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Human Cytomegalovirus is the Cause of Glioblastoma Multiforme

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Abstract

Objective: The relationship between Human cytomegalovirus (HCMV) and glioblastoma multiforme (GBM) is investigated.

Methods: A systematic review and re-analysis of some impressive key studies was conducted aimed to answer the following question. Is there a cause-effect relationship between HCMV and GBM? The method of the conditio sine qua non relationship was used to proof the hypothesis whether the presence of HCMV guarantees the presence of GBM. In other words, *without* HCMV *no* GBM. The mathematical formula of the causal relationship k was used to proof the hypothesis, whether there is a cause-effect relationship between HCMV and GBM. Significance was indicated by a p-value of less than 0.05.

Results: The studies analysed were able to provide strict evidence that HCMV is a necessary condition (a conditio sine qua non) of GBM. Furthermore, the cause-effect relationship between HCMV and GBM ($k \sim + 0.8608$, p value < 0.0001) was highly significant.

Conclusion: Without a human cytomegalovirus infection no glioblastoma multiforme. Human cytomegalovirus is the cause of glioblastoma multiforme.

Keywords: Cytomegalovirus, Glioblastoma multiforme, Causal relationship

1. Introduction

Glioblastoma (Bailey & Cushing, 1926) multiforme (GBM) is a highly lethal (Zhu et al., 2002), non-curable grade IV diffuse astrocytoma (brain tumour) which is affecting children and adults to such an extent that to date the majority of affected patients are dying from their disease by 2,5 years following diagnosis (Smoll et al., 2013). Glioblastoma multiforme consist primarily of neoplastic astrocytes but includes also other non-neoplastic cell types (Yuan et al., 2004) like neural stem cells, macrophages et cetera. The commonly used World Health Organization (WHO) classification distinguishes different types of glioblastoma multiforme (Louis et al., 2007) due to the presumed cell of origin. In general, glioblastoma multiforme may first appear as a grade 4 glioblastoma (GBM) and is called primary GBM while secondary glioblastoma multiforme develops from a lower grade astrocytoma. The Cancer Genome Atlas (Verhaak et al., 2010) researchers classified four subtypes of GBM as Proneural, Neural, Classical, and Mesenchymal subtypes. In point of fact, even if Glioblastoma multiforme progresses rapidly and is fatal within a very short time despite current therapies, to date the aetiology of glioblastoma multiforme is completely unknown. Among several risk factors supposed to be involved in glioblastoma including exposure to electrical or magnetic fields or ionizing radiation (Ohgaki, 2009) human cytomegalovirus too has been proposed as a contributing agent of glioblastoma multiforme. To our knowledge, HCMV as a member of the Betaherpesvirinae subfamily (Landolfo et al., 2003) is containing a linear double-stranded DNA of 230 kb surrounded by a proteinaceous tegument, which itself is enclosed by a loosely applied lipid bilayer and contains more than 60 virus-encoded proteins and about 70 host-proteins. The proteins produced by the HCMV can be detected (Landolfo et al., 2003) in various human cellular compartments i.e. by means of immunohistochemistry (IHC). A primary human cytomegalovirus infection leads to a life-long viral persistence. In the latent phase of a HCMV infection HCMV virions are not produced and patients are more or less clinically without symptoms (Priel et al., 2015) but HCMV itself can be present in the monocytes. The seroprevalence of HCMV in the general human population ranges between 50 to 100% (Gandhi & Khanna, 2004; Ludwig & Hengel, 2009; Yi et al., 2013; Najafi et al., 2016). Even a foetus itself is not protected against a vertical transmission. Thus far, HCMV represents the major infectious cause of serious birth defects or developmental disabilities. During maternal primary infection, and to a lesser extent during recurrent infection, human

cytomegalovirus can translocate the placental barrier and can cause infection of the developing foetus too. Human cytomegalovirus is occurring in 0.5-2% of pregnancies in Europe and the United States (Kenneson et al., 2007; Wang et al., 2011) and neonatal infections (Fowler et al., 2018) caused by human cytomegalovirus have been reported too. In particular, many breast milk-acquired infections in premature infants are asymptomatic. Several studies demonstrated the presence of human cytomegalovirus in glioblastoma tissues suggesting that HCMV may participate in tumour pathogenesis. But the relationship between GBM and HCMV is controversial because many other studies were unable to detect HCMV in Glioblastoma multiforme tissues.

2. Material and methods

2.1 Material

2.1.1 Search Strategy

To answer the questions addressed in this paper, the electronic database PubMed was searched for appropriate studies conducted in any country which investigated the relationship between human cytomegalovirus and glioblastoma multiforme i. e. sero-epidemiologically or by polymerase chain reaction (PCR) et cetera. The search in PubMed was performed while using some medical key words like "case control study" and "cytomegalovirus" and "glioblastoma multiforme" et cetera. The articles found where saved as a *.txt file while using the support of PubMed. The created *.txt file was converted into a *.pdf file. The abstracts where studied within the *.pdf file. Those articles were considered for a re-view which provided access to data without any data access barrier. Additionally the reference list of identified articles was used as a potential source of articles appropriate for this study.

