_t	Yes =+1	a_t	b_t	A_t
(risk factor)	Not = +0	c_t	d_t	$\underline{A}_t$
	Total	B_t	$\underline{B}_t$	N_t

In general it is $(a_t+b_t) = A_t$, $(c_t+d_t) = \underline{A}_t$, $(a_t+c_t) = B_t$, $(b_t+d_t) = \underline{B}_t$ and $a_t+b_t+c_t+d_t=N_t$. Equally, it is $B_t+\underline{B}_t = A_t + \underline{A}_t = N_t$. In this context, it is $p(a_t)=p(A_t \cap B_t)$, $p(A_t) = p(a_t)+p(b_t)$ or $p(A_t)= p(A_t \cap B_t)+ p(b_t) =p(A_t \cap B_t)+p(A_t \cap \underline{B}_t)$ while $p(A_t)$ is not defined as $p(a_t)$. In the same context, it is $p(B_t) = p(a_t)+p(c_t) = p(A_t \cap B_t) +p(c_t)$ and equally in the same respect $p(\underline{B}_t) = 1-p(B_t) =p(b_t)+p(d_t)$. Furthermore, the joint probability of A_t and B_t is denoted in general by $p(A_t \cap B_t)$. Thus far, it is $p(A_t \cap B_t) = p(A_t) - p(b_t) = p(B_t) - p(c_t)$ or in other words it follows clearly that $p(B_t) + p(b_t) - p(c_t) = p(A_t)$. In general, it is $p(a_t)+p(c_t)+p(b_t)+p(d_t) = 1$.

The data of the studies analysed

The data of the studies[10-12, 16-56] analysed, are presented by several tables (Table 2, Table 3, Table 5). The meaning of the abbreviations a_t, b_t, c_t, d_t, N_t of tables (Table 2, Table 3, Table 4, Table 5) is explained by a 2 by 2-table (Table 1). Some studies (Table 4) provided self-contradictory data and were not considered for a re-analysis.

EBV EBER-ISH and/or PCR Study of Hassani et al.

Several studies investigated whether EBV is present in the CNS with conflicting[57] results. Due to variations in terms of practical and technical approaches and other factors. Asma Hassani *et al*.[58] demonstrated (Table 5) the presence of EBV in the involved tissues of the central nervous system of postmortem MS and non-MS autopsied human brain tissues.

