Epstein-Barr virus is the cause of multiple sclerosis.

Ilija Barukčić
Internist: Horandstrase, DE-26441, Jever, Germany.
Email: Barukcic@t-online.de

How to cite this paper: Ilija Barukčić (2018) Epstein-Barr virus is the cause of multiple sclerosis.. *viXra*, **12 (3),** 1-24.
http://vixra.org/author/ilija_barukcic

Received: 2018 03, 26
Accepted: 2018 03, 26
Published: 2018 03, 26

Abstract

Objective: 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.
Result: The studies analyzed 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.

Keywords

Epstein-Barr virus, multiple sclerosis, cause effect relationship, causality

1. 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 2.5 million [1] people worldwide and is driven by 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 etiology of multiple sclerosis is still not generally accepted but 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. Although the etiology of multiple sclerosis is not generally accepted yet, several studies found a higher prevalence of EBV antibodies [5]-[7] in multiple sclerosis cases than controls. Epidemiological studies [8]-[10] reported some evidence that EBV might be involved in the pathogenesis of MS. One study provided evidence of a causal relationship [11] between Epstein-Barr virus and multiple sclerosis. The prevalence of IgG antibodies to herpes simplex virus (HSV), varicella zoster virus (VZV), and cytomegalovirus (CMV) did not differ between multiple sclerosis cases and controls [12]. The relationship between Epstein-Barr virus and multiple sclerosis remains a matter of controversy.

2. Material and methods

MS 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.

2.1. 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-Barr virus” and “multiple sclerosis” and “PCR DNA” et cetera. 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. 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.

2.2. The data of the studies analyzed

The data of the studies [12]-[21] analyzed, are presented by the table (**Table 1**). The meaning of the abbreviations a_t, b_t, c_t, d_t, N_t of table 1 (**Table 1**), table 2 (**Table 2**), table

3 (**Table 3**) , table 4 (**Table4**) are explained by a 2 by 2-table (**Table 5**). It is difficult to establish a relationship between Epstein-Barr virus (EBV) and multiple sclerosis while relying only on EBV antibodies. In this context, novel laboratory techniques [22] (Southern Blot hybridization, Immunohistochemistry (IHC), introduced by Coons [23] in 1941, In-situ hybridization (ISH), described in the year 1969 by Joseph G. Gall [24], Fluorescent ISH (FISH), RNA in situ hybridization (RNA ISH), Polymerase chain reaction (PCR), Nested PCR, Quantitative polymerase chain reaction (QPCR) et cetera) can improve our understanding of the pathogenesis of multiple sclerosis.

Table 1. *Without* EBV infection *no* MS.

Author	Year	Country	a_t	b_t	c_t	d_t	$a_t+b_t+d_t$	N_t	$(a_t+b_t+d_t)/N_t$	X^2(Sine)	k	p val (k)
Myhr et al. [12]	1998	Norway	141	138	3	32	311	314	0,99044586	0,17857143	0,26505141	2,64369E-06
Wandinger et al. [14]	2000	Germany	108	147	0	16	271	271	1	0,015625	0,20389566	0,000789225
Levin et al. [15] (follow up)	2010	USA	10	10	0	18	38	38	1	0,01388889	0,56694671	0,00047425
Ramroodi et al. [17]	2013	Iran	71	101	7	22	194	201	0,965174129	1,45689655	0,12359561	0,079727365
Abdelrahman et al. [18]	2014	Egypt	75	60	0	15	150	150	1	0,01666667	0,33333333	4,45571E-05
Gieß et al. [21]	2017	Germany	98	57	2	3	158	160	0,9875	0,45	0,083473	0,291032534
Myhr et al. [12]	1998	Norway	143	160	1	10	313	314	0,996815287	0,02272727	0,14059839	0,012723724
Abdelrahman et al. [18]	2014	Egypt	70	68	5	7	145	150	0,966666667	1,6875	0,04914732	0,547221223
Mouhieddine et al. [19]	2015	Lebanon	240	206	9	24	470	479	0,981210856	2,18939394	0,13453778	0,003234738
Karampoor et al. [20]	2016	Iran	60	41	0	9	110	110	1	0,02777778	0,32700259	0,0006044
Gieß et al. [21]	2017	Germany	96	44	4	16	156	160	0,975	0,6125	0,33180602	2,70413E-05
Munch et al. [13]	2015	Denmark	240	206	9	24	470	479	0,981210856	2,18939394	0,13453778	0,003234738
Mouhieddine et al. [19]	2015	Lebanon	248	224	1	6	478	479	0,997912317	0,03571429	0,09188899	0,044316091
Santón at al. [16]	2011	Spain	70	123	5	63	256	261	0,980842912	0,29779412	0,28047333	5,86537E-06
Total			1670	1585	46	265	3520	3566	0,986931818	9,19444987	0,5029032	