2.1.2. The 2x2 Table

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

Table 1. The sample space of a contingency table.

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

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

2.1.3 The Studies not Analyzed

The studies of Baumgarten et al. (2014), Holdhoff et al. (2017) and Wrensch et al. (2005) which investatigated the relationship between HCMV serostatus and glioblastoma patients were not considered for a review. The study of Yamashita et al. (2014) did not detect HCMV DNA in any of the glioblastoma cases by real-time quantitative PCR (QPCR). Still, while using immunoblotting and immunohistochemistry tissue samples were partly positive according to Yamashita et al. (2014). Thus, it remains unclear the extent to which the methods used by Yamashita et al. (2014) were able to detect the entire HCMV genome when present. Yang et al. (2017) investigated the presence of HCMV genes in human glioblastoma multiforme cases by quantitative PCR using inappropriate HCMV *UL73*. The data were not re-analyzed.

2.1.4 The Studies Used to Analyze the Conditio Sine Qua non Relationship between HCMV and GBM

The studies used to analyze the conditio sine qua non relationship between HCMV and GBM are viewed by the **Table 2**.

Table 2. *Without* human cytalomegalovirus infection *no* glioblastoma multiforme.

Study Id	Year	Country	N	a_t	b_t	c_t	d_t	p(SINE)	X^2(Sine)	k	X^2(k)	p val (k)
Cobbs et al.	2002	USA	45	22	0	0	23	1	0.0114	1.0000	45.0000	< 0.0001
Mitchell et al.	2008	USA	90	42	0	3	45	0.9666667	0.1389	0.9354	78.7500	< 0.0001
Scheurer et al.	2008	USA	42	21	0	0	21	1	0.0119	1.0000	42.0000	< 0.0001
Dziurzynski et al.	2011	USA	10	5	0	0	5	1	**Rule of 3**	1.0000	-	-
Ranganathan et al.	2012	USA	90	73	2	2	13	0.9777778	0.0300	0.8400	63.5040	< 0.0001
Rahbar et al.	2012	Sweden	160	79	0	1	80	0.99375	0.0031	0.9876	156.0494	< 0.0001
Libard et al.	2014	Sweden	86	65	0	7	14	0.9186047	0.5868	0.7758	51.7593	< 0.0001
Ding et al.	2014	China	73	51	0	16	6	0.7808219	3.5858	0.4556	15.1547	0.0001
Wakefield et al.	2015	USA	48	14	0	10	24	0.7916667	3.7604	0.6417	19.7647	< 0.0001
Xing et al	2016	China	51	40	0	3	8	0.9411765	0.1453	0.8225	34.5032	< 0.0001
Stangherlin et al.	2016	Brazil	23	9	1	1	12	0.9565217	0.0250	0.8231	-	-
Slinger et al.	2010	Netherlands	42	20	**12***	1	**9***	0.9761905	0.0119	-	-	-
Lucas et al.	2011	USA	90	25	**25***	20	**20***	0.7777778	8.4500	-	-	-
Bhattacharjee et al.	2012	USA	34	16	**10***	1	**7***	0.9705882	0.0147	-	-	-
Rahbar et al.	2013	Sweden	150	74	**40***	1	**35***	0.9933333	0.0033	-	-	-
dos Santos et al.	2014	Brazil	44	21	**12***	1	**10***	0.9772727	0.0114	-	-	-
		Total	**1078**	577	102	67	332	0.9378479	16.19			
		Alpha =				0.05						
		Degrees of freedom (d. f.) =				15						
		X^2 Critical (SINE) =				**24.996**						
		X^2 Calculated (SINE) =				16.19						

***fictive values (due to a missing control group)**

The data as presented by Ranganathan et al. (2012) clearly demonstrated that HCMV genomes are associated with GBM tumors. Even if presentation and illustration of the data of the study of Ranganathan et al. (2012) was difficult to analyze, it was possible to use the data of HCMV UL69. Several of the studies presented above are missing an own control group. Especially the studies of dos Santos et al. (2014), Slinger et al. (2010), Bhattacharjee et al. (2012), Lucas et al. (2011), Holdhoff et al. (2017), Baumgarten et al. (2014) did not provide a suitable control group. This fact has no mathematical influence on the calculation of the chi square value of the necessary condition. Still, we calculated a fictive control group due to the fact that the seroprevalence of HCMV in the general human population ranges between 50 to 100% (Gandhi & Khanna, 2004; Ludwig & Hengel, 2009; Yi et al., 2013; Najafi et al., 2016).

