Multiple sclerosis is caused by an Epstein Bar virus infection

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ABSTRACT

Aim: The relationship between Epstein-Barr virus and multiple sclerosis is assessed once again in order to gain a better understanding of this disease.
Methods: A systematic review and meta-analysis is provided aimed to answer among other the following question. Is there a cause effect relationship between Epstein-Barr virus and multiple sclerosis? The conditio sine qua non relationship proofed the hypothesis without an Epstein-Barr virus infection no multiple sclerosis. The mathematical formula of the causal relationship k proofed the hypothesis of a cause effect relationship between Epstein-Barr virus infection and multiple sclerosis. Significance was indicated by a p-value of less than 0.05.
Results: The data of the studies analysed provide evidence that an Epstein-Barr virus infection is a necessary condition (a conditio sine qua non) of multiple sclerosis. In particular and more than that. The data of the studies analysed provided impressive evidence of a cause-effect relationship between Epstein-Barr virus infection and multiple sclerosis.
Conclusion: Multiple sclerosis is caused by an Epstein-Barr virus infection.

Introduction

Multiple sclerosis (MS) is a very common inflammatory and demyelinating disease of the central nervous system, which is affecting people of almost all ages and in many parts of the world. In point of fact, MS affects more than 2.5 million[1] people worldwide and is driven by a pathological inflammation. The first description of MS dates back as far as the 14th century[2], while *Jean-Martin Charcot* (1825-1893), the father of neurology[2], was the first to provide a detailed description of MS in 1868 (described as '*la sclérose en plaques*'[3]). Thus far, there is no evidence that MS is directly inherited even if the aetiology of MS is still not understood. Different environmental factor like vitamin D, latitude, cigarette smoking[4], different viruses[5] and other genetic and environmental factors[6] have been investigated repeatedly but are unlikely to promptly contribute to a full and true clarification of a cause or of the cause of MS. Especially, the prevalence of immunglobulin G (IgG) antibodies to herpes simplex virus (HSV), to varicella zoster virus (VZV) and to cytomegalovirus (CMV) did not differ between multiple sclerosis cases and controls[5]. In spite of all, numerous studies[7–9] investigated the relationship between Epstein-Barr virus[10] (EBV) and MS and provided some evidence that EBV might be involved in the aetiology of MS. EBV itself is identified as a member of the herpes family of viruses with the property to persists after a primary infection latently in resting memory B cells[11,12] more or less during the lifetime of a host. It is worth noting in this context that the titres of EBV antibodies are significantly lower among sero-positive controls when compared with sero-positive MS cases[13,14]. In line with observations like these, recent systematic reviews and meta-analysis[15,16] failed to establish a causal relationship between EBV and MS but provided some evidence of an association between MS and sero-positivity for different EBV antibodies. Two studies published a significant causal relationship[17,18] between EBV and MS. However, the relationship between EBV and MS remains a matter of controversy and is still disputed.

Material and methods

Multiple sclerosis is a very complex disease of the central nervous system (CNS) characterized by inflammation, demyelination and a wide variety of clinical symptomatology including among other visual, sensory, motor, cerebellar and brainstem dysfunction. The incidence of MS varies with rates as high as 8 to 10 new cases per 100,000.[19,20] There is some reason to assume that over 700,000 people are affected in Europe, with over 2.5 million cases worldwide,[1] which represent a significant burden in terms of impact on quality of life, societal costs and personal expenses.[21,22] The pathogenesis and etiology of MS is likely to involve several different factors which are more or less interacting with each other. In point of fact, the role of viral or other infectious agents is still under debate. However, the evidence provided by studies is mounting that EBV is related with MS.

Search strategy and selection criteria

The electronic database PubMed was searched for scientific papers on the subject. The search used combinations of the terms "multiple sclerosis"and 'Epstein Barr virus"to ensure as wide search strategy as possible.Bibliographies of relevant publications and review articles were searched and additional relevant references identified and, where appropriate, included in the review. Studies were excluded if insufficient, non-transparent or self-contradictory data were provided or if there were data access barriers. A list of the detailed search strategy used is summarised in the flow diagram in table 1.

		Size	Total
1. Identification of records			
Records identified			
	PubMed	778	
	Additional sources	3	801
2. Clean-up of search			
Inappropriate articles excluded		760	
3. Eligibility			
Articles evaluated for eligibility		41	
Articles excluded for various reasons		4	
Self-contradictiory data		7	
4. Included			
Articles included in the meta-analysis			30

Table 1. Flow Diagram of the article selection process. Adopted from PRISMA 2009.[23,24]

The studies of Guiterez et al.[25], Zivadinov et al.[26], Jilek et al.[27], Jaquiery et al.[28] and Villoslada et al.[29] were self-contradictory ($k < 0$). Martyn et al.[30] did not provide clear information about the IgG antibodies measured. The study was not considered for a re-analysis. The control group of the study of Waubant et al.[31] was inappropriate, data presentation[32] was insufficient, at least partially[33], by view studies. The studies[31,34] with respect to EBV EBNA-1 IgG were to some extent self-contradictory. These studies have not been considered completely or partially for a re-analysis.

Data extraction and analysis

The presence of EBV viral capsid antigen (VCA) serum IgG antibodies often represents evidence of remote EBV infection, whereas Epstein-Barr nuclear antigen (EBNA)–1 IgG seropositivity is indicating evidence of EBV latency. Table 2 represents the data of the studies on the relationship between EBV VCA IgG antibodies and MS and the statistical analysis.

Without EBV VCA IgG sero-positivity **no** MS.

