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EPSTEIN-BARR VIRUS IS THE CAUSE OF RHEUMATOID ARTHRITIS

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Abstract

Aim. Many studies presented some evidence that EBV might play a role in the pathogenesis of rheumatoid arthritis. Still, there are conflicting reports concerning the existence of EBV in the synovial tissue of patients suffering from rheumatoid arthritis. This systematic review assesses the causal relationship between Epstein-Barr virus (EBV) and rheumatoid arthritis (RA) for gaining a better understanding of the pathogenesis of RA.
Methods. This systematic review and meta-analysis aim to answer among other questions the following: Is there a cause effect relationship between Epstein-Barr virus and rheumatoid arthritis? The method of the conditio sine qua non relationship was used to proof the hypothesis *without* Epstein-Barr virus *no* rheumatoid arthritis. In other words, if rheumatoid arthritis is present, then Epstein-Barr virus has to be 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 rheumatoid arthritis. Significance was indicated by a p-value of less than 0.05.
Results. The studies analysed were able to provide convincing evidence that Epstein-Barr virus is a necessary condition (a conditio sine qua non) of rheumatoid arthritis. Furthermore, the studies analysed provide impressive evidence of a cause-effect relationship between Epstein-Barr virus and rheumatoid arthritis.
Conclusion. EBV infection of human synovial tissues is a conditio sine qua non, a conditio per quam of rheumatoid arthritis. In other words, Epstein-Barr virus is the cause of rheumatoid arthritis.

Keywords: Epstein-Barr virus, rheumatoid arthritis, causal relationship

INTRODUCTION

Rheumatoid arthritis (RA), a systemic, predominantly (1) CD4+ T helper type 1 (Th1)-driven disease characterized by an extensive synovial hyperplasia and infiltration by macrophages, monocytes, lymphocytes and fibroblasts. Rheumatoid arthritis is a destructive, chronic and debilitating arthritis and can cause systemic complications. RA affects more or less about 1% of the world's population (2). The prevalence of rheumatoid arthritis in men is twofold to fourfold less (3,4) than in women. The long-term prognosis of rheumatoid arthritis remains very poor. In particular, the average life expectancy of RA patients is reduced by 3 to 18 years (5). The direct costs of treatment of RA, the loss of employment and the indirect costs of disability due to RA are very high (6,7). At present there is no known cure for rheumatoid arthritis, an adequate use of various kinds of disease-modifying anti-rheumatic drugs may achieve complete remission in about 30-50% of RA patients. Many exposures investigated as possible risk factors for the development of rheumatoid arthritis such as dietary (antioxidants) factors (8) red meat protein (9), fat intake (10,11) breast feeding, the use of oral contraceptives or hormone replacement therapy (12) have shown no strong associations. Only cigarette smoking (13) has been found to increase the risk of rheumatoid arthritis. In the quest to uncover the unknown etiology of rheumatoid arthritis, viruses including Epstein-Barr virus (EBV), human herpesvirus-6, human herpesvirus-8, parvovirus (14) B19 (B19), HTLV-1, and human endogenous retroviruses-5 have all been hypothesized for many years to be involved in the pathogenesis of rheumatoid arthritis (15,16).

Epstein-Barr virus (EBV) is an ancient, ubiquitous virus determined by a 184 kbp-sized, double-stranded DNA genome which has infected probably more than 90% of the world's population (17). Many studies presented some evidence suggesting

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that especially EBV might play a role in the pathogenesis of RA. Among them Alspaugh and Tan (18-19) were one of the first. RA patients have higher levels of serum antibodies against EBV (20-24) than normal individuals. However, due to conflicting reports concerning the existence of EBV in the synovial tissue of RA patients a cause or the cause of rheumatoid arthritis remains unknown.

MATERIAL AND METHODS

RA is an autoimmune disease characterized by progressive and more or less persistent inflammation of joints of human body. At present, prognosis of RA may be very poor in the absence of an appropriate early treatment (25) with disease-modifying antirheumatic drugs (DMARDs) like methotrexate, sulphasalazine, azathioprine, antimalarials, gold-containing compounds, D-penicillamine and cyclosporin. In particular, an additional short-term duration treatment with corticosteroid is expected to prevent progressive course of RA with erosive joint damage and functional impairment.

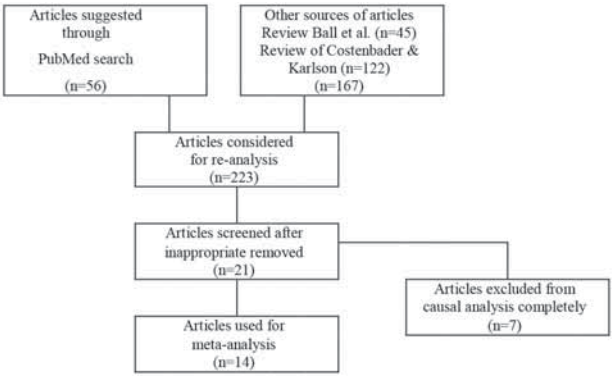

FIGURE 1. *Studies identification in search strategy. Adopted from PRISMA 2009 Flow Diagram (Moher26 et al., 2009; Liberati27 et al., 2009)*

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 increase the transparency, to correct some of the misprints of former publications and to simplify the understanding of this article several of the following lines are repeated sometimes word by word and taken from my former publications.