Alpha =	0,05		
Degrees of freedom =	14	Degr. of fr. =	1
X^2 (Critical) SINE =	23,6847913	Chi crit. k =	3,841458821
X^2 (Calculatedl) SINE=	9,19444987	X^2 calc. (k)=	901,883014
		k=	0,50290324
		p Value (k) =	3,8236E-198

Table 2. *Without* EBV VCA IgG antibody positivity *no* MS.

Author	Year	Country	a_t	b_t	c_t	d_t	$a_t+b_t+d_t$	N_t	$(a_t+b_t+d_t)/N_t$	X^2(Sine)	k	p val (k)
Myhr et al. [12]	1998	Norway	141	138	3	32	311	314	0,99044586	0,17857143	0,26505141	2,64369E-06
Levin et al. [15] (follow up)	2010	USA	10	10	0	18	38	38	1	0,01388889	0,56694671	0,00047425
Ramroodi et al. [17]	2013	Iran	71	101	7	22	194	201	0,965174129	1,45689655	0,12359561	0,079727365
Abdelrahman et al. [18]	2014	Egypt	75	60	0	15	150	150	1	0,01666667	0,33333333	4,45571E-05
Gieß et al. [21]	2017	Germany	98	57	2	3	158	160	0,9875	0,45	0,083473	0,291032534
Total			395	366	12	90	851	863	0,985898942	2,116023536	0,548883111	

Alpha =	0,05		
Degrees of freedom =	5	Degr. of fr. =	1
X^2 (Critical) SINE =	11,07049769	Chi crit. (k) =	3,841458821
X^2 (Calculatedl) SINE=	2,116023536	X^2 calc. (k)=	259,9983143
		k=	0,548883111
		p Value (k) =	1,71745E-58

Table 3. *Without* EBV EBNA1 IgG antibody positivity *no* MS.

Author	Year	Country	a_t	b_t	c_t	d_t	$a_t+b_t+d_t$	N	$(a_t+b_t+d_t)/N_t$	X^2(Sine)	k	p val (k)
Myhr et al. [12]	1998	Norway	143	160	1	10	313	314	0,996815287	0,02272727	0,14059839	0,012723724
Wandinger et al. [14]	2000	Germany	108	147	0	16	271	271	1	0,015625	0,203895658	0,000789225
Abdelrahman et al. [18]	2014	Egypt	70	68	5	7	145	150	0,966666667	1,6875	0,04914732	0,547221223
Mouhieddine et al. [19]	2015	Lebanon	240	206	9	24	470	479	0,981210856	2,18939394	0,13453778	0,003234738
Karampoor et al. [20]	2016	Iran	60	41	0	9	110	110	1	0,02777778	0,32700259	0,0006044
Gieß et al. [21]	2017	Germany	96	44	4	16	156	160	0,975	0,6125	0,33180602	2,70413E-05
Total			717	666	19	82	1465	1484	0,987030717	4,55552399	0,452799793	

Alpha =	0,05		
Degrees of freedom =	6	Degr. of fr. =	1
X^2 (Critical) SINE =	12,59158724	Chi crit. k =	3,841458821
X^2 (Calculatedl) SINE=	4,55552399	X^2 calc. (k)=	304,2610357
		k=	0,452799793
		p Value (k) =	3,88559E-68

Table 4. *Without* EBV positivity *no* MS.

Author	Year	Country	a_t	b_t	c_t	d_t	$a+b+d_t$	N_t	$(a_t+b_t+d_t)/N_t$	X^2(Sine)	k	p val (k)
Munch et al. [13]	2015	Denmark	240	206	9	24	470	479	0,981210856	2,18939394	0,13453778	0,003234738
Mouhieddine et al. [19]	2015	Lebanon	248	224	1	6	478	479	0,997912317	0,03571429	0,09188899	0,044316091
Santón at al. [16]	2011	Spain	70	123	5	63	256	261	0,980842912	0,29779412	0,28047333	5,86537E-06
Total			558	553	15	93	1204	1219	0,987541528	2,52290234	0,5059626	

Alpha =	0,05		
Degrees of freedom =	3	Degr. of fr. =	1
X^2 (Critical) SINE =	7,8147279	Chi crit. k =	3,841458821
X^2 (Calculatedl) SINE=	2,52290234	X^2 calc. (k)=	312,061772
		k=	0,50596262
		p Value (k) =	7,76401E-70

2.3. 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.