Study Id	Year	n	Case+ a	Case tot B	Con. + b	Con. tot B	k	p value (k)	$p(A_t \leftarrow B_t)$	$X^2(B)$	$X^2(\underline{A})$	p value[35]	p(IOU)	p(IOI)
Sumaya et al.[36]	1980	238	155	157	76	81	0,1374	0,0469	0,9916	0,0255	0,5714	0,0084	0,6303	0,3109
Bray et al.[37]	1983	719	309	313	363	406	0,1868	0,0000	0,9944	0,0511	0,3404	0,0055	0,3700	0,4993
Larsen et al.[38]	1985	186	93	93	78	93	0,2962	0,0000	1,0000	0,0000	0,0000	0,0000	0,4194	0,4194
Sumaya et al.[39]	1985	130	104	104	23	26	0,3074	0,0073	1,0000	0,0000	0,0000	0,0000	0,7769	0,1769
Ferrante et al.[40]	1987	72	29	30	31	42	0,3024	0,0091	0,9861	0,0333	0,0833	0,0138	0,2500	0,4167
Shirodaria et al.[41]	1987	52	26	26	24	26	0,2000	0,2451	1,0000	0,0000	0,0000	0,0000	0,4615	0,4615
Myhr et al.[5]	1998	314	141	144	138	170	0,2651	0,0000	0,9904	0,0625	0,2571	0,0095	0,3471	0,4299
Ascherio et al.[42]	2001	431	143	144	269	287	0,1282	0,0040	0,9977	0,0069	0,0526	0,0023	0,2900	0,6218
Sandström et al. (a)[43]	2004	292	73	73	217	219	0,0479	0,5619	1,0000	0,0000	0,0000	0,0000	0,2432	0,7432
Alotaibi et al.[13]	2004	173	25	30	82	143	0,2026	0,0054	0,9711	0,8333	0,3788	0,0285	0,2081	0,4451
Sundström et al. (b)[43]	2004	644	161	161	476	483	0,0605	0,1320	1,0000	0,0000	0,0000	0,0000	0,2391	0,7391
Ponsonby et al.[44]	2005	397	136	136	252	261	0,1099	0,0219	1,0000	0,0000	0,0000	0,0000	0,3199	0,6348
Pohl et al.[14]	2006	294	145	147	106	147	0,3754	0,0000	0,9932	0,0272	0,0930	0,0068	0,3537	0,3537
Banwell et al.[33]	2007	222	108	126	61	96	0,2577	0,0001	0,9189	2,5714	6,1132	0,0779	0,3288	0,1937
Nociti et al.[45]	2010	405	265	267	129	138	0,1683	0,0014	0,9951	0,0150	0,3636	0,0049	0,6321	0,3136
Lucas et al.[46]	2011	423	202	206	208	217	0,0639	0,1511	0,9905	0,0777	1,2308	0,0094	0,4563	0,4823
Mowry et al.[34]	2011	140	109	120	13	20	0,2701	0,0050	0,9214	1,0083	6,7222	0,0756	0,7286	0,0143
Lalive et al.[47]	2011	42	22	22	15	20	0,3855	0,0182	1,0000	0,0000	0,0000	0,0000	0,4048	0,3571
Ramroodi et al.[48]	2013	201	71	78	101	123	0,1236	0,0585	0,9652	0,6282	1,6897	0,0342	0,2438	0,4677
Abdelrahman et al.[49]	2014	150	75	75	60	75	0,3333	0,0000	1,0000	0,0000	0,0000	0,0000	0,4000	0,4000
Mouhieddine et al.[50]	2015	479	248	249	224	230	0,0919	0,0492	0,9979	0,0040	0,1429	0,0021	0,5052	0,4656
Karampoor et al.[51]	2016	110	60	60	41	50	0,3270	0,0005	1,0000	0,0000	0,0000	0,0000	0,4636	0,3727
Gieß et al.[52]	2017	160	98	100	57	60	0,0835	0,2726	0,9875	0,0400	0,8000	0,0124	0,5938	0,3438
	Total	6274	2798	2861	3044	3413	0,2054	0,0691	0,9870	5,3846	18,8391	0,0127	0,4203	0,4201
								Alpha =	0,05					
								Degrees of freedom =	23					
								Chi sqaure critical =	35,1725					
								Chi sqaure calculated =		5,3846	18,8391			
								p Value (Chi square) =		0,9999	0,7105			

Table 2. Epstein-Barr virus VCA IgG antibodies and multiple sclerosis

Without EBV EBNA-1 IgG sero-positivity **no** MS.