The 2x2 Table

The meaning of the abbreviations at, bt, ct, dt, Nt 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 Bt (Outcome)		Total
		Yes = 1	Not = +0	
Condition At (risk factor)	Yes =+1	at	bt	At
	Not = +0	ct	dt	$\underline{A}t$
	Total	Bt	$\underline{B}t$	Nt

In general it is (at+bt) = At, (ct+dt) = $\underline{A}t$, (at+ct) = Bt, (bt+dt) = $\underline{B}t$ and at+bt+ct+dt=Nt. Equally, it is Bt+$\underline{B}t$ = At + $\underline{A}t$ = Nt. In this context, it is p(at)=p(At ÇBt), p(At) = p(at)+p(bt) or p(At)= p(At ÇBt)+ p(bt) =p(At ÇBt)+p(At Ç$\underline{B}t$) while p(At) is not defined as p(at). In the same context, it is p(Bt) = p(at)+p(ct) = p(At ÇBt) +p(ct) and equally in the same respect p($\underline{B}t$) = 1- p(Bt) =p(bt)+p(dt).

Furthermore, the joint probability of At and Bt is denoted in general by p(At ÇBt). Thus far, it is p(At ÇBt) = p(At) - p(bt) = p(Bt) - p(ct) or in other words it follows clearly that p(Bt) + p(bt) - p(ct) = p(At). In general, it is p(at)+p(ct)+p(bt)+p(dt) = 1.

The data of the studies analysed

The data of the studies analysed are presented by several tables (Table 2, Table 4, Table 6, Table 7, Table 8, Table 9, Table 10, Table 11). The meaning of the abbreviations at, bt, ct, dt, Nt of tables is explained by a 2 by 2-table (Table 1) too. Some studies provided self-contradictory data (Table 3, Table 5) and were not considered for a re-analysis.

Independence

In the case of independence of At and Bt it is generally valid that

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

Exclusion (At Excludes Bt and Vice Versa Relationship)

The mathematical formula of the *exclusion* relationship (28-48) (At excludes Bt and vice versa) of a population was defined as

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

and used to proof the hypothesis: At *excludes* Bt and vice versa.

TABLE 2. **Without** *EBV VCA IgG positivity* **no** *RA.*

Study Id	Year	Country	Risk Factor	Case_P	Case_T	Con_P	Con_T	k	p-val	X^2(SINE)	X^2(IMP)	X^2(IMP^SINE)	X^2(EXCL)
Ng et al.	1980	UK	EBV VCA IgG	59	64	41	50	0.1540205	0.06110335	0.32	16.40	16.72	87.70
Ferrell et al.	1981	USA	EBV VCA IgG	76	80	45	51	0.1242185	0.09875740	0.15	16.37	16.52	118.36
Venables et al.	1985	UK	EBV VCA IgG	37	38	23	26	0.1807168	0.15549847	0.01	8.44	8.44	57.26
Yao et al.	1986	UK	EBV VCA IgG	31	33	24	26	0.0322235	0.37703844	0.07	10.04	10.11	45.10
Shirodaria et al.	1987	UK	EBV VCA IgG	26	26	24	26	0.2	0.24509803	0.01	11.05	11.05	38.01
Youinou et al.	1992	France	EBV VCA IgG	98	100	49	50	0.0000000	0.44893887	0.02	16.00	16.02	159.73
Blashke et al.	2000	Germany	EBV VCA IgG	55	55	53	60	0.2437490	0.00881473	0.00	25.52	25.53	81.51
Us et al.	2011	Turkey	EBV VCA IgG	85	85	48	50	0.1598871	0.13543394	0.00	16.96	16.97	137.69
Sherina et al., 2017	2017	Sweden	EBV VCA IgG	970	987	679	700	0.0424232	0.02949588	0.28	279.18	279.45	1522.31
			Total	1437	1468	986	1039			0.8597			

Alpha =	0.05
Degrees of freedom (d. f.) =	9
X^2 Critical (SINE) =	**16.919**
X^2 Calculated (SINE) =	0.8597

Case_P: cases, positive; Case_T: cases, total; Con_P: controls, positive; Con_T: controls, total.

TABLE 3. *EBV VCA IgG self-contradictory data, not considered for a meta-analysis.*

Study Id	Year	Country	Risk Factor	Case_P	Case_T	Con_P	Con_T	k	X^2(SINE)	X^2(IMP)	X^2(IMP^SINE)	X^2(EXCL)
Phillips et al.	1976	USA	EBV VCA IgG	31	33	32	33	**-0.0727393**	**0.07**	15.75	15.82	42.96
Nakabayshi	1981	Japan	EBV VCA IgG	32	32	15	15	**#DIV/0!**	**0.01**	4.47	4.48	52.12
Venables et al.	1981	UK	EBV VCA IgG	94	100	32	33	**-0.0574427**	**0.30**	7.88	8.18	156.81
Musiani et al.	1987	Italy	EBV VCA IgG	35	35	40	40	**#DIV/0!**	**0.01**	20.80	20.81	49.88
Zhang et al.	1993	Finland	EBV VCA IgG	50	50	49	49	**#DIV/0!**	**0.01**	23.76	23.77	73.76
Mousavie-Jazi et al.	1998	Sweden	EBV VCA IgG	27	28	12	12	**-0.10482848**	**0.01**	3.39	3.40	43.09
Zhang et al.	1999	China	EBV VCA IgG	75	91	38	45	**-0.02544181**	**2.64**	12.44	15.08	110.11
Jorgensen et al.	2008	Denmark	EBV VCA IgG	31	33	238	245	**-0.0585413**	**0.07**	209.69	209.76	31.65
Lünemann et al.	2008	USA	EBV VCA IgG	25	25	20	20	**#DIV/0!**	**0.01**	8.45	8.46	37.35
			Total	400	427	476	492					

When using data to perform some analysis, several conditions must be taken into consideration. Unfortunately, not all data are appropriate for detailed analysis. Due to formal mathematical requirements it is possible to identify data as *self-contradictory* and it is necessary to exclude these data from further analysis. The reason for the *self-contradiction of the data* is marked in **bold** numbers/letters. These studies were not considered for further analysis even if all these studies supported the hypothesis *without* EBV VCA IgG sero-positivity *no* RA. The term #DIV/0! denote the case that there is a division by zero.