2.3.1. The 2x2 table

The 2x2 table in this article is defined [11] , [25]-[47] in general more precisely (**Table 5**) as follows.

Table 5. The sample space of a contingency table

		Conditioned B_t (Multiple sclerosis)		
		Yes = +1	**Not = +0**	**Total**
Condition A_t (EBV positive)	**Yes =+1**	a_t	b_t	$\mathbf{A_t}$
	Not = +0	c_t	d_t	$\underline{A}_t$
	Total	$\mathbf{B_t}$	$\underline{B}_t$	$\mathbf{N}_t$

In general it is $(a+b) = A_t$, $(c+d) = \underline{A}_t$, $(a+c) = B_t$, $(b+d) = \underline{B}_t$ 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 in other words $p(A_t)= p(A_t \cap B_t)+p(A_t \cap \underline{B}_t)$ while $p(A_t)$ is not defined as $p(a_t)$. In the same context, it should be considered that $p(B_t) = p(a_t)+p(c_t) = p(A_t \cap B_t) +p(c_t)$ and equally that $p(\underline{B}_t) = 1- p(B_t) =p(b_t)+p(d_t)$. In point of fact, the joint probability of A_t and B_t is denoted by $p(A_t \cap B_t)$. It is $p(a_t)+p(c_t)+p(b_t)+p(d_t) = 1$. These relationships are viewed by the table (**Table 6**) as follows.

Table 6. The probabitlities of a contingency table

		Conditioned B_t (Multiple sclerosis)		
		Yes = +1	**No = +0**	**Total**
Condition A_t (EBV positive)	**Yes =+1**	$p(a_t) = p(A_t \cap B_t)$	$p(b_t)$	$p(A_t)$
	No = +0	$p(c_t)$	$p(d_t)$	$p(\underline{A}_t)$
	Total	$p(B_t)$	$p(\underline{B}_t)$	**1**

2.3.2. Independence

In the case of independence of A_t and B_t it is

$$p\left(A_t \cap B_t\right) \equiv p\left(A_t\right) \times p\left(B_t\right) \tag{1}$$

2.3.3. Sufficient condition (conditio per quam; material conditional)

The mathematical formula of the *sufficient condition* relationship (conditio per quam) [11] , [25]-[47]of a population was defined as

$$p\left(A_t \rightarrow B_t\right) \equiv \frac{a_t + c_t + d_t}{N_t} \equiv +1 \tag{2}$$

and used to proof the hypothesis: *if* A_t *then* B_t . In particular it is

$$\begin{aligned} p\left(A_t \rightarrow B_t\right) &\equiv p\left(a_t\right) + p\left(c_t\right) + p\left(d_t\right) \equiv +1 \\ p\left(A_t \rightarrow B_t\right) &\equiv p\left(A_t \cap B_t\right) + p\left(\underline{A}_t\right) \equiv +1 \\ p\left(A_t \rightarrow B_t\right) &\equiv p\left(A_t \cap B_t\right) + \left(1 - p\left(A_t\right)\right) \equiv +1 \\ p\left(A_t \rightarrow B_t\right) &\equiv +1 \end{aligned} \tag{3}$$

Scholium.

Although the work on study bias is vast and therefore quite difficult to survey adequately, we can at least point out that several factors including the study design can have an impact on bias with respect to the sufficient condition too. The question is, what is the relationship between the independence of an event A_t (a condition) and another event B_t (conditioned) and the sufficient condition relationship. Especially, is it possible that an event A_t is a sufficient condition of an event B_t even if event A_t (a sufficient condition) is independent of an event B_t (the conditioned). In this context, the conditio per quam was defined as

$$p\left(A_t \rightarrow B_t\right) \equiv p\left(A_t \cap B_t\right) + p\left(\underline{A}_t\right) \equiv +1 \tag{4}$$

or a

$$p\left(A_t \rightarrow B_t\right) \equiv p\left(A_t \cap B_t\right) + \left(1 - p\left(A_t\right)\right) \equiv +1 \tag{5}$$

Under conditions where an event A_t is independent of an even B_t it is equally true that

$$p\left(A_t \cap B_t\right) \equiv p\left(A_t\right) \times p\left(B_t\right) \tag{6}$$