Independence

In the case of independence of A_t and B_t it is generally valid that

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \quad (1)$$

Table 2 Without EBV VCA IgG Antibody positivity no MS

Study Id	Year	Country	N	a_t	b_t	c_t	d_t	k	p val (k)	X^2(SINE)
Sumaya *et al.*	1980	USA	238	155	76	2	5	0.137385437	0.0340	0.01
Bray *et al.*	1983	USA	719	309	363	4	43	0.186809738	0.0000	0.04
Martyn *et al.*	1983	UK	374	170	116	44	44	0.08093851	0.1175	8.84
Larsen *et al.*	1985	Unknown	186	93	78	0	15	0.296174439	0.0001	0.00
Sumaya *et al.*	1985	USA	130	104	23	0	3	0.307389312	0.0005	0.00
Ferrante *et al.*	1987	Italy	72	29	31	1	11	0.302371578	0.0103	0.01
Shirodaria *et al.*	1997	UK	52	26	24	0	2	0.2	0.1492	0.01
Myhr *et al.*	1998	Norway	314	141	138	3	32	0.265051413	0.0000	0.04
Ascherio *et al.*	2001	USA	431	143	269	1	18	0.128151392	0.0078	0.00
Sandström *et al.* (a)	2004	Sweden	292	73	217	0	2	0.04794633	0.4126	0.00
Alotaibi *et al.*	2004	Kuwait	173	25	82	5	61	0.202573375	0.0077	0.68
Sundström *et al.* (b)	2004	Sweden	644	161	476	0	7	0.060522753	0.1246	0.00
Ponsonby *et al.*	2005	Australia	397	136	252	0	9	0.109939711	0.0285	0.00
Pohl *et al.*	2006	Germany	294	145	106	2	41	0.375399352	0.0000	0.02
Banwell *et al.*	2007	Canada	222	108	61	18	35	0.257665693	0.0001	2.43
Nociti *et al.*	2010	Italy	405	265	129	2	9	0.168316954	0.0007	0.01
Lucas *et al.*	2011	Australia	423	202	208	4	9	0.063877783	0.1889	0.06
Mowry *et al.*	2011	USA	140	109	13	11	7	0.270065993	0.0014	0.92
Waubant *et al.*	2011	USA	255	164	34	25	32	0.370665642	0.0000	3.18
Lalive *et al.*	2011	CH	42	22	15	0	5	0.3855498	0.0125	0.01
Ramroodi *et al.*	2013	Iran	201	71	101	7	22	0.123595607	0.0797	0.54
Abdelrahman *et al.*	2014	Egypt	150	75	60	0	15	0.333333333	0.0000	0.00
Mouhieddine *et al.*	2015	Lebanon	479	248	224	1	6	0.091888987	0.0443	0.00
Karampoor *et al.*	2016	Iran	110	60	41	0	9	0.327002589	0.0006	0.00
Gieß *et al.*	2017	Germany	160	98	57	2	3	0.083473001	0.2910	0.02
		Total	6903	3132	3194	132	445	0.063369994		16.84
				Alpha =		0.05				
				Degrees of freedom (d. f.) =		25				
				X^2 Critical (SINE) =		**37.6525**				
				X^2 Calculated (SINE) =		16.8382				

Table 3 Without EBV EBNA Antibody positivity no MS.

Study Id	Year	Country	N	a_t	b_t	c_t	d_t	p(SINE)	X²(Sine)	k
Sumaya *et al*.	1985	USA	130	102	23	2	3	0.9846154	0.0216	0.2000
Larsen *et al*.	1985	Unknown	186	93	78	0	15	1	0.0027	0.2962
Ferrante *et al*.	1987	Italy	72	25	28	5	14	0.9305556	0.6750	0.1864
Shirodaria *et al*.	1997	UK	52	26	21	0	5	1	0.0096	0.3262
Myhr *et al*.	1998	Norway	314	143	160	1	10	0.9968153	0.0017	0.1406
Munch *et al*.	1998	Denmark	276	137	124	1	14	0.9963768	0.0018	0.2078
Wandinger *et al*.	2000	Germany	271	108	147	0	16	1	0.0023	0.2039
Ascherio *et al*.	2001	USA	424	141	266	1	16	0.9976415	0.0018	0.1196
Sundström *et al*. (b)	2004	Sweden	644	160	459	1	24	0.9984472	0.0016	0.0975
Sandström *et al*. (a)	2004	Sweden	292	73	210	0	9	1	0.0034	0.1030
Haahr *et al*.	2004	Denmark	106	53	50	0	3	1	0.0047	0.1707
Selter *et al*.	2010	Germany	83	16	25	9	33	0.8915663	2.8900	0.1918
Sellner *et al*.	2010	Germany	111	54	49	1	7	0.990991	0.0045	0.2065
Ingram *et al*.	2004	UK	100	70	18	5	7	0.95	0.2700	0.2843
Alotaibi *et al*.	2004	Kuwait	173	25	60	5	83	0.9710983	0.6750	0.3133
Pohl *et al*.	2006	Germany	268	124	77	10	57	0.9626866	0.6735	0.4050
Riverol *et al*.	2007	Spain	257	167	75	5	10	0.9805447	0.1177	0.1778
Banwell *et al*.	2007	Canada	222	108	61	18	35	0.9189189	2.4306	0.2577
Lindsey *et al*.	2010	USA	160	78	74	2	6	0.9875	0.0281	0.1147
Nociti *et al*.	2010	Italy	405	261	128	6	10	0.9851852	0.1133	0.1216
Jaquiery *et al*.	2010	CH	123	39	73	1	10	0.9918699	0.0063	0.1567
Jafari *et al*.	2010	Netherlands	176	108	51	6	11	0.9659091	0.2654	0.2018
Villegas *et al*.	2011	Spain	151	66	62	10	13	0.9337748	1.1875	0.0581
Lucas *et al*.	2011	Australia	423	199	198	7	19	0.9834515	0.2051	0.1115
Sundqvist *et al*.	2011	Sweden	1249	580	616	5	48	0.9959968	0.0346	0.1578
Lalive *et al*.	2011	CH	42	22	16	0	4	1	0.0114	0.3403
Mowry *et al*.	2011	USA	139	108	11	11	9	0.9208633	0.9265	0.3576
Waubant *et al*.	2011	USA	255	167	36	22	30	0.9137255	2.4458	0.3676
Abdelrahman *et al*.	2014	Egypt	150	70	68	5	7	0.9666667	0.2700	0.0491
Mouhieddine *et al*.	2015	Lebanon	479	240	206	9	24	0.9812109	0.2902	0.1345
Karampoor *et al*.	2016	Iran	110	60	41	0	9	1	0.0042	0.3270
Gieß *et al*.	2017	Germany	160	96	44	4	16	0.975	0.1225	0.3318
		Total	8003	3719	3555	152	577	0.9810071	13.6983	
				Alpha =		0.05				
				Degrees of freedom (d. f.) =		32				
				X² Critical (SINE) =		**47.39**				
				X² Calculated (SINE) =		13.7				