TABLE 4. **Without** *EBV EBNA IgG positivity* **no** *RA.*

Study Id	Year	Country	Risk Factor	Case_P	Case_T	Con_P	Con_T	k	p-val	X^2(SINE)	X^2(IMP)	X^2(IMP^SINE)	X^2(EXCL)
Ferrell et al.	1981	USA	EBV EBNA-1 IgG	83	83	47	53	0.26884692	0.002921342	0.00	16.63	16.64	134.36
Shirodaria et al.	1987	UK	EBV EBNA-1 IgG	23	26	21	26	0.10660036	0.227268212	0.24	9.55	9.79	30.98
Youinou et al.	1992	France	EBV EBNA-1 IgG	90	100	41	50	0.11338681	0.078226412	0.90	12.52	13.42	141.25
Mousavi-Jazi et al.	1998	Sweden	EBV EBNA-1 IgG	27	28	10	12	0.22783558	0.187044534	0.01	2.44	2.45	44.06
Blashke et al.	2000	Germany	EBV EBNA-1 IgG	48	55	51	60	0.03280399	0.200258806	0.77	25.76	26.53	63.81
Lünemann et al.	2008	USA	EBV EBNA-1 IgG	21	25	16	20	0.05198752	0.284334686	0.49	6.49	6.98	28.17
Erre et al.	2015	Italy	EBV EBNA-1 IgG	69	77	40	58	0.25916219	0.002049224	0.73	14.31	15.04	103.99
			Total	361	394	226	279			3.1435			

Alpha =	0.05
Degrees of freedom (d. f.) =	7
X^2 Critical (SINE) =	14.0671
X^2 Calculated (SINE) =	3.1435

Case_P: cases, positive; Case_T: cases, total; Con_P: controls, positive; Con_T: controls, total.

TABLE 5. *EBV EBNA IgG self-contradictory data, not considered for a meta-analysis.*

Study Id	Year	Country	Risk Factor	Case_P	Case_T	Con_P	Con_T	k	X^2(SINE)	X^2(IMP)	X^2(IMP^SINE)	X^2(EXCL)
Sculley	1986	Australia	EBV EBNA-1 IgG	49	72	41	49	**-0.175625**	7.03	18.23	25.26	**58.81**
Musiani et al.	1987	Italy	EBV EBNA-1 IgG	35	35	40	40	**#DIV/0!**	**0.01**	20.80	20.81	49.88
Davis et al.	1999	Australia	EBV EBNA-1 IgG	39	50	35	43	**-0.04198663**	**2.21**	16.08	18.29	49.68
Jorgensen et al.	2008	Denmark	EBV EBNA-1 IgG	29	33	231	245	**-0.08421061**	**0.37**	204.35	204.72	27.74
Us et al.	2011	Turkey	EBV EBNA-1 IgG	85	87	50	50	**-0.092273**	**0.03**	18.15	18.18	134.96
Yazbek et al.	2011	Brazil	EBV EBNA-1 IgG	127	140	130	143	**-0.00337194**	**1.12**	65.25	66.37	176.57
			Total	315	345	486	521					

The reason for the *self-contradiction of the data* above is marked in **bold** numbers/letters. . These studies were not considered for further analysis even if most of these studies supported the hypothesis *without* EBV EBNA IgG sero-positivity *no* RA. #DIV/0! denotes the case that there is a division by zero.

Necessary Condition (Conditio Sine Qua Non)

The mathematical formula of the *necessary* condition relationship (28-48) (conditio sine qua non) of a population was defined as

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

and used to proof the hypothesis: *without* At *no* Bt .

Sufficient Condition (Conditio per Quam)

The mathematical formula of the *sufficient* condition relationship (28-48) (conditio per quam) of a population was defined as

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

and used to proof the hypothesis: *if* At *then* Bt .

The X² Goodness of Fit Test of a Necessary Condition

Under conditions where the chi-square goodness (8-48) of fit test cannot be used it is possible to use an approximate and conservative (one sided) confidence interval known as *the rule of three*. Using *the continuity correction* , the chi-square value of a conditio sine qua non distribution before changes to

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

The X² Goodness of Fit Test of the Exclusion Relationship

The chi square value with degree of freedom 2-1=1of the exclusion relationship (28-48) with a *continuity correction* can be calculated as

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

The chi square Goodness of Fit Test of the exclusion relationship examines how well observed data are compared with the expected theoretical distribution of an exclusion relationship.

The Mathematical Formula of the Causal Relationship k

The mathematical formula of the causal relationship (28-48) k is defined *at every single event, at every single Bernoulli trial t,* as

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

where At denotes the cause and Bt denotes the effect. The chi-square distribution can be applied to determine the significance of causal relationship k. Pearson's (49) concept of correlation (50) is not identical with causation (28,36,37). Causation as such is not identical with correlation. This has been proven many times and is widely discussed in many publications (51).