Substituting this relationship into the equation before and rearranging equation it is

$$p\left(A_t\right) \times p\left(B_t\right) + \left(1 - p\left(A_t\right)\right) \equiv +1 \tag{7}$$

or

$$p\left(A_t\right) \times p\left(B_t\right) \equiv p\left(A_t\right) \tag{8}$$

or

$$p(B_t) \equiv +1. \tag{9}$$

Only under conditions where $p(B_t) = 1$, it is possible that A_t as a sufficient condition of B_t even if A_t is independent of B_t and vice versa, otherwise not. In other words, a statistically significant conditio per quam relationship is very convincing if at the same time an event A_t is not independent of and event B_t and vice versa. Thus far, an inappropriate study design and other sources of possible bias, diminish in their importance if a statistical significant conditio per quam relationship is supported by the absence of independence of the same two events.

2.2.3. Necessary condition (conditio sine qua non)

The formula of the *necessary condition* (conditio sine qua non) [11] , [25]-[47] relationship was derived as

$$p(A_t \leftarrow B_t) \equiv p(A_t \cap B_t) + p(\underline{B}_t) \equiv \frac{a_t + b_t + d_t}{N} \equiv +1 \tag{10}$$

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

2.2.4. Necessary and sufficient condition (material biconditional)

The *necessary and sufficient condition* relationship was defined [11], [25]-[47] as

$$p(A_t \leftrightarrow B_t) \equiv p(A_t \cap B_t) + p(\underline{A}_t \cap \underline{B}_t) \equiv \frac{a_t + d_t}{N} \equiv +1 \tag{11}$$

2.3.4. The X^2 goodness of fit test of a necessary condition

Under conditions where the chi-square [48] goodness of fit test cannot be used it is possible to use an approximate and conservative (one sided) confidence interval as discussed by Rumke [49], Louis [50], Hanley et al. [51] and Jovanovic [52] known as *the rule of three*. Under some circumstances, the rule three and other methods can be used to test the significance of a necessary condition. In this publication, the chi-square goodness of fit test was used to determine whether sample data are consistent with a hypothesized (theoretical) distribution of a necessary condition. In particular, the hypotheses can take the following form.

H_0: The sample distribution do agree with the hypothetical (theoretical) distribution of a necessary condition.

H_A: The sample distribution do not agree with the hypothetical (theoretical) distribution of a necessary condition.

The X^2 Goodness-of-Fit Test can be shown schematically as

$$\chi^2 \equiv \sum_{t=+1}^{t=+N} \left(\frac{\left(\text{Observed}_t - \text{Expected}_t\right)^2}{\text{Expected}_t} \right) \tag{12}$$

The degrees of freedom are calculated as N-1. Interestingly, if there is no discrepancy between an observed and a theoretical distribution at all, then the value of the calculated $X^2=0$. As the discrepancy between an observed and the theoretical distribution of a necessary condition becomes larger, the X^2 becomes larger. This X^2 values are evaluated by the known X^2 distribution. An adjustment (*Yate's correction for continuity*) can be used when there is one degree of freedom. When there is more than one degree of freedom, the same adjustment is not used. Applying this to the formula above, we find the X^2 Goodness-of-Fit Test *with continuity correction* shown schematically as

$$\chi^2 \equiv \sum_{t=+1}^{t=+N} \left(\frac{\left(\left|\text{Observed}_t - \text{Expected}_t\right| - \left(\frac{1}{2}\right) \right)^2}{\text{Expected}_t} \right) \tag{13}$$

Under circumstances, where the term ($|\text{Observed}_t - \text{Expected}_t|$) is less than ½, the continuity correction should be omitted. The theoretical (hypothetical) distribution of a necessary condition is shown schematically by the 2x2 table (**Table 7**).

Table 7. The theoretical distribution of a necessary condition (conditio sine qua non).