Study Id	Year	n	Case+ a	Case tot B	Con. + b	Con. tot $\underline{B}$	k	p value (k)	$p(A_t \leftarrow B_t)$	$X^2(B)$	$X^2(\underline{A})$	p value[35]	p(IOU)	p(IOI)
Sumaya et al.[39]	1985	130	102	104	23	26	0,2000	0,0543	0,9846	0,0385	0,8000	0,0153	0,7615	0,1615
Larsen et al.[38]	1985	186	93	93	78	93	0,2962	0,0000	1,0000	0,0000	0,0000	0,0000	0,4194	0,4194
Ferrante et al.[40]	1987	72	25	30	28	42	0,1864	0,0937	0,9306	0,8333	1,3158	0,0671	0,1528	0,3194
Shirodaria et al.[41]	1997	52	26	26	21	26	0,3262	0,0253	1,0000	0,0000	0,0000	0,0000	0,4038	0,4038
Myhr et al.[5]	1998	314	143	144	160	170	0,1406	0,0110	0,9968	0,0069	0,0909	0,0032	0,4236	0,5064
Munch et al.[53]	1998	276	137	138	124	138	0,2078	0,0004	0,9964	0,0072	0,0667	0,0036	0,4457	0,4457
Wandinger et al.[54]	2000	271	108	108	147	163	0,2039	0,0002	1,0000	0,0000	0,0000	0,0000	0,3395	0,5424
Ascherio et al.[42]	2001	424	141	142	266	282	0,1196	0,0083	0,9976	0,0070	0,0588	0,0024	0,2948	0,6250
Sundström et al. (b)[43]	2004	644	160	161	459	483	0,0975	0,0063	0,9984	0,0062	0,0400	0,0016	0,2112	0,7112
Sandström et al. (a)[43]	2004	292	73	73	210	219	0,1030	0,0720	1,0000	0,0000	0,0000	0,0000	0,2192	0,7192
Haahr et al.[55]	2004	106	53	53	50	53	0,1707	0,1214	1,0000	0,0000	0,0000	0,0000	0,4717	0,4717
Selter et al.[56]	2010	83	16	25	25	58	0,1918	0,0655	0,8916	3,2400	1,9286	0,1028	0,2048	0,1928
Sellner et al.[57]	2010	111	54	55	49	56	0,2065	0,0321	0,9910	0,0182	0,1250	0,0090	0,4234	0,4324
Ingram et al.[58]	2004	100	70	75	18	25	0,2843	0,0093	0,9500	0,3333	2,0833	0,0488	0,6300	0,1300
Alotaibi et al.[13]	2004	173	25	30	60	143	0,3133	0,0000	0,9711	0,8333	0,2841	0,0285	0,3353	0,3179
Pohl et al.[14]	2006	268	124	134	77	134	0,4050	0,0000	0,9627	0,7463	1,4925	0,0366	0,2500	0,2500
Riverol et al.[59]	2007	257	167	172	75	85	0,1778	0,0064	0,9805	0,1453	1,6667	0,0193	0,6109	0,2724
Lindsey et al.[60]	2010	160	78	80	74	80	0,1147	0,1382	0,9875	0,0500	0,5000	0,0124	0,4500	0,4500
Nociti et al.[45]	2010	405	261	267	128	138	0,1216	0,0168	0,9852	0,1348	2,2500	0,0147	0,6198	0,3012
Jaquiery et al.[28]	2010	123	39	40	73	83	0,1567	0,0736	0,9919	0,0250	0,0909	0,0081	0,2358	0,5854
Jafari et al.[61]	2010	176	108	114	51	62	0,2018	0,0092	0,9659	0,3158	2,1176	0,0335	0,5511	0,2557
Lucas et al.[46]	2011	423	199	206	198	206	0,1115	0,0171	0,9835	0,2379	1,8846	0,0164	0,4255	0,4515
Sundqvist et al.[62]	2011	1249	580	585	616	585	0,1578	0,0000	0,9960	0,0427	0,4717	0,0040	0,4259	0,4892
Lalive et al.[47]	2011	42	22	22	16	22	0,3403	0,0433	1,0000	0,0000	0,0000	0,0000	0,4286	0,3810
Mowry et al.[34]	2011	140	108	120	11	120	0,3430	0,0004	0,9143	1,2000	6,8571	0,0821	0,7071	0,0071
Waubant et al.[31]	2011	255	167	189	36	189	0,3676	0,0000	0,9137	2,5608	9,3077	0,0827	0,5373	0,0549
Abdelrahman et al.[49]	2014	150	70	75	68	75	0,0491	0,3824	0,9667	0,3333	2,0833	0,0328	0,4200	0,4200
Mouhieddine et al.[50]	2015	479	240	249	206	249	0,1345	0,0026	0,9812	0,3253	2,4545	0,0186	0,4509	0,4113
Karampoor et al.[51]	2016	110	60	60	41	60	0,3270	0,0005	1,0000	0,0000	0,0000	0,0000	0,4636	0,3727
Gieß et al.[52]	2017	160	96	100	44	100	0,3318	0,0000	0,9750	0,1600	0,8000	0,0247	0,5000	0,2500
	Total	7631	3545	3670	3432	4165	0,2129	0,0397	0,9771	11,6014	38,7700	0,0223	0,4271	0,3784
								Alpha =	0,05					
								Degrees of freedom =	30					
								Chi square critical =	43,7730					
								Chi square calculated =		11,6014	38,7700			
								p Value (Chi square) =		0,9990	0,1310			

Table 3. Epstein-Barr virus EBNA-1 IgG antibodies and multiple sclerosis

MS and In Situ Hybridization and Polymerase Chain Reaction

In Situ Hybridization[63,64] (ISH) is a technique which enables researcher a precise localization of a specific segment of nucleic acid within a histologic section, if the nucleic acid is preserved adequately within a histologic specimen. Polymerase Chain Reaction[65] (PCR) deoxyribonucleic acid (DNA) investigations can detect (segments of) EBV DNA within a histologic specimen. Several studies investigated the presence of EBV in human central nervous system (CNS) with conflicting[66] results and linking EBV to the pathogenesis of MS remain to be established. Asma Hassani et al.[67] detected EBV in human brain by PCR and/or EBER-in situ hybridization (EBER-ISH) only in only 5/21 (24%) of non-MS autopsied human brain tissues (controls) compared to 91/101 (90%) of postmortem MS cases. Table 4 provides an overview of the results achieved by Asma Hassani et al.[67].

Methods

Historically, the search for a mathematical solution to *the issue of causal inferences* is as old as human mankind itself ("*Aristotle's Doctrine of the Four Causes*")[68] but there is still little to go on. With more or less meaningless or none progress on the matter in hand even in the best possible conditions, it is not surprising that authors are still suggesting different approaches and models for causal inference. However, logically consistent *statistical methods of causal inference* can help scientist to achieve so much with so little. In general, the known *Henle-Koch postulates*[69,70] are applied many times for the identification of a causative agent of an (infectious) disease. However, the pathogenesis of most chronic diseases is more or less very complex and potentially involves the interaction of several factors. In practice, from the 'pure culture'requirement of the Koch-Henle postulates insurmountable difficulties may emerge. In light of subsequent developments (PCR methodology, immune antibodies et cetera) it is appropriate to review the full validity of the Henle-Koch postulates in our days. In 1965, Sir Austin Bradford Hill[71] published nine criteria (the '*Bradford Hill Criteria* ') in order to determine whether observed epidemiologic associations are causal. Somewhat worrying, is at least the fact that, Hill's "... fourth characteristic is *the temporal relationship of the association* "and so-to-speak just a reformulation of the '*post hoc ergo propter hoc*'[72,73] logical fallacy through the back-door and much more then this. It is questionable whether association can be treated as being identical with causation. Unfortunately, due to several reasons, it seems therefore rather problematic to rely on Bradford Hill Criteria carelessly. Meanwhile, several other and competing mathematical or statistical approaches for causal inference have been discussed[72,74–89] or even established[72,82,84,87–89]. Nevertheless, the question is still not answered, is it at all possible to establish a cause effect relationship between two factors while applying only certain statistical[90] methods?