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

TABLE 6. *EBV PCR DNA and ISH studies and RA.*

Study Id	Year	Country	Risk Factor	Case_P	Case_T	Con_P	Con_T	k	p-val	X²(SINE)	X²(IMP)	X²(IMP^SINE)	X²(EXCL)
Mousavie-Jazi et al.	1998	Sweden	EBV PCR DNA	2	31	0	14	0.1449318	0.46969697	26.20	0.13	26.33	1.20
Saal et al.	1999	Germany	EBV PCR DNA	29	84	8	81	0.2954235	9.29228E-05	35.36	1.52	36.88	31.62
Takeda et al.	2000	Japan	EBV PCR DNA	15	32	0	30	0.5469937	6.07959E-06	8.51	0.02	8.52	20.59
Chiu et al.	2013	Taiwan	EBV ISH	23	23	0	13	1	4.32753E-10	0.01	0.01	0.02	44.02
Erre et al.	2015	Italy	EBV PCR DNA PBMC	61	77	33	58	0.2403144	0.00322558	3.12	11.24	14.36	86.47
			Total	130	247	41	196						

data can help to estimate the true value of an unknown population parameter with a certain probability. Under some conditions, the 95% interval for the causal relationship k is derived (47) as

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

Hypergeometric distribution

The hypergeometric distribution with its own and very long history (52,53,54,55) is defined by the parameters population size, event count in population, sample size and can be used to calculate the exact probability of an event even for small samples which are drawn from relatively small populations, without replacement.

The hypergeometric distribution differs from the binomial distribution. In contrast to the hypergeometric distribution, the probability of a binomially distributed random variable is the same from trial to trial.

The probability of having exactly at (Table 1) successes or the significance of the causal relationship k can be tested under conditions of sampling without replacement by the hypergeometric distribution (56) as

$$p\left(a_t\right)=\frac{\binom{A_t}{a_t}\times\binom{N_t-A_t}{B_t-a_t}}{\binom{N_t}{B_t}} \quad (9)$$

TABLE 7. *The parvovirus B19 Study of Sherina et al., 2017*

		RA <B>		
		Yes	No	Total
B19 IgG	Yes	742	504	1246
<A>	No	237	188	425
	Total	979	692	1671
		k =	+0.0335	
	p value (k) =		0.017813306	
	95% CI (k) =		(-0.0212;0.0882)	
	WITHOUT <A>		NO <B>.	
	p (SINE) =		0.8582	
	X²(SINE) =		**57.1320**	
	Odds ratio =		1.1678	
95% CI (Odds ratio) =			(0.9350;1.4587)	
		IF <A>	THEN <B>	
		p (IMP)=	0.6984	
		X² (IMP)=	**203.4609**	

TABLE 8. *The CMV Study of Sherina et al., 2017*

		RA <B>		
		Yes	No	Total
CMV IgG	Yes	713	531	1244
<A>	No	274	169	443
	Total	987	700	1687
		k =	**-0.0405**	
	p value (k) =		0.011242387	
	95% CI (k) =		(-0.0139;0.0950)	
	WITHOUT <A>		NO <B>.	
	p (SINE) =		0.8376	
	X²(SINE) =		**75.7875**	
	Odds ratio =		0.8282	
95% CI (Odds ratio) =			(0.6632; 1.0343)	
		IF <A>	THEN <B>	
		p (IMP)=	0.6852	
		X² (IMP)=	**226.2301**	

Odds Ratio

The odds ratio (OR) is given57,58,59 by

$$OR\left(A_t,B_t\right)\equiv\frac{a_t/b_t}{c_t/d_t}=\frac{a_t\times d_t}{c_t\times b_t} \quad (10)$$

It is necessary to point to the case were ct=0. Under conditions were **ct=0**, there is *a conditio sine qua non relationship* between At and Bt while the Odds ratio collapses. To date, it is not generally accepted to divide by zero.

The Odds ratio cannot speak about the natural, profound and far reaching conditio sine qua non relationship but must pass over in silence on this relationship. Pagano & Gauvreau (60) are quietly returning through the back door to circumvent this fundamental problem of Odds ratio by adding (60) 0.5 to the cells at, bt, ct, dt.

This simple way to circumvent the inconsistency and spectacular methodological incompleteness of Odds ratio is fundamentally misleading. To date, a substantial amount of research is analyzed by the Odds ratio. The more serious difficulty of this point of view is that it appears to be impossible to rely on Odds ratio in principle.

Furthermore, under conditions were ***bt=0***, *a conditio per quam relationship* between At and Bt is given while the Odds ratio collapses again.

For this reason, the Odds ratio is overshadowed by a deep theoretical inconsistency and appears not to be grounded on a seemingly sound piece of reasoning.

More likely, the Odds ratio (OR) is nothing more but *Yule's coefficient of association (6)1 Q* re-written (62) in a non-normalized form and given by

$$Q(A_t, B_t) \equiv \frac{OR(A_t, B_t) - 1}{OR(A_t, B_t) + 1}$$

$$Q(A_t, B_t) = \frac{\frac{(a_t \times d_t)}{(b_t \times c_t)} - 1}{\frac{(a_t \times d_t)}{(b_t \times c_t)} + 1} \qquad (11)$$

$$Q(A_t, B_t) = \frac{\frac{(a_t \times d_t) - (b_t \times c_t)}{(b_t \times c_t)}}{\frac{(a_t \times d_t) + (b_t \times c_t)}{(b_t \times c_t)}}$$

$$Q(A_t, B_t) = \frac{(a_t \times d_t) - (b_t \times c_t)}{(a_t \times d_t) - (b_t \times c_t)}$$

Under conditions where Yule's coefficient of association (Yule, 1900) Q = 0, there is no association. Although severely and justifiably criticized especially by Karl Pearson (1857–1925), the long-time and rarely challenged leader of statistical science and Heron (63), Odds ratio is still regularly referred to. The standard error and 95% confidence interval of the Odds ratio (OR) can be calculated according to Altman (64). Given the severely limited character of odds ratio, the standard error of the log Odds ratio is calculated as