		Conditioned B_t		
		Yes = +1	**No = +0**	**Total**
Condition A_t	**Yes =+1**	a_t	b_t	(a_t+b_t)
	No = +0	**c_t=0**	d_t	(c_t+d_t)
	Total	(a_t+c_t)	(b_t+d_t)	$(a_t+b_t+c_t+d_t)$

The theoretical distribution of a necessary condition (conditio sine qua non) is determined by the fact that **c=0**. The X^2 Goodness-of-Fit Test *with continuity correction* of a necessary condition (conditio sine qua non) is calculated as

$$\chi^2(\text{SINE}) \equiv \left(\frac{\left(\left|(a_t+b_t)-(a_t+b_t)\right| - \left(\frac{1}{2}\right) \right)^2}{(a_t+b_t)} \right) + \left(\frac{\left(\left|(d_t)-(c_t+d_t)\right| - \left(\frac{1}{2}\right) \right)^2}{(c_t+d_t)} \right) = 0 + \left(\frac{\left(\left|d_t-(c_t+d_t)\right| - \left(\frac{1}{2}\right) \right)^2}{(c_t+d_t)} \right) \tag{14}$$

or more simplified as

$$\chi^2(\mathrm{SINE}) \equiv \left(\frac{\left(|-c_i| - \left(\frac{1}{2}\right) \right)^2}{(c_i + d_i)} \right) + 0 \tag{15}$$

Under these circumstances, the degree of freedom is d.f. = N-1=2-1=1. The *conditio sine qua non model* can be used widely and is one of the new and appropriate methods of analysis of binary outcome variables. In this context, *meta-analysis and systematic reviews* aims to combine effects estimated from several studies to achieve greater precision of the conclusions drawn and can provide us with more convincing and reliable evidence of some special aspects of medicine. In meta-analysis the heterogeneity between the studies can be modelled via the additive properties of the chi square distribution too. In general, let X_i denote n independent random variables which follow a chi-square distribution. The sum of these independent chi-square variate is itself a chi-square variate which is known as the additive property of independent chi-squares. There may be disadvantages in the use of the chi-square-goodness-of-fit test. Still, the chi square distribution, a continuous probability distribution, is related to the standard normal distribution and is a simple and good measure of model adequacy. However, a particular concern with the use of the chi-square-goodness-of-fit test is a priori justified if expected cell frequencies of a 2x2 table are too small (all are less than one).

2.3.5. The mathematical formula of the causal relationship k

Huxley [53] and Darwin [54] claimed more than a century ago that humans share recent common ancestors with the African apes. Modern molecular methods have spectacularly confirmed their prediction. Genomic divergences between humans and other hominoids and especially our closest living evolutionary relatives the common chimpanzee (Pan troglodytes) and bonobo (Pan paniscus or pygmy chimpanzee) are very small but not zero. Ebersberger et al. [55], Fujiyama et al. [56] and other sequenced the chimpanzee genome. According to Ebersberger et al. “the chimpanzee genome were sequenced and compared to corresponding human DNA sequences ... the average sequence difference is low (1.24%)” [55]. The Chimpanzee Sequencing and Analysis Consortium calculated “the genome-wide nucleotide divergence between human and chimpanzee to be 1.23%” [57] and confirmed results from other and more limited studies. In other words, the difference between chimpanzee genome and compared to corresponding human DNA sequences is very small. Still there is a difference and this very small difference makes the difference. A chimpanzee is not a human being, a human being is not a chimpanzee. Even if both are similar and “relatives” both are equally not the same. The relationship between the mathematical formula of the causal relationship k [11] , [25]-[47] and the closest existing mathematical relatives, Pearson's measures of relationships, is similar to the circumstances aforementioned. In contrast to Pearson's product-moment correlation coefficient [58] or to Pearson's Phi [59] Coefficient (Mean Square Contingency Coefficient et

cetera, the mathematical formula of the causal relationship k [11] , [25]-[47] is defined *at every single event*, *at every single Bernoulli trial t*, as

$$k\left({}_{R}U_{t},{}_{0}W_{t}\right)\equiv\frac{\left(p\left({}_{R}U_{t}\times{}_{0}W_{t}\right)-\left(p\left({}_{R}U_{t}\right)\times p\left({}_{0}W_{t}\right)\right)\right)}{\sqrt[2]{\left(p\left({}_{R}U_{t}\right)\times p\left({}_{R}\underline{U}_{t}\right)\right)\times\left(p\left({}_{0}W\right)\times p\left({}_{0}\underline{W}_{t}\right)\right)}}\tag{16}$$

where ${}_{R}U_{t}$ denotes the cause and ${}_{0}W_{t}$ denotes the effect while the chi-square distribution [48] can be applied to determine the significance of causal relationship k. This small difference makes the difference. Only under conditions where *the probability of events is constant from trial to trial*, we can extrapolate *from one Bernoulli trial to N Bernoulli trials* with some consequences one of which is that