		Multiple sclerosis		
		TRUE	FALSE	
EBV positive	TRUE	91	5	96
	FALSE	10	16	26
		101	21	122

Causal relationship k =	+0,6111
p Value right tailed (HGD) =	0,000000001635078
p (SINE) =	0,9180
$\tilde{\chi}^2$ (SINE) =	0,9901
p (IMP) =	0,9590
$\tilde{\chi}^2$ (IMP) =	1,190
p (SINE∩IMP) =	0,8770
$\tilde{\chi}^2$ (SINE∩IMP) =	2,1806
p(IOI) =	0,0410
p(IOU) =	0,6148

Table 4. The study of Hasani et al.[67]

Definitions

Definition 3.1 (Two by two table of Bernoulli random variables). Karl Pearson was the first to introduce the notion of a two by two or contingency[91] table in 1904. A contingency table is an appropriate theoretical model for studying the relationships between two *Bernoulli*[92] *(i. e. +0/+1) distributed random variables* existing or occurring at the same *Bernoulli trial*[93] (period of time) t. In this context, let a Bernoulli distributed random variable A_t denote a risk factor, a condition or a cause et cetera and occur or exist with the probability $p(A_t)$ at the *Bernoulli trial*[93] (period of time) t. Let $E(A_t)$ denote the expectation value of A_t. In the case of +0/+1 distributed Bernoulli random variables it is

$$E(A_t) \equiv A_t \times p(A_t) \equiv p(a_t) + p(b_t) \equiv p(A_t) \tag{1}$$

Let a Bernoulli distributed random variable B_t denote an outcome, a conditioned event or an effect and occur or exist et cetera with the probability $p(B_t)$ at the Bernoulli trial (period of time) t. Let $E(B_t)$ denote the expectation value of B_t. It is

$$E(B_t) \equiv B_t \times p(B_t) \equiv p(a_t) + p(c_t) \equiv p(B_t) \tag{2}$$

Let $p(a_t) = p(A_t \cap B_t)$ denote the joint probability distribution of A_t and B_t at the same Bernoulli trial (period of time) t. In general it is

$$E(a_t) \equiv E(A_t \cap B_t) \equiv (A_t \times B_t) \times p(A_t \cap B_t) \equiv p(A_t \cap B_t) \equiv p(a_t) \tag{3}$$

Let $p(b_t) = p(A_t \cap \neg B_t)$ denote the joint probability distribution of A_t and not B_t at the same Bernoulli trial (period of time) t. In general it is

$$E(b_t) \equiv E(A_t \cap \neg B_t) \equiv (A_t \times \neg B_t) \times p(A_t \cap \neg B_t) \equiv p(A_t \cap \neg B_t) \equiv p(b_t) \tag{4}$$

Let $p(c_t) = p(\neg A_t \cap B_t)$ denote the joint probability distribution of not A_t and B_t at the same Bernoulli trial (period of time) t. In general it is

$$E(c_t) \equiv E(\neg A_t \cap B_t) \equiv (\neg A_t \times B_t) \times p(\neg A_t \cap B_t) \equiv p(\neg A_t \cap B_t) \equiv p(c_t) \tag{5}$$

Let $p(d_t) = p(\neg A_t \cap \neg B_t)$ denote the joint probability distribution of not A_t and not B_t at the same Bernoulli trial (period of time) t. In general it is

$$E(d_t) \equiv E(\neg A_t \cap \neg B_t) \equiv (\neg A_t \times \neg B_t) \times p(\neg A_t \cap \neg B_t) \equiv p(\neg A_t \cap \neg B_t) \equiv p(d_t) \tag{6}$$

In general, it is

$$p(a_t) + p(b_t) + p(c_t) + p(d_t) \equiv +1 \tag{7}$$

		Conditioned B_t		
		TRUE	FALSE	
Condition	TRUE	$p(a_t)$	$p(b_t)$	$p(A_t)$
A_t	FALSE	$p(c_t)$	$p(d_t)$	$p(\underline{A}_t)$
		$p(B_t)$	$p(\underline{B}_t)$	+1

Table 5. The two by two table of Bernoulli random variables

Table 5 provides an overview of the definitions above.

Definition 3.2 (**Two by two table of Binomial random variables**). Under conditions where *the probability of an event, an outcome, a success et cetera is constant from Bernoulli trial to Bernoulli trial t*, it is

$$A = N \times E(A_t) \equiv N \times (A_t \times p(A_t)) \equiv N \times (p(a_t) + p(b_t)) \equiv N \times p(A_t) \tag{8}$$

and

$$B = N \times E(B_t) \equiv N \times (B_t \times p(B_t)) \equiv N \times (p(a_t) + p(c_t)) \equiv N \times p(B_t) \tag{9}$$

where N denotes the population size. Furthermore, it is

$$a \equiv N \times (E(a_t)) \equiv N \times (p(a_t)) \tag{10}$$

and

$$b \equiv N \times (E(b_t)) \equiv N \times (p(b_t)) \tag{11}$$

and

$$c \equiv N \times (E(c_t)) \equiv N \times (p(c_t)) \tag{12}$$

and

$$d \equiv N \times (E(d_t)) \equiv N \times (p(d_t)) \tag{13}$$

and

$$a + b + c + d \equiv A + \underline{A} \equiv B + \underline{B} \equiv N \tag{14}$$

Table 6 provides an overview of a two by two table of Binomial random variables.