TABLE 9. *The EBV Study of Sherina et al., 2017*

		RA <B>		
		Yes	No	Total
EBV VCA IgG <A>	Yes	970	679	1649
	No	**17**	21	38
	Total	987	700	1687
		k =	**+0.0424**	
	p value (k) =		**0.029495888**	
	95% CI (k) =		(-0.0120; 0.0969)	
	WITHOUT <A>		NO <B>.	
	p (SINE) =		0.9899	
	X^2(SINE) =		**0.2758**	
	Odds ratio =		1.7647	
	95% CI (Odds ratio) =		(0.9241; 3.3700)	

$$SE\left(\ln\left(OR\left(A_t, B_t\right)\right)\right) \equiv \sqrt{\frac{1}{a_t} + \frac{1}{b_t} + \frac{1}{c_t} + \frac{1}{d_t}} \qquad (12)$$

where ***ln*** denotes the *logarithmus naturalis*. The 95% confidence interval of the odds ratio is given by

$$95\%\ CI = \exp\left(\ln\left(OR\left(A_t, B_t\right)\right) - \left(1.96 \times SE\left(\ln\left(OR\left(A_t, B_t\right)\right)\right)\right)\right)$$

to (13)

$$\exp\left(\ln\left(OR\left(A_t, B_t\right)\right) + \left(1.96 \times SE\left(\ln\left(OR\left(A_t, B_t\right)\right)\right)\right)\right)$$

TABLE 10. *The Study of Saal et al.*

		RA <B>		
		Yes	No	Total
EBV PCR DNA <A>	Yes	29	**8**	37
	No	55	73	128
	Total	84	81	165
		k =	**+0.2954**	
	p value (k) =		**9.29228E-05**	
	95% CI (k) =		(0.1213;0.4695)	
	Odds ratio =		4.8114	
95% CI (Odds ratio) =			(2.0413; 11.3405)	
		IF <A>	THEN <B>	
		p (IMP)=	0.9515	
		X^2 (IMP)=	**1.5203**	

TABLE 11. *The Study of Takeda et al.*

		RA <B>		
		Yes	No	Total
EBV PCR DNA <A>	Yes	15	**0**	15
	No	17	30	47
	Total	32	30	62
		k =	**+0.5470**	
	p value (k) =		**6.07959E-06**	
	95% CI (k) =		(0.2630; 0.8310)	
		IF <A>	THEN <B>	
		p (IMP)=	1.0000	
		X^2 (IMP)=	**0.0167**	

The unknown population proportion pupper

Tests of hypotheses concerning the sampling distribution of the sample proportion **p** (i. e. conditio sine qua non p(SINE), conditio per quam p(IMP) et cetera) can be performed using the normal approximation. The calculation of the rejection region based on the sample proportion to construct a confidence interval for an unknown (65,66) population propor-

tion pupper can be performed under conditions of *sampling without replacement* by the formula

$$\pi_{\text{critical upper}} = \left(p - \frac{1}{2 \times n}\right) - \left(Z \times \sqrt{\left(\frac{p \times (1-p)}{n}\right) \times \left(\frac{N-n}{N-1}\right)}\right) \quad (14)$$

while the term ((N-n)/(N-1)) denotes *the finite population correction* (67).

TABLE 12. *The Study of Chiu et al.*

		RA <B>		
		Yes	No	Total
EBV ISH <A>	Yes	23	0	23
	No	0	13	13
	Total	23	13	36
		k =	**+1.0000**	
	p value (k) =		**4.32753E-10**	
	WITHOUT <A>		NO <B>.	
		p (SINE) =	1.0000	
	X^2(SINE) =		**0.0109**	
		IF <A>	THEN <B>	
		p (IMP)=	1.0000	
		X^2 (IMP)=	**0.0109**	
	<A> is SINE		and IMP of <B>	
	p(SINE ^ IMP) =		1.0000	
	X^2(SINE ^ IMP) =		**0.0217**	

The Chi Square Distribution

The following critical values (65,66) of the chi square distribution (68) as visualized by Table 13 are used in this publication.

TABLE 13. *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

The rule of three

The Chi-square goodness of fit test (68) used to test whether a sample distribution is identical with a *theoretical distribution* yields only an approximate p-value and works when the dataset analyzed is large enough (n ~ 30 and more). An approximate and conservative (one sided) confidence interval as discussed by Rumke (69), Louis (70), Hanley et al. (71) and Jovanovic & Levy (72) and known as the rule of three can be used if the Chi-square goodness of fit test (with a *continuity correction) (*73) cannot be applied.

RESULTS

Rheumatoid arthritis is an inflammatory progressive disease with more or less a very poor prognosis. In this context, the studies (74-99) considered for a re-analysis should help us to get a better understanding of this disease.

Without EBV IgG antibody positivity no rheumatoid arthritis

EBV VCA IgG antibodies can be used to investigate the relationship between EBV and RA.

Claims

Null hypothesis: (no causal relationship)

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

Alternative hypothesis: (causal relationship)

The presence of EBV VCA IgG antibodies is not a necessary condition (a conditio sine qua non) of rheumatoid arthritis. 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 rheumatoid arthritis are presented by Table 2. In total, 9 studies with 2507 cases and controls provided non self-contradictory data and were meta-analysed while the level of significance was alpha = 0.05. In particular, all studies provided significant evidence of a conditio sine qua non relationship between EBV VCA IgG antibodies and rheumatoid arthritis (X^2(Calculated [conditio sine qua non]) =0.8597 and is less than X^2 (Critical [conditio sine

qua non]) =16.919). In fact, the presence of EBV VCA IgG antibodies is a necessary condition (a conditio sine qua non) of rheumatoid arthritis. Ultimately, for this reason, **without** the presence of EBV VCA IgG antibodies **no** rheumatoid arthritis.