$$k\left({}_{R}U_{t},{}_{0}W_{t}\right)\equiv\frac{N_{t}\times N_{t}\times\left(p\left({}_{R}U_{t}\times{}_{0}W_{t}\right)-\left(p\left({}_{R}U_{t}\right)\times p\left({}_{0}W_{t}\right)\right)\right)}{N_{t}\times N_{t}\times\sqrt[2]{\left(p\left({}_{R}U_{t}\right)\times p\left({}_{R}\underline{U}_{t}\right)\right)\times\left(p\left({}_{0}W\right)\times p\left({}_{0}\underline{W}_{t}\right)\right)}}\tag{17}$$

or that

$$k\left({}_{R}U_{t},{}_{0}W_{t}\right)\equiv\frac{\left(N_{t}\times N_{t}\times p\left({}_{R}U_{t}\times{}_{0}W_{t}\right)-\left(N_{t}\times p\left({}_{R}U_{t}\right)\times N_{t}\times p\left({}_{0}W_{t}\right)\right)\right)}{\sqrt[2]{\left(N_{t}\times p\left({}_{R}U_{t}\right)\times N_{t}\times p\left({}_{R}\underline{U}_{t}\right)\right)\times\left(N_{t}\times p\left({}_{0}W\right)\times N_{t}\times p\left({}_{0}\underline{W}_{t}\right)\right)}}\tag{18}$$

or at the end

$$k\left({}_{R}U_{t},{}_{0}W_{t}\right)\equiv\frac{\left(\left(N_{t}\times a_{t}\right)-\left({}_{R}U_{t}\times{}_{0}W_{t}\right)\right)}{\sqrt[2]{\left({}_{R}U_{t}\times{}_{R}\underline{U}_{t}\right)\times\left({}_{0}W\times{}_{0}\underline{W}_{t}\right)}}\tag{19}$$

where N is the sample size, $a_{t}=N_{t}\times p({}_{R}U_{t}\cap{}_{0}W_{t})$, ${}_{R}U_{t}=N\times p({}_{R}U_{t})$, ${}_{R}\underline{U}_{t}=N_{t}\times p({}_{R}\underline{U}_{t})$, ${}_{0}W_{t}=N_{t}\times p({}_{0}W_{t})$, ${}_{0}\underline{W}_{t}=N_{t}\times p({}_{0}\underline{W}_{t})$. Several factors can have an impact on the calculated causal relationship k with the potential of bias.

Scholium.

Firstly, the relationship between condition and cause has an impact on the causal relationship k. A proper and deeper analysis of the relationship between cause and condition is beyond the scope of this article and can be found in literature [11], [25]-[47]. We will be concerned with the latter sort of entity in this article from a pragmatically point of view. In the hope of casting light on the tricky problems of the relationship between condition and cause, the concept of independence is of use too. The question whether an event A_{t} can be a (necessary, sufficient, necessary and sufficient) condition of an event B_{t} even if both are independent of each other, is already answered few lines before. Still,

under which circumstances can we treat an event as a cause or as the cause of another event? Can an event be a cause of another event without being a (necessary, sufficient, necessary and sufficient et cetera) condition of the same event? The concept of this article is restricted on its capacity to bring high degrees of conceptual exactness and rigour to questions like these but not incapable. Most authors who have written on the question of the relationship between condition and cause came to different conclusions. Currently still worthy of consideration is the remark of von Bar.

"Die erste Voraussetzung, welche erforderlich ist, damit eine Erscheinung als die Ursache einer anderen bezeichnet werden könne, ist, daß jene eine der Bedingungen dieser sein. Würde die zweite Erscheinung auch dann eingetreten sein, wenn die erste nicht vorhanden war, so ist sie in keinem Falle Bedingung und noch weniger Ursache. Wo immer eine Kausalzusammenhang behauptet wird, da muß er wenigstens diese Probe aushalten. … Jede Ursache ist nothwendig auch eine Bedingung eines Ereignisses; aber nicht jede Bedingung ist Ursache zu nennen. " [60]

Translated into English:

'The first requirement, which is required, thus that something could be called as the cause of another, is that the one has to be one of the conditions of the other. If the second something had occurred even if the first one did not exist, so it is by no means a condition and still less a cause. Wherever a causal relationship is claimed, the same must at least withstand this test. ... Every cause is necessarily also a condition of an event too; but not every condition is cause too.'

A cause is a condition of an event too but not necessarily vice versa. A condition of an event must not be equally the cause of the same event. Thus far, a study which provides evidence of a significant causal relationship k without at the same time providing evidence of a significant necessary condition, or of a significant sufficient condition or of a significant necessary and sufficient condition should be treated with some cautious.