		Conditioned B_t		
		TRUE	FALSE	
Condition	TRUE	a	b	A
A_t	FALSE	c	d	$\underline{A}$
		B	$\underline{B}$	N

Table 6. The two by two table of Binomial random variables

Definition 3.3 (**Independence**). The concept of independence is of fundamental[94] importance in (natural) sciences as such. In fact, it is insightful to recall again Einstein's theoretical approach to the concept of independence. "*Ohne die Annahme einer ... Unabhängigkeit der ... Dinge voneinander ... wäre physikalisches Denken ... nicht möglich.*"[95]. In other words, the existence or the occurrence of an event A_t at the Bernoulli trial t need not but can be independent of the existence or of the occurrence of another event B_t *at the same* Bernoulli trial t. Mathematically, independence[94,96] in terms of probability theory is defined as

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \tag{15}$$

Definition 3.4 (**Necessary Condition (Conditio sine qua non)**). Scientific knowledge and objective reality are deeply interrelated. An event (i. e. A_t) which is a necessary condition of another event or outcome (i.e. B_t) must be given, must be present for a conditioned, for an event or for an outcome B_t to occur. A necessary condition (i. e. A_t) is a requirement which must be fulfilled at every single Bernoulli trial t, in order for a conditioned or an outcome (i.e. B_t) to occur but it alone does not determine the occurrence of an event. In other words, if a necessary condition (i. e. A_t) is given, an outcome (i.e. B_t) need not to occur. A necessary condition of an event can but need not to be at the same Bernoulli trial t a sufficient condition for an event to occur. However, if an event or an outcome is determined by many necessary conditions then every single of these necessary conditions must be given otherwise the conditioned or the outcome will not occur. For example, it is generally known that air is necessary for (human) life. It is generally speaking the case that *without* air, *no* no (human) life. However, *without* water *no* human life too. Mathematically, the necessary condition (SINE) relationship, denoted by $p(A_t \leftarrow B_t)$ in terms of probability theory, is defined as

$$p\left(A_t \leftarrow B_t\right) \equiv p\left(a_t\right) + p\left(b_t\right) + p\left(d_t\right) \equiv \frac{a+b+d}{N} \equiv +1 \tag{16}$$

Under some known circumstances, testing hypothesis about the conditio sine qua non relationship $p(A_t \leftarrow B_t)$ is possible by the the chi-square distribution (also chi-squared or $\tilde{\chi}^2$-distribution), first described by the German statistician Friedrich Robert Helmert *(Helmert, Ueber die Wahrscheinlichkeit der Potenzsummen der Beobachtungsfehler und über einige damit im Zusammenhange stehende Fragen, Zeitschrift für Mathematik und Physik 21(3), 1876, pp. 102–219)* and later rediscovered by Karl Pearson[97] in the context of a goodness of fit test. The $\tilde{\chi}^2$ goodness of fit test of a conditio sine qua non relationship[98,99] with degree of freedom (d. f.) of d. f. = 1 is calculated as

$$\tilde{\chi}^2{}_{\text{Calculated}}\left(A_t \leftarrow B_t\right) \equiv \frac{c^2}{B} + 0 \equiv \frac{c^2}{\underline{A}} + 0 \tag{17}$$

and can be compared with a theoretical chi-square value at a certain level of significance α. It has not yet been finally clarified whether the use of Yate's[100] continuity correction is necessary at all.

The left-tailed p Value[35] of the conditio sine qua non relationship can be calculated as follows.

$$pValue\left(A_t \leftarrow B_t\right) \equiv 1 - e^{-(1-p(A_t \leftarrow B_t))} \equiv 1 - e^{-(c/N)} \tag{18}$$

A low p-value indicates statistical significance.

Table 7 provides an overview of the definition of the necessary condition.

		Conditioned B_t		
		TRUE	FALSE	
Condition	TRUE	$p(a_t)$	$p(b_t)$	$p(A_t)$
A_t	FALSE	**+0**	$p(d_t)$	$p(\underline{A}_t)$
		$p(B_t)$	$p(\underline{B}_t)$	+1

Table 7. The two by two table of a necessary condition relationship

Definition 3.5 (**Sufficient Condition (Conditio per quam)**). In contrast to a necessary condition, a sufficient condition (i. e. A_t) alone does determine the occurrence of the event (i.e. B_t). In other words, if a sufficient condition (i. e. A_t) at a certain Bernoulli trial (or period of time) t is given, then the conditioned (i.e. B_t) is given too or must be there or must occur too. Mathematically, the sufficient condition (IMP) relationship, denoted by $p(A_t \rightarrow B_t)$ in terms of probability theory, is defined as

$$p\left(A_t \rightarrow B_t\right) \equiv p\left(a_t\right) + p\left(c_t\right) + p\left(d_t\right) \equiv \frac{a+c+d}{N} \equiv +1 \tag{19}$$

The $\tilde{\chi}^2$ goodness of fit test of a conditio per quam[98,99] relationship without Yate's[100] for degree of freedom (d. f.) of d. f. = 1 is calculated as

$$\tilde{\chi}^2{}_{\text{Calculated}}\left(A_t \rightarrow B_t\right) \equiv \frac{b^2}{A} + 0 \equiv \frac{b^2}{\underline{B}} + 0 \tag{20}$$

and can be compared with a theoretical chi-square value. It has not yet been finally clarified whether the use of Yate's[100] continuity correction is necessary at all.