Q. e. d.

Without EBV EBNA IgG antibody positivity no rheumatoid arthritis

Claims

Null hypothesis

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

Alternative hypothesis

The presence of EBV EBNA IgG antibodies is not a necessary condition (a conditio sine qua non) of rheumatoid arthritis. 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 EBNA IgG antibodies and rheumatoid arthritis are shown in Table 3. At this point it might be important that 7 studies with 794 cases and controls provided non self-contradictory data and were considered for a meta-analysis while the level of significance was alpha=0.05. We can point to the fact that all 7 studies (Table 4) provided significant evidence of a conditio sine qua non relationship between EBV EBNA IgG antibodies and rheumatoid arthritis (X^2 (Calculated [conditio sine qua non]) = 3.1435 and is less than X^2 (Critical [conditio sine qua non]) = 14.0671). By that very fact, the presence of EBV EBNA IgG antibodies is a necessary condition (a conditio sine qua non) of rheumatoid arthritis. The last point suggests that **without** the presence of EBV EBNA IgG antibodies **no** rheumatoid arthritis.

Q. e. d.

EBV is a cause of rheumatoid arthritis

(The Study of Saal et al. (Table 10))

The presence of EBV DNA in synovial tissues is a possible method to show an etiological link between EBV and the pathogenesis of rheumatoid arthritis. Several studies published convincing results on this topic.

Claims

Null hypothesis: (no causal relationship)

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

Alternative hypothesis: (causal relationship)

There is a significant causal relationship between an infection by Epstein-Barr virus and rheumatoid arthritis. ($k^1 0$).

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 Saal et al. (Table 10) and are illustrated by the Table 10. The causal relationship k(Epstein-Barr virus, rheumatoid arthritis) was calculated as k = +0.2954 (p value (k) = 9.29228E-05; 95% CI (k) = [0.1213;0.4695]) while the level of significance was alpha=0.05. The data of Saal et al. (Table 10) provide evidence that EBV is a sufficient condition ($X^2(IMP) = 1.5203$; X^2 Critical (IMP) = 3.841458821) of rheumatoid arthritis while the cause effect relationship between EBV and RA is highly significant (k = +0.2954 (p value (k) = 9.29228E-05).

Q. e. d.

EBV is a cause of rheumatoid arthritis

(The Study of Takeda et al. (Table 11))

Claims

Null hypothesis: (no causal relationship)

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

Alternative hypothesis: (causal relationship)

There is a significant causal relationship between an infection by Epstein-Barr virus and rheumatoid arthritis. ($k^1 0$).

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 Study of Takeda et al. (Table 11) and are illustrat-

ed by the Table 11. The causal relationship k(Epstein-Barr virus, rheumatoid arthritis) was calculated as k = +0.5470 (p value (k) = 6.07959E-06; 95% CI (k) = [0.2630; 0.8310]) while the level of significance was alpha=0.05. The data of Takeda et al. (Table 11) provide evidence that EBV is a sufficient condition (X^2(IMP) = 0.0167; X^2 Critical (IMP) = 3.841458821) of rheumatoid arthritis while the cause effect relationship between EBV and RA is highly significant (k = +0.5470 (p value (k) = 6.07959E-06).

Q. e. d.

EBV is the cause of rheumatoid arthritis

The Study of Chiu et al. (Table 12)

Claims

Null hypothesis: (no causal relationship)

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

Alternative hypothesis: (causal relationship)

There is a significant causal relationship between an infection by Epstein-Barr virus and rheumatoid arthritis. ($k^1$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 Study of Chiu et al. (Table 12) and are illustrated by the Table 12. The causal relationship k(Epstein-Barr virus, rheumatoid arthritis) was calculated as k = +1.0 (p value (k) = 4.32753E-10) while the level of significance was alpha=0.05. The data of Study of Chiu et al. (Table 12) provide evidence that EBV is *a necessary* (X^2(SINE) = 0.0109; X^2 Critical (SINE) = 3.841458821), *a sufficient* (X^2(IMP) = 0.0109; X^2 Critical (IMP) = 3.841458821) and equally *a necessary and sufficient* condition (X^2(SINE and IMP) = 0.0217; X^2 Critical (SINE and IMP) = 3.841458821) of rheumatoid arthritis while the cause effect relationship is highly significant (k = +1.0; p value (k) = 4.32753E-10). Epstein-Barr virus is the cause of rheumatoid arthritis (k = +1.0; p value (k) = 4.32753E-10).

Q. e. d.

DISCUSSION

Epstein-Barr Virus discovered 1964 by Epstein et al. (100) is a widely disseminated lymphotropic herpes virus. As key results, several studies suspected that particularly Epstein-Barr virus is involved in etiology of rheumatoid arthritis. Catalano et al. (21) reported that patients with RA had a significantly higher frequency and titer of rheumatoid arthritis-associated nuclear antigen (anti-RANA) antibodies than did control subjects and confirmed the previous results of Alspaugh and Tan (18). Using the protein blot technique, Billings et al. (23) were able to provide evidence that rheumatoid arthritis nuclear antigen (RANA) and Epstein-Barr virus nuclear antigen identify the same polypeptide.