Table 4 Studies with self-contradictory data.

Study Id	Year	Country	N	a_t	b_t	c_t	d_t	k	p val (k)	X²(SINE)
Guiterez *et al*.	2002	Spain	72	38	30	3	1	-0.088439467	0.4530	0.15
Zivadinov *et al*.	2006	USA	271	133	131	7	0	-0.157513828	0.0095	0.30
Jilek *et al*.	2008	CH	56	25	29	1	1	-0.013781637	0.9179	0.01
Jaquiery *et al*.	2010	CH	123	38	79	2	4	-0.003930191	0.9652	0.06
Villoslada *et al*.	2003	Spain	148	44	24	54	26	-0.0294		

Table 5 The EBV EBER-ISH and/or PCR Study of Hassani *et al*.

		Multiple sclerosis<B>		
		Yes	No	Total
EBV positive <A>	Yes	91	5	96
	No	10	16	26
	Total	101	21	122
		k =	+0.6111	
		p value (k) <	0.00001	
		95% CI (k) =	[+0.4086, +0.8135]	
		WITHOUT <A>	NO <B>.	
		p (SINE) =	0.9180	
		X²(SINE) =	0.8936	
		Odds ratio =	29.1200	
		95% CI (Odds ratio) =	[8.7898 , 96.4722]	
		IF <A>	THEN <B>	
		p (IMP)=	0.9590	
		X² (IMP)=	0.2109	
		<A> is SINE	and IMP of <B>	
		p(SINE ^ IMP) =	0.8770	
		X²(SINE ^ IMP) =	1.1045	

Exclusion (A_t Excludes B_t and Vice Versa Relationship)

The mathematical formula of the *exclusion* relationship (A_t excludes B_t and vice versa) of a population was defined [15, 59-63] as

$$\begin{aligned} p(A_t \mid B_t) &\equiv \frac{b_t + c_t + d_t}{N_t} \equiv 1 - p(a_t) \\ &\equiv p(b_t) + p(c_t) + p(d_t) \\ &\equiv p(c_t) + (1 - p(B_t)) \\ &\equiv p(b_t) + (1 - p(A_t)) \\ &\equiv +1 \end{aligned} \quad (2)$$

and used to proof the hypothesis: A_t *excludes* B_t and vice versa.