2.3.6. The X^2 goodness of fit test of a causal relationship k

Under some circumstances the chi-square [48] goodness of fit test can be used to test the significance of a causal relationship. Under conditions where *the probability of events is constant from trial to trial*, we expect a constant causal relationship k_t. In other words, at each Bernoulli trial *t* it is

$$\left|k\left({}_{R}U_{t}, {}_{0}W_{t}\right)\right| \equiv |1| \tag{20}$$

Performing N Bernoulli trials (Sample size N), the basic relationship will not change. It follows that

$$N \times \left| k\left({}_{R}U_{t}, {}_{0}W_{t} \right) \right| \equiv N \times |1| \tag{21}$$

or that

$$N \times \left| k\left({}_{R}U_{t}, {}_{0}W_{t} \right) \right| - N \times |1| = 0 \tag{22}$$

Simplifying equation we obtain

$$N \times \left(\left| k\left({}_{R}U_{t}, {}_{0}W_{t} \right) \right| - |1| \right) = 0 \tag{23}$$

Multiplying equation by itself it is

$$N \times \left(\left| k\left({}_{R}U_{t}, {}_{0}W_{t} \right) \right| - |1| \right) \times N \times \left(\left| k\left({}_{R}U_{t}, {}_{0}W_{t} \right) \right| - |1| \right) = 0 \times 0 \tag{24}$$

or

$$N^{2} \times \left(\left| k\left({}_{R}U_{t}, {}_{0}W_{t} \right) \right| - |1| \right)^{2} = 0 \tag{25}$$

Dividing equation by N*|1|=N, we obtain

$$\frac{N^{2} \times \left(\left| k\left({}_{R}U_{t}, {}_{0}W_{t} \right) \right| - |1| \right)^{2}}{N} = \frac{0}{N} = 0 \tag{26}$$

or

$$N \times \left(\left| k\left({}_{R}U_{t}, {}_{0}W_{t} \right) \right| - |1| \right)^{2} = 0 \tag{27}$$

or the X^2 value as

$$\chi^{2} = N \times \left(\left| k\left({}_{R}U_{t}, {}_{0}W_{t} \right) \right| - |1| \right)^{2} = 0 \tag{28}$$

The chi square (X^2) statistic can be used to investigate whether the observed distribution of the causal relationship differ from the theoretical expected distribution of the causal relationship. The table 8 (**Table 8**) contains the critical values of the chi-square distribution (degrees of freedom, df =1). Upper-tail and lower-tail critical values of the chi-square distribution with *v* degrees of freedom are provided by software packages.

2.3.7. The chi square distribution

The chi-squared distribution [48] is a widely known distribution and used in hypothesis testing, in inferential statistics or in construction of confidence intervals. The critical values of the chi square distribution are visualized by **Table 8**.

Table 8. The critical values of the chi square distribution (degrees of freedom: 1).

	p-Value	One sided X^2	Two sided X^2
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

3. Results

3.1. *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 the presence of EBV VCA IgG antibodies and multiple sclerosis are viewed by **Table 1** and especially by **Table 2**. Altogether, 5 studies with N=863 cases and controls were meta-analyzed while the level of significance was alpha = 0,05. Altogether, 5 from 5 studies provide significant evidence of a conditio sine qua non relationship between EBV VCA IgG antibodies and multiple sclerosis(X^2 (Calculated [conditio sine qua non]) =2,116023536 and is less than X^2 (Critical [conditio sine qua non]) =11,07049769). In the same respect, the causal relationship between EBV VCA IgG antibodies and multiple sclerosis was highly significant (k= +0,548883111, p value = 1,71745E-58). In other words, *without* EBV VCA IgG antibodies *no* multiple sclerosis. Due to methodological inconsistencies, the study of Ramroodi et al. [17] and Gieß et al. [21] failed to provide evidence of a statistically significant cause effect relationship. 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.

3.2. *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 the presence of EBV EBNA1 IgG antibodies and multiple sclerosis are viewed by **Table 1** and especially by **Table 3**. Altogether, 6 studies with N= 1484 cases and controls were meta-analyzed while the level of significance was alpha = 0,05. Altogether, 6 from 6 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]) =4,55552399 and is less than X^2 (Critical [conditio sine qua non]) =12,59158724). In the same respect, the causal relationship between EBV EBNA1 IgG antibodies and multiple sclerosis was highly significant (k=+0,452799793, p value =3,88559E-68). In other words, *without* EBV EBNA1 IgG antibodies *no* multiple sclerosis. Due to methodological inconsistencies, the study of Abdelrahman et al. [18] failed to provide evidence of a statistically significant cause effect relationship. In point fact, 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.