The left-tailed p Value[35] of the conditio sine qua non relationship can be calculated as follows.

$$pValue\left(A_t \rightarrow B_t\right) \equiv 1 - e^{-(1-p(A_t \rightarrow B_t))} \equiv 1 - e^{-(b/N)} \tag{21}$$

A low p-value indicates statistical significance.

Table 8 provides an overview of the definition of a sufficient condition.

		Conditioned B_t		
		TRUE	FALSE	
Condition	TRUE	$p(a_t)$	**+0**	$p(A_t)$
A_t	FALSE	$p(c_t)$	$p(d_t)$	$p(\underline{A}_t)$
		$p(B_t)$	$p(\underline{B}_t)$	+1

Table 8. The two by two table of a sufficient condition relationship

Definition 3.6 (**Necessary and sufficient conditions**)**.** Mathematically, like other fundamental concepts, the concepts of necessary and sufficient conditions, denoted by $p((A_t \leftarrow B_t) \cap (A_t \rightarrow B_t))$ can prove as a handy tool in the hope of casting light on the tricky problems of causal relationships. However, to-date there is no straightforward way to give a generally accepted and precise account of the meaning of the term necessary and sufficient condition itself. What, then, is it for one event A_t at a certain Bernoulli trial t to be a cause or the cause of another event B_t at the same Bernoulli trial t? Are causes just "*Insufficient but Necessary parts of a condition which is itself Unnecessary but Sufficient* "[101]. Perhaps we do not often enough say what, then, is *a necessary and a sufficient condition*? In terms of probability theory, a necessary and sufficient condition relationship is defined as

$$p\left((A_t \leftarrow B_t) \cap (A_t \rightarrow B_t)\right) \equiv p\left(a_t\right) + p\left(d_t\right) \equiv \frac{a+d}{N} \equiv +1 \tag{22}$$

The $\tilde{\chi}^2$ goodness of fit test of the necessary and sufficient condition[98,99] relationship without Yate's[100] continuity correction for degree of freedom (d. f.) of d. f. = 1 is calculated as follows.

$$\tilde{\chi}^2{}_{\text{Calculated}}\left((A_t \leftarrow B_t) \cap (A_t \rightarrow B_t)\right) \equiv \frac{b^2}{A} + \frac{c^2}{\underline{A}} \equiv \frac{c^2}{B} + \frac{b^2}{\underline{B}} \tag{23}$$

The left-tailed p Value[35] of the necessary and sufficient condition relationship can be calculated as follows.

$$pValue\left((A_t \leftarrow B_t) \cap (A_t \rightarrow B_t)\right) \equiv 1 - e^{-(1-p((A_t \leftarrow B_t) \cap (A_t \rightarrow B_t)))} \equiv 1 - e^{-((b+c)/N)} \tag{24}$$

Table 9 provides an overview of the necessary and sufficient condition relationship.

		Conditioned B_t		
		TRUE	FALSE	
Condition	TRUE	a	**0**	A
A_t	FALSE	**0**	d	$\underline{A}$
		B	$\underline{B}$	N

Table 9. The two by two table of necessary and sufficient condition

Definition 3.7 (**Exclusion (A_t Excludes B_t and Vice Versa)**)**.** If we hypothetically suppose that the occurrence or the existence of an event A_t *excludes* the occurrence or the existence of another event B_t at a certain (point in space-time or) Bernoulli trial t, then in its most abstract terms, such a view implies the possibility to describe this relationship mathematically. Theoretically, an exclusion relationship, denoted by $p(A_t \mid B_t)$ in terms of probability theory, is defined as

$$p\left(A_t \mid B_t\right) \equiv p\left(b_t\right) + p\left(c_t\right) + p\left(d_t\right) \equiv \frac{b+c+d}{N} \equiv +1 \tag{25}$$

The $\tilde{\chi}^2$ goodness of fit test of an exclusion[99] relationship without Yate's[100] continuity correction for degree of freedom (d. f.) of d. f. = 1 is calculated as follows.

$$\tilde{\chi}^2{}_{\text{Calculated}}\left(A_t \mid B_t\right) \equiv \frac{(b-(a+b))^2}{A} + \frac{((c+d)-\underline{A})^2}{\underline{A}} \equiv \frac{a^2}{A} + 0 \equiv \frac{a^2}{A} \tag{26}$$

or as

$$\tilde{\chi}^2{}_{\text{Calculated}}\left(A_t \mid B_t\right) \equiv \frac{(c-(a+c))^2}{B} + \frac{((b+d)-\underline{B})^2}{\underline{B}} \equiv \frac{a^2}{B} + 0 \equiv \frac{a^2}{B} \tag{27}$$

The calculated $\tilde{\chi}^2$ value without Yate's[100] continuity correction can be compared with a theoretical chi-square value at a certain level of significance α. The left-tailed p Value[35] of the exclusion relationship can be calculated as follows.

$$pValue\left(A_t \mid B_t\right) \equiv 1 - e^{-(1-p(A_t|B_t))} \equiv 1 - e^{-(a/N)} \tag{28}$$

Table 10 provides an overview of the definition of an exclusion relationship.

		Conditioned B_t		
		TRUE	FALSE	
Condition	TRUE	**+0**	$p(b_t)$	$p(A_t)$
A_t	FALSE	$p(c_t)$	$p(d_t)$	$p(\underline{A}_t)$
		$p(B_t)$	$p(\underline{B}_t)$	+1

Table 10. The two by two table of an exclusion relationship

The mathematics of other conditions[72,82,89] and time series[82] can be found in literature.