However, data about EBV burden in RA patients reported have been contradictory and the role of EBV still remains elusive. Indeed, on this matter, as with so many other major medical issues, several reviews101, 102 and meta-analysis were not able to find a definite solution on this fundamental topic. Thus far, it is not excluded that this meta-analyses is susceptible to different kind of publication bias. In its broadest sense, the studies analysed differ in various aspect. Thus, the question arises why not all patients were diagnosed according to the American Rheumatism Association 1987 revised criteria for the classification 103 of RA. While some studies considered for a meta-analysis provided no diagnostic criteria for the diagnosis of rheumatoid arthritis other studies utilised a form of the American College of Rheumatology (ACR) or American Rheumatology Association criteria. Additionally, reporting of data of some studies are to some extent unsatisfactory, because not all studies provided detailed cut-off values for EBV sero-positivity. RA patients and non-RA controls both were tested quantitatively for different antibodies against Epstein-Barr virus while using different substrates or kits or antigens and various technologies. Hence we need to take into consideration under what conditions is it appropriate to use antibodies against Epstein-Barr virus to investigate the relationship between EBV and rheumatoid arthritis? To date it is known that IgG molecules with two antigen binding sites are created and released by human plasma B cells not without any reason but i. e. to control an infection in human body. Especially IgM, IgG et cetera molecules are not existing for ever but suffer a kind of *pharmacokinetics*. The *half-live* (104) for total IgG was found to be

25.8 days. In this context EBV antibodies are major components of human humoral immunity allowing controlling an EBV infection of human body tissues through several mechanisms. A natural concern is whether EBV antibodies suffer a turnover rate with regard to the infectious status. Several factors can influence the pharmacokinetics of EBV antibodies. The half-lives for antibodies specific for Epstein-Barr virus antigens depend on EBV infection status. In the case of recent EBV infection or during the course of EBV reactivation the humoral response of human immune system against EBV antigens will lead to different changes in antibodies specific for Epstein-Barr virus antigens. An acute EBV (re-) infection is indicated by the presence of VCA IgM and VCA IgG but without EBNA-1 IgG. Typical for a past EBV infection is the presence of VCA IgG and EBNA-1 IgG but without VCA IgM (105).

At the very least, enough is published to convince our self that after a primary EBV infection, EBV persists for life in vivo in a quiescent state in resting human memory B cells (106) which circulate in the peripheral blood. This fact considerably leads to the conclusion that VCA IgG or EBNA IgG provide evidence of an EBV infection of human body and are therefore helpful in causal analysis. And yet, despite contradictory results several studies give convincing evidence of the linkage between EBV and RA. Many studies demonstrated remarkable higher levels of different serum antibodies against Epstein-Barr virus in patients suffering from rheumatoid arthritis than in healthy controls (21, 22, 24, 76, 107, 108, 109). Baecklund et al. (110) provided evidence that a high inflammatory activity of RA rather than the treatment of RA is a major risk determinant of lymphoma in a subset of patients with RA.

Sherina et al. (99) conducted the largest epidemiological study to date and investigated the prevalence of EBV, human cytomegalovirus (CMV) and parvovirus B19 antibodies by ELISA in serum samples from 990 RA patients and 700 controls. The prevalence of EBV IgG was 98.3% in patients with RA and 97.0% in controls. Parvovirus B19 IgG were detected in 75.8% of patients with RA and in 72.8% of healthy controls. CMV IgG was documented in 75.9% of controls and in 72.2% of patients with RA. For the first time, the viruses EBV, CMV and parvovirus B19 have been examined by Sherina et al. (99) in the context of a very large and impressive epidemiological study in patients with RA and in non-RA subjects. Sherina et al. used the presence of anti-viral antibodies as surrogate markers for viral infection.

The data of Sherina et al. (99) with a sample size of n= 1690 cases and controls concerning the relationship between *parvovirus B19* and rheumatoid arthritis (Table 7) were not self-contradictory and could be used for further analysis. The data of Sherina et al. (99) *do not support* the Null-hypothesis: **without** parvovirus B19 infection **no** rheumatoid arthritis (X^2 (SINE) Calculated = 57.9396 and thus far greater than X^2 (SINE) Critical = 3.841458821). The data of Sherina et al. (99) *do not support* the Null-hypothesis: **if** parvovirus B19 infection **then** rheumatoid arthritis (X^2 (IMP) *Calculated* = 205.3791 and thus far greater than X^2 (IMP) *Critical* = 3.841458821). In other words, according to the data of Sherina et al. (99) parvovirus B19 is neither a cause nor the cause of rheumatoid arthritis (Table 7) even if statistically not independent (111) of each other.

Contradicting the study Sherina et al. (99), Takahashi (112) et al., 1998 found Human parvovirus B19 DNA (B19) in the synovium of 30/39 RA patients in contrast to 9/57 controls while neither the study of Kerr (113) et al. nor the study of Naciute (114) et al. with B19 DNA in 30/118 of RA patients vs. 9/49 in healthy controls confirmed the data of Takahashi (112) et al., 1998.