Necessary Condition (Conditio Sine Qua Non)

The mathematical formula of the *necessary* condition relationship (conditio sine qua non) of a population was defined [15, 59-63] as

$$\begin{aligned} p(A_t \leftarrow B_t) &\equiv \frac{a_t + b_t + d_t}{N_t} \\ &\equiv p(a_t) + p(b_t) + p(d_t) \\ &\equiv p(a_t) + (1 - p(B_t)) \\ &\equiv +1 \end{aligned} \quad (3)$$

and used to proof the hypothesis: *without* A_t *no* B_t .

Sufficient Condition (Conditio per Quam)

The mathematical formula of the *sufficient* condition relationship (conditio per quam) of a population was defined [15, 59-63]as

$$\begin{aligned} p(A_t \rightarrow B_t) &\equiv \frac{a_t + c_t + d_t}{N_t} \\ &\equiv p(a_t) + p(c_t) + p(d_t) \\ &\equiv p(d_t) + p(B_t) \\ &\equiv +1 \end{aligned} \quad (4)$$

and used to proof the hypothesis: *if* A_t*then* B_t .

The X² Goodness of Fit Test of a Necessary Condition

Under conditions where the chi-square goodness of fit test[65]cannot be used it is possible to use an approximate and conservative (one sided) confidence interval known as *the rule of three*[65-68]. Using *the continuity correction*[69], the chi-square value of a conditio sine qua non distribution before changes to

$$\chi^2(\mathrm{SINE}) \equiv \frac{\left(c_t - \left(\frac{1}{2}\right)\right)^2}{(B_t)} + 0 = 0 \quad (5)$$

The X² Goodness of Fit Test of the Exclusion Relationship

The chi square value with degree of freedom 2-1=1of the exclusion relationship with a *continuity correction*[69] can be calculated as

$$\chi^2(\mathrm{EXCL}) = \frac{(-(a_t) - 0{,}5)^2}{A_t} + \frac{(-(a_t) - 0{,}5)^2}{B_t} \quad (6)$$

The Mathematical Formula of the Causal Relationship k

The mathematical formula of the causal relationship k [15, 59-63]is defined *at every single event, at every single Bernoulli trial t,* as

$$k(A_t, B_t) \equiv \frac{\left(p(A_t \cap B_t) - \left(p(A_t) \times p(B_t)\right)\right)}{\sqrt[2]{\left(p(A_t) \times p(\underline{A}_t)\right) \times \left(p(B_t) \times p(\underline{B}_t)\right)}} \quad (7)$$

where A_t denotes the cause and B_t denotes the effect. The chi-square distribution can be applied to determine the significance of causal relationship k. Pearson's concept of correlation[70] is not identical with causation, causation is not identical with correlation. In particular, the relationship between correlation and causation has already been discussed in many publications[71]. Thus far, repeating itself over and over again on this topic is only a waste of time and will not contribute anything new to further scientific progress.

The 95% Confidence Interval of the Causal Relationship k

A confidence interval (CI) of the causal relationship k calculated from the statistics of the observed data can help to estimate the true value of an unknown population parameter with a certain probability. The 95% interval for the causal relationship k is derived [63]as

$$\left\{ k(A_t, B_t) - \sqrt[2]{\frac{5}{n}}, k(A_t, B_t) + \sqrt[2]{\frac{5}{n}} \right\} \quad (8)$$

The Chi Square Distribution

The following critical values[72] of the chi square distribution as visualized by Table 6 are used in this publication.