Definition 3.8 (Causal relationship k). Mathematically, the causal relationship[72,82,84,87–89] between a cause A_t and an effect B_t, denoted by $k(A_t, B_t)$ in terms of probability theory, is defined *at each single*[102] *Bernoulli trial t* as

$$k\left(A_t, B_t\right) \equiv \frac{\sigma\left(A_t, B_t\right)}{\sigma\left(A_t\right) \times \sigma\left(B_t\right)} \equiv \frac{p\left(A_t \cap B_t\right) - p\left(A_t\right) \times p\left(B_t\right)}{\sqrt[2]{\left(p\left(A_t\right) \times \left(1 - p\left(A_t\right)\right)\right) \times \left(p\left(B_t\right) \times \left(1 - p\left(B_t\right)\right)\right)}} \tag{29}$$

where $\sigma\left(A_t, B_t\right)$ denotes the co-variance between a cause A_t and an effect B_t *at every single Bernoulli trial t*, $\sigma\left(A_t\right)$ denotes the standard deviation of a cause A_t at the same single Bernoulli trial t, $\sigma\left(B_t\right)$ denotes the standard deviation of an effect B_t at same single Bernoulli trial t.

Table 11 provides an overview of the definition of the causal relationship k.

		Effect B_t		
		TRUE	FALSE	
Cause	TRUE	$p(a_t)$	$p(b_t)$	$p(A_t)$
A_t	FALSE	$p(c_t)$	$p(d_t)$	$p(\underline{A}_t)$
		$p(B_t)$	$p(\underline{B}_t)$	+1

Table 11. The two by two table of the causal relationship k

There are some formal similarities between Karl Pearson's (1857-1936) "*product-moment coefficient of correlation*"[103,104] and the causal relationship k[72,82,84,87–89]. Neither does it make much sense to elaborate again on the issue causation[105] and correlation, since both are not identical[90] nor does it make sense to insist on the fact that "*Pearson's philosophy discouraged him from looking too far behind phenomena.*"[106] Whereas it is essential to consider that the causal relationship k, in contrast to Pearson's product-moment coefficient of correlation[104] or to Pearson's phi coefficient[91], is defined at every single Bernoulli trial t. This *small*[107] difference makes the difference.

Definition 3.9 (Fisher's exact test). Under some circumstances, the statistical significance of the sampling distribution of a test statistic of a necessary or sufficient condition or of a exclusion relationship et cetera is approximately equal to the theoretical

chi-squared distribution and a chi-squared goodness of fit test[108,109] might provide only approximative significance values. Sir Ronald Aylmer Fisher (1890 – 1962) published an exact statistical significance test ("*Fisher's exact test*")[110] for the analysis of contingency tables *valid for all sample sizes*. The *one sided right tailed P Value* calculated by the hyper-geometric[111–113] distribution[114,115] (HGD) is defined as

$$pValue_{\text{One sided right tailed}}\left(X \geq a_{\mathrm{t}}\right) \equiv 1 - \sum_{t=0}^{a_{\mathrm{t}}-1} \left(\frac{\binom{A}{t} \times \binom{N-A}{B-t}}{\binom{N}{B}} \right) \tag{30}$$

Study design

Definition 3.10 (Index of unfairness). Medical literature need to consider different types of bias which is present to some degree in all observational research. Has a study measured at all what it set out to? In assessing the significance of bias and a fair study design of medical studies, some measures of publication bias[108,109,116–118] are available but already labelled with critical remarks[119,120]. The index of unfairness,[108] denoted as IOU, is defined as

$$IOU\left(A,B\right) \equiv \left(\frac{A+B}{N} \right) - 1 \tag{31}$$

The index of unfairness is of help in order to determine ex post whether the data of a study are appropriate enough to be analysed for risk factors or for conditions[108,109]. A fair study design should assure an IOU as near as possible to zero.

Definition 3.11 (Index of independence). An appropriate study design is an important and many times a seriously underappreciated aspect of any medical study. The significance of study design for the conclusions drawn and the ability to generalise the results from the sample investigated for the whole population cannot be underestimated. The index of independence,[109] denoted as IOI, is defined as

$$IOI\left(A,\underline{B}\right) \equiv \left(\frac{A+\underline{B}}{N} \right) - 1 \tag{32}$$

The index of independence is of help to prove whether the data of a study can be used for the analysis of the exclusion relationship and the causal relationship. A study design should assure an IOI as near as possible to zero.

Statistical analysis

The statistical analyses were performed by Microsoft® Excel® version 14.0.7166.5000 (32-Bit) software (© Microsoft ® GmbH, Munich, Germany). The level of significance was set to 0.05.

Results

Without EBV VCA IgG antibody positivity no MS

Claims.

Null hypothesis.

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

Proof.

The data which investigated the relationship between EBV VCA IgG antibodies and MS are viewed by Table 2. At the end 23 studies with N=6274 cases and controls were reanalysed while two studies provided slightly self-contradictory results. No less than 21 out of 25 studies provided significant evidence of a conditio sine qua non relationship between EBV VCA IgG antibodies and multiple sclerosis ($\tilde{\chi}^2$(SINE(B)) (Calculated [conditio sine qua non]) = 5,3846 i. e. $\tilde{\chi}^2$(SINE($\underline{A}$)) (Calculated [conditio sine qua non]) = 18,8391) and is less than $\tilde{\chi}^2$ (Critical [conditio sine qua non]) = 35,1725. All studies provided evidence of a positive causal relationship k while 17/23 study were significant in this context. The presence of EBV VCA IgG antibodies is a necessary condition (conditio sine qua non) of MS. Without the presence of EBV VCA IgG antibodies no MS.

Quod erat demonstrandum.

Without EBV EBNA1 IgG antibody positivity no MS

Claims.

Null hypothesis.

The presence of EBV EBNA 1 IgG antibodies is a necessary condition (conditio sine qua non) of MS. In other words, the sample distribution agrees with the hypothetical (theoretical) distribution of a necessary condition.

Alternative hypothesis.