The data of Sherina et al. (99) concerning the relationship between *CMV* and rheumatoid arthritis were not self-contradictory (Table 8) and could be considered for further analysis. The data of Sherina et al. (99) *do not support* the Null-hypothesis: **without** CMV infection **no** rheumatoid arthritis (p(SINE) = 0.8376; X^2(SINE) Calculated = 75.7875 and thus far greater than X^2 (SINE) Critical = 3.841458821). The data of Sherina et al. (99) *do not support* the Null-hypothesis: **if** CMV infection **then** rheumatoid arthritis (p(IMP)=0.6852; X^2(IMP) Calculated =226.2301 and thus far greater than X^2 (IMP) *Critical* = 3.841458821). Thus far, according to the data of Sherina et al. (99) it appears not to be highly probable that CMV might somehow be involved in the pathogenesis of RA. CMV is neither a cause nor the cause (Table 8) of RA (k=-0.0405; p value (k) =0.011242387). The data of Sherina et al. (99) concerning the relationship between EBV VCA IgG and rheumatoid arthritis were not self-contradictory (Table 9) and were used for further analysis. The data of Sherina et al. (99) *do support* the Null-hypothesis: **without** EBV infection (documented by EBV VCA IgG antibodies) **no** rheumatoid arthritis (p (SINE) =0.9899; X^2(SINE) *Calculated* = 0.2750 and is thus far not greater than X^2 (SINE) *Critical* = 3.841458821,

k > 0; p value (k) = 0.029020429). This Null-hypothesis is supported by other studies too. In other words, according to the data (Table 9) of the very large epidemiological study conducted by Sherina et al. (99) EBV infection is the cause of rheumatoid arthritis.

However, even EBV DNA analysis provided view contradictory results; while some studies failed to detect EBV DNA in RA patients (115) other studies were successful. Saal et al. (88) (Table 10) investigated the presence of the Epstein-Barr virus (EBV) in rheumatoid arthritis (RA) synovium and concluded that EBV is an environmental risk factor for RA. According to the study of Saal et al. (88) there is a highly significant cause effect relationship (Table 10) between an EBV infection of human joints and RA (k =+0.2954; p value (k) =9.29228E-05) while the conditio per quam relationship between EBV and RA is significant. In other words, **if** EBV infection of human joints **then** RA (p(IMP)=0.9515; X^2 (IMP)=1.5203).

Takeda et al. (91) (Table 11) detected the existence of EBV DNA by PCR in the synovial tissue in 15 of the 32 samples from the RA patients (47%), but not in any of the 30 osteoarthritis patients (Table 11). Takeda et al. (91) were able to provide evidence that an infection of human joints by EBV is a *conditio per quam* of rheumatoid arthritis. In other words, according to the study of Takeda et al. (91) (Table 11) **if** infection of human joints by EBV **then** RA (p (IMP)=1; X^2 (IMP)=0.0167). The same study of Takeda et al. (91) (Takeda et al., 2000) provided evidence of a highly significant cause effect relationship between an infection of human joints by EBV and RA (k =+0.5470; p value (k) =6.07959E-06).

Using real-time polymerase chain reaction Balandraud et al. (116) were able to document that Epstein-Barr virus DNA load in the peripheral blood (116) of patients with rheumatoid arthritis was increased almost 10-fold .

In-situ hybridization

In-situ hybridization (ISH), has been described in the year 1969 by Joseph G. Gall (117). According to Fan & Gulley (118), In situ hybridization (ISH) to Epstein-Barr virus (EBV)-encoded RNA (EBER) is an appropriate method to detect and localize EBV DNA in biopsy samples of rheumatoid arthritis patients and healthy controls. Like any other method, even the in situ hybridization is not completely free of bias and can be labelled with some severe limitations. The study group of Chiu et al. (96) (Table 12) conducted a study to investigate the expression of Epstein-Barr virus-encoded small RNA1 (EBER1) by ISH in the synovial tissues taken from 23 patients with rheumatoid arthritis and 13 patients with OA. The RA patients were diagnosed according to the American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis (103). All synovial samples from RA showed positive expression of EBER1 (23/23,100%), but none of the control group patients (0/13).

According to the study of Chiu et al. (96) (Table 12), an EBV virus infection is *a necessary condition* (p (SINE) =1; X^2(SINE) =0.0109), an EBV virus infection is *a sufficient condition* (p (IMP)=1; X^2 (IMP)=0.0109) and an EBV virus infection is *a necessary and sufficient condition* (p(SINE AND IMP) = 1; X^2(SINE AND IMP) = 0.0217) of rheumatoid arthritis while the cause effect relationship (Table 12) between an EBV infection and RA is highly significant (k = +1; p value (k) = 4.32753E-10).

Mehraein et al. (119) investigated the influence of synovial virus infections in rheumatoid arthritis, and found evidence of increased synovial persistence of EBV in 5/29 rheumatoid arthritis (RA) patients.

Mahabadi et al. (98) investigated Epstein-Barr virus DNA by PCR in synovial fluid of 50 rheumatoid arthritis patients and detected EBV DNA by PCR in 30 cases (60%). Mahabadi et al. (98) concluded that EBV may play a role in the pathogenesis of RA.A control group was not provided and it was not possible to consider the data for causal analysis.

Although it has been investigated and speculated for over 40 years that Epstein-Barr virus is a strong candidate to contribute to the cause of RA definite evidence was wanting. Considering the half-life (120) of EBV antibodies and the results of the reviews (121) mentioned, the studies re-analysed in the present article indicate a high degree of confidence that an EBV infection is the cause RA and the etiology of rheumatoid arthritis no longer remains unknown. The lack of appropriate ancient medical texts regarding rheumatoid arthritis has forced many researchers to acknowledge the first description of RA by modern medicine to Augustin Jacob Landré-Beauvais (122, 123) from the year 1800 published in his dissertation. In the year 2018 and about 218 years later, the cause of rheumatoid arthritis is finally identified.

CONCLUSION

The results of the present study are consistent with the hypothesis that there is a relationship between EBV and RA and give further evidence of the linkage between EBV and RA. The data not only do support the hypothesis that EBV infection is somehow involved in the pathogenesis of RA but demand us to accept that EBV is the cause of RA (k =+1.0000; p value (k) =4.32753E-10).

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