Table 6 The critical values of the chi square distribution (degrees of freedom: 1)

	p-Value	One sided X²	Two sided X²
The chi square distribution	0.1000000000	1.642374415	2.705543454
	0.0500000000	2.705543454	3.841458821
	0.0400000000	3.06490172	4.217884588
	0.0300000000	3.537384596	4.709292247
	0.0200000000	4.217884588	5.411894431
	0.0100000000	5.411894431	6.634896601
	0.0010000000	9.549535706	10.82756617
	0.0001000000	13.83108362	15.13670523
	0.0000100000	18.18929348	19.51142096
	0.0000010000	22.59504266	23.92812698
	0.0000001000	27.03311129	28.37398736
	0.0000000100	31.49455797	32.84125335
	0.0000000010	35.97368894	37.32489311
	0.0000000001	40.46665791	41.82145620

RESULTS

Without EBV VCA IgG antibody positivity no multiple sclerosis.

Claims

Null hypothesis

The presence of EBV VCA IgG antibodies is a necessary condition (a conditio sine qua non) of multiple sclerosis. In other words, the sample distribution agrees with the hypothetical (theoretical) distribution of a necessary condition.

Alternative hypothesis

The presence of EBV VCA IgG antibodies is not a necessary condition (a conditio sine qua non) of multiple sclerosis. In other words, the sample distribution does not agree with the hypothetical (theoretical) distribution of a necessary condition. The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0,05.

Proof

The data reviewed by this article which investigated the relationship between EBV VCA IgG antibodies and multiple sclerosis are viewed by **Table 2**. Altogether, 25 studies with N=6903 cases and controls provided non self-contradictory data and were meta-analysed while the level of significance was alpha = 0.05. Altogether, 24 from 25 studies provided significant evidence of a conditio sine qua non relationship between EBV VCA IgG antibodies and multiple sclerosis(X² (Calculated [conditio sine qua non]) =16.8382 and is less than X² (Critical [conditio sine qua non]) =37.6525). Only the study of Martyn *et al*.[23]failed to document a significant evidence. In point fact, the presence of EBV VCA IgG antibodies is a necessary condition (a conditio sine qua non) of Multiple sclerosis. In other words, *without* the presence of EBV VCA IgG antibodies *no* Multiple sclerosis.
Q. e. d.

Without EBV EBNA1 IgG antibody positivity no Multiple sclerosis

Claims

Null hypothesis

The presence of EBV EBNA1 IgG antibodies is a necessary condition (a conditio sine qua non) of Multiple sclerosis. In other words, the sample distribution agrees with the hypothetical (theoretical) distribution of a necessary condition.

Alternative hypothesis

The presence of EBV EBNA1 IgG antibodies is not a necessary condition (a conditio sine qua non) of Multiple sclerosis. In other words, the sample distribution does not agree with the hypothetical (theoretical) distribution of a necessary condition.
The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0,05.

Proof

The data reviewed by this article which investigated the relationship between EBV EBNA1 IgG antibodies and Multiple sclerosis are viewed by Table 3. Altogether, 32 studies with N=8003 cases and controls provided non self-contradictory data and were considered for a meta-analyses while the level of significance was alpha = 0.05. Altogether, 32 from 32 studies provided significant evidence of a conditio sine qua non relationship between EBV EBNA1 IgG antibodies and Multiple sclerosis (X^2 (Calculated [conditio sine qua non]) =13.7 and is less than X^2 (Critical [conditio sine qua non]) =47.39). In particular, the presence of EBV EBNA1 IgG antibodies is a necessary condition (a conditio sine qua non) of Multiple sclerosis. In other words, *without* the presence of EBV EBNA1 IgG antibodies *no* Multiple sclerosis.
Q. e. d.

EBV is the cause of Multiple sclerosis

The presence of EBV DNA in the involved brain tissues is one appropriate way to show an etiological link between EBV and the pathogenesis of MS. Several studies performed published conflicting[73-76] results on this matter. Hassani *et al*.[58]carried out a study on autopsied human brain tissues and combined conventional PCR quantitative Taqman PCR targeting EBV BamH1 W fragment EBER-ISH and found that 91/101 (90%) of MS cases were EBV positive by PCR and/or EBER-ISH compared with 5/21 (24%) controls.