The presence of EBV EBNA 1 IgG antibodies is not a necessary condition (conditio sine qua non) of MS. In other words, the sample distribution does not agree with the hypothetical (theoretical) distribution of a necessary condition. The significance level (α) by which the null hypothesis will be rejected is set as $\alpha = 0{,}05$.

Proof.

The data which investigated the relationship between EBV EBNA 1 IgG antibodies and MS are viewed by Table 3. Finally, 30 studies with N=7631 cases and controls were reanalysed while two studies provided slightly self-contradictory results. No less than 28 out of 30 studies provided significant evidence of a conditio sine qua non relationship between EBV EBNA 1 IgG antibodies and MS ($\tilde{\chi}^2$(SINE(B)) (Calculated [conditio sine qua non]) = 11,6014 i. e. $\tilde{\chi}^2$(SINE(A)) (Calculated [conditio sine qua non]) = 38,7700) and is less than $\tilde{\chi}^2$ (Critical [conditio sine qua non]) = 43,7730. All studies provided evidence of a positive causal relationship k while 24/30 studies were significant in this context. The presence of EBV EBNA 1 IgG antibodies is a necessary condition (conditio sine qua non) of MS. Without the presence of EBV EBNA 1 IgG antibodies no MS.

Quod erat demonstrandum.

EBV is the cause of MS

The documentation of the presence of EBV in the CNS of MS patients is one way to link EBV to the pathogenesis of MS. Hassani et al.[67] investigated the contribution of an EBV infection in the pathology of MS using PCR and EBER-in situ hybridization (EBER-ISH) and found that 91/101 of MS cases were EBV positive by PCR and/or EBER-ISH compared to 5/21 non-MS cases. However, the non-MS controls were not truly 'normal brains'.

Claims.

Null hypothesis.

An EBV infection of human brain is not the cause of MS.

In other words, k = 0

Alternative hypothesis.

An EBV infection of human brain is the cause of MS.

In other words, $k \neq 0$.

The significance level (α) by which the null hypothesis will be rejected is set as $\alpha = 0{,}05$.

Proof.

Hassani et al.[67] provided evidence of a significant conditio sine qua non relationship between an EBV brain infection and MS (table 4). Furthermore, the same study group documented a significant conditio per quam relationship between an EBV brain infection and MS (table 4). In addition, Hassani et al.[67] provided data (table 4) which support the hypothesis of a necessary and sufficient condition between an EBV brain infection and MS. Last but not least, Hassani et al.[67] documented (table 4) a highly significant cause effect relationship between an EBV brain infection and MS (k = +0,6111; p Value = 0,000000001635078) while p(IOI) was very appropriate with p(IOI) = 0,0410. According to the data of Hassani et al.[67] (table 4) an EBV brain infection is the cause MS.

Quod erat demonstrandum.

Discussion

Poskanzer et al.[121] were one of the first to discuss in the year 1963 the hypothesis that multiple sclerosis is more or less a late manifestation of an infectious disease. Only one year later, Epstein Barr virus or human herpesvirus 4 (HHV-4) has been discovered by Epstein, Achong and Barr[10] in 1964. In 1968, Henle et al.[122] identified EBV as the cause of infectious mononucleosis. In the following, Adams[123] and Nikoskelainen et al.[124] discussed already 1972 the possible relationship between EBV to MS. Meanwhile, EBV is etiologically linked with Hogdkin[125] and non-Hodgin[115] lymphoma, with rheumatoid arthitis[126] and potentially with several other diseases too. The risk of acquiring MS is explained by the exposure to different environmental[4] factors including non-infectious agents and infectious agents too. In point of fact, several reviews and meta-analysis[15,16,127] detected an association between EBV and MS through the investigation of EBV VCA IgG and EBV EBNA-1 IgG antibodies. However, it is not firmly established yet whether EBV is a cause or the cause of MS. This review is based on studies with as sample size of more than 7000 cases and controls. The retrospective nature of the studies analysed has the

potential to restrict our confidence to draw a generally valid conclusion on the relationship between EBV and MS. In point of fact, the McDonald criteria[128] for the diagnosis of multiple sclerosis are more or less widely used in research and clinical practice. However, not all studies documented the use of these, meanwhile revised[129] criteria for the diagnosis of multiple sclerosis. A further source of bias and a limitation of this study to be considered is the definition used for classifying the viral status of a participant. Antibodies to various Epstein-Barr virus antigens were determined by very different methods while individuals were considered as EBV negative depending upon preferences of a single author. Gieß et al.[52] defined in this context levels of EBV VCA IgG < 20 U/ml as EBV VCA IgG negative and EBV VCA IgG levels > 20 U/ml were treated as EBV VCA IgG positive with the consequence that 2 out of 100 MS cases were at the end EBV VCA IgG negative (false negative result). Despite the above weaknesses, the possible shortcomings and some remaining inconsistencies and severe deficiencies the average p(IOI) of the studies analysed was about p(IOI) = 0,3784. In other words, the studies are more or less of use to re-analyse the relationship between EBV and MS. All studies re-analysed support the hypothesis: without EBV VCA IgG or EBV EBNA1 IgG antibodies no MS with clear consequences for the relationship between EBV and MS. In point of fact, according to this review, an EBV infection is a necessary condition of MS. In addition to these findings, the PCR and in situ hybridization based study of Hassani et al.[67] with a **p(IOI)= 0,0410** investigated autopsied human brain tissues and documented a significant necessary (table 4) condition, a significant sufficient (table 4) condition, a significant necessary and sufficient (table 4) condition and equally a highly significant (table 4) cause effect relationship (k = +0,6111; p Value = 0,000000001635078) between an EBV infection of human brain and MS. A causal role of an EBV infection in the complex pathogenesis of multiple sclerosis is established, the results in the present study indicate that EBV participates causally in the development of MS.

Conclusion

An Epstein-Barr virus infection of human brain structures is the cause of multiple sclerosis.

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