3.3. *Without* EBV seropositivity *no* multiple sclerosis

Claims.

Null hypothesis:

The presence of EBV 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 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 the presence of EBV and multiple sclerosis are viewed by **Table 1** and especially by **Table 4**. Altogether, 3 studies with N= 1219 cases and controls were meta-analyzed while the level of significance was alpha = 0,05. Munch et al. [13] investigated the significance of the previously found 100% *seropositivity toward Epstein-Barr virus* (EBV) in multiple sclerosis (MS) patients in contrast to healthy controls using a commercially available ELISA-test (Biotest) which differentiates EBV seropositive and EBV seronegative. Mouhieddine et al. [19] investigated the prevalence of *EBV seropositivity* and other known risk factors for MS. Santón at al. [16] used a polymerase chain reaction (PCR) which amplified a strain-specific sequence in the EBV nuclear antigen 2 as a sign of *EBV seropositivity*. Altogether, 3 from 3 studies provided significant evidence of a conditio sine qua non relationship between EBV seropositivity and multiple sclerosis (X^2 (Calculated [conditio sine qua non]) = 2,52290234 and is less than X^2 (Critical [conditio sine qua non]) = 7,8147279). In the same respect, the causal relationship between EBV seropositivity and multiple sclerosis was highly significant (k=+0,50596262, p value =7,76401E-70). In other words, *without* EBV seropositivity *no* multiple sclerosis. In point fact, the presence of EBV is a necessary condition (a conditio sine qua non) of multiple sclerosis. In other words, **without** the presence of EBV **no** multiple sclerosis.

Q. e. d.

3.4. EBV is the cause of multiple sclerosis

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≠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 different studies and are illustrated by the **Table 1**. The causal relationship k(Epstein-Barr virus, multiple sclerosis) was calculated according to [11], [25]-[47]. Again, 9 studies were meta-analyzed with n= 3566 number of cases and controls (**Table 1**) while the level of significance was alpha = 0,05. Thus far, the studies analyzed provided evidence of a highly significant (**Table 1**) cause effect relationship between Epstein-Barr virus and multiple sclerosis (k= +0,50290324, p Value = 3,8236E-198). In other words, Epstein-Barr virus and multiple sclerosis are not only not independent of each other. In the same respect, we were able to provide evidence that *without* EBV *no* multiple sclerosis (**Table 2, Table 3, Table 4**). Besides of the methodological difficulties associated with veiw studies analyzed the conclusion is inescapable: Epstein-Barr virus *is the cause of* multiple sclerosis (k=+0,50290324, p Value = 3,8236E-198).

Q. e. d.

4. Discussion

Epstein-Barr virus (EBV) is a ubiquitous herpesvirus which is associated with a number of clinical manifestations. Designing an effective vaccine to prevent Epstein-Barr virus-associated diseases is a major public health care challenge but a historical opportunity and necessity too. However even this study has some limitations which is necessary to point out. The review is based on view studies with small patient population and the retrospective nature of the most of the studies restrict our confidence to draw a generally valid and everlasting conclusion. Furthermore, another type of 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. For example, Gieß et al. [21] considered levels of EBV VCA IgG levels <20 U/ml as EBV VCA IgG negative and EBV VCA IgG levels $\geq$ 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*). In addition, to increase the problems, some studies used PCR for the detection of EBV DNA while using special nucleotide sequences of the primers and probes while other did not. In accordance with previous reports, is it possible at all to say anything generally valid under such circumstances? Besides of the several and severe limitations that must be acknowledged and which may contain several potential sources of bias the studies analyzed agree on several points. All studies analyzed support the hypothesis: *without* EBV *no* multiple sclerosis while the cause effect relationship between Epstein-Barr virus and multiple sclerosis (k= +0,50290324, p Value = 3,8236E-198) is highly significant. This article provides a review of recent works on the relationship between Epstein-Barr virus and multiple sclerosis. The findings of this article provide further support for the relationship between Epstein-Barr virus and multiple sclerosis and invites us to consider the following inescapable conclusion.

5. Conclusion

Epstein-Barr virus is the cause of multiple sclerosis.

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