Claims

Null hypothesis: (no causal relationship)

There is no significant causal relationship between an infection by Epstein-Barr virus and Multiple sclerosis. (k=0).

Alternative hypothesis: (causal relationship)

There is a significant causal relationship between an infection by Epstein-Barr virus and Multiple sclerosis. ($k \neq 0$).

Conditions. Alpha level = 5%.

The two tailed critical Chi square value (degrees of freedom = 1) for alpha level 5% is 3.841458821.

Proof

The data for this hypothesis test were provided by Hassani *et al*.[58] and are illustrated by the Table 5. The causal relationship k(Epstein-Barr virus, Multiple sclerosis) was calculated according to[15,59-63], while the level of significance was alpha=0,05. The data of Hassani *et al*.[58]provide evidence that EBV is a necessary (X^2(SINE) = 0.8936; X^2 Critical (SINE) = 3.841458821), a sufficient (X^2(IMP) = 0.2109; X^2 Critical (IMP) = 3.841458821) and equally a necessary and sufficient condition (X^2(SINE and IMP) = 1.1045; X^2 Critical (SINE and IMP) = 3.841458821) of Multiple sclerosis while the cause effect relationship is highly significant (k = +0.6111; p value (k) < 0.00001; 95% CI (k) = [+0.4086, +0.8135]). Epstein-Barr virus is the cause of Multiple sclerosis (k = +0.6111; p value (k) < 0.00001; 95% CI (k) = [+0.4086, +0.8135]).
Q. e. d.

DISCUSSION

Epstein, Achong and Barr[77] discovered 1964 a virus named Epstein-Barr virus (EBV). Soon after their discovery, Adams[78] and Nikoskelainen *et al*.[79]discussed already 1972 the possible relationship between EBV to Multiple sclerosis. The risk of acquiring this complex disease was linked to exposure to different environmental[80] factors among them non-infectious agents and infectious agents too. Thus far, several meta-analysis reviews[13-14,81]detected an association between EBV and MS through the investigation of antibodies, mainly EBV VCA IgG and EBV EBNA-1 IgG but without a definite solution.

This review is based on studies with as sample size of more than 8000 cases and controls. The retrospective nature of the studies may restrict our confidence to draw a generally valid and everlasting conclusion. Furthermore, another type of a limitation to consider is the definition used for classifying the viral status of a participant. Antibodies to various Epstein-Barr virus antigens were determined by different methods and individuals were considered EBV negative depending upon the preferences of the authors. In accordance with previous reports, is it possible at all to say anything generally valid under such circumstances?

For example, Gieß *et al*.[56] considered levels of EBV VCA IgG levels <20 U/ml as EBV VCA IgG negative and EBV VCA IgG levels > 20 U/ml as EBV VCA IgG positive with the consequence that 2 out of 100 MS cases were treated as EBV VCA IgG negative (false negative result).

Besides of the several different and severe limitations that must be acknowledged and which may contain several potential sources of bias the studies analysed agree on several points. All studies analysed support the hypothesis: without EBV VCA IgG or EBV EBNA1 IgG antibodies no Multiple sclerosis. Hassani *et al*.[58]studied autopsied human brain tissues and documented a necessary (Table 5) condition, a sufficient (Table 5) condition, a necessary and sufficient condition(Table 5) and equally a highly significant cause effect relationship between Epstein-Barr virus and Multiple sclerosis (k = +0.6111; p value (k) < 0.00001; 95% CI (k) = [+0.4086, +0.8135]).The findings of this article provide further support for the causal[15]relationship between Epstein-Barr virus and Multiple sclerosis. In particular, it is necessary to consider the following inescapable conclusion.

CONCLUSION

Epstein-Barr virus is the cause of Multiple sclerosis.

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How to cite this article:

Ilija Barukčić (2018) 'Epstein-Barr Virus is the Cause of Multiple Sclerosis', *International Journal of Current Medical And Pharmaceutical Research,* 04(9), pp. 3674-3682.

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