2.1.5 The studies Used to Analyze the Necessary and Sufficient Condition Relationship and the Causal Relationship Between HCMV and GBM

Table 3. The necessary and sufficient condition relationship and the causal relationship between HCVM and GBM

Study Id	Year	Country	N	a_t	b_t	c_t	d_t	p(IMP^SINE)	X^2(IMP^SINE)	k	X^2(k)	p val (k)
Cobbs et al.	2002	USA	45	22	0	0	23	1	0.0227	1	45.00	< 0.0001
Mitchell et al.	2008	USA	90	42	0	3	45	0.966666667	0.1448	0.935	78.75	< 0.0001
Scheurer et al.	2008	USA	42	21	0	0	21	1	0.0238	1	42.00	< 0.0001
Dziurzynski et al.	2011	USA	10	5	0	0	5	1	**Rule of 3**	1	10.00	0.0016
Ranganathan et al.	2012	USA	90	73	2	2	13	0.955555556	0.0600	0.84	63.50	< 0.0001
Rahbar et al.	2012	Sweden	160	79	0	1	80	0.99375	0.0063	0.9875	156.05	< 0.0001
Libard et al.	2014	Sweden	86	65	0	7	14	0.918604651	0.5907	0.7757	51.76	< 0.0001
Ding et al.	2014	China	73	51	0	16	6	0.780821918	3.5907	0.4556	15.15	0.0001
Wakefield et al.	2015	USA	48	14	0	10	24	0.791666667	3.7783	0.6416	19.76	< 0.0001
Xing et al.	2016	China	51	40	0	3	8	0.941176471	0.1516	0.8225	34.50	< 0.0001
Stangherlin et al.	2016	Brazil	23	9	1	1	12	0.913043478	**Rule of 3**	0.8230	15.58	0.0001
		Total	**718**	421	3	43	251	0.935933148	8.3689	0.8608	532.06	
		Alpha =				0.05	Alpha =			0.05		
		Degrees of freedom (d. f.) =				9	Degrees of freedom (d. f.) =			11		
		X^2 Critical (SINE^IMP) =				**16.91**	**X^2 Critical (k) =**			**19.6751**		
	X^2 Calculated (SINE^IMP) =					8.368	X^2 Calculated (k) =			532.06		
									p value (k) <	0.0001		

2.2 Methods

2.2.1 Statistical Analysis

All statistical analyses (Barukčć. 1989; Barukčć. 2017a; Barukčć. 2017b; Barukčć. 2017c; Barukčć. 2018a; Barukčć. 2018b; Barukčć. 2018c) were performed with Microsoft Excel version 14.0.7166.5000 (32-Bit) Software (Microsoft GmbH. Munich. Germany). The level of significance was set to 0.05. The probabilities of the contingency table are viewed by the following table (**Table 4**).

Table 4. The probabitlities of a contingency table

		Conditioned B_t		
		Yes = +1	**No = +0**	**Total**
Condition A_t	**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**

2.2.2 Independence

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

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

2.2.3 Exclusion (A_t Excludes B_t and Vice Versa Relationship)

The mathematical formula of the *exclusion* relationship (A_t excludes B_t and vice versa) of a population was defined (Barukčć, 2016a; Barukčć, 2017a; Barukčć, 2017b; Barukčć, 2017c; Barukčć, 2018a; Barukčć, 2018b; Barukčć, 2018c) as

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

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

2.2.4 Necessary Condition (Conditio Sine Qua Non)

The mathematical formula of the *necessary* condition relationship (conditio sine qua non) of a population was defined (Barukčć, 2016a; Barukčć, 2017a; Barukčć, 2017b; Barukčć, 2017c; Barukčć, 2018a; Barukčć, 2018b; Barukčć, 2018c) as

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

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

2.2.5. Sufficient Condition (Conditio per Quam)

The mathematical formula of the *sufficient* condition relationship (conditio per quam) of a population was defined (Barukčć, 2016a; Barukčć, 2017a; Barukčć, 2017b; Barukčć, 2017c; Barukčć, 2018a; Barukčć, 2018b; Barukčć, 2018c) as

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

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

2.2.6 The X^2 Goodness of Fit Test of a Necessary Condition

Under conditions where the chi-square goodness of fit test (Pearson, 1900) cannot be used it is possible to use an approximate and conservative (one sided) confidence interval known as *the rule of three* (Rumke, 1975; Hanley et

al., 1983; Louis, 1981; Jovanovic et al., 1997). According to the definition of the conditio sine qua non relationship it is

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

or

$$p\left(A_t \cap B_t\right) + 1 - p\left(B_t\right) \equiv +1 \tag{6}$$

Rearranging this equation, we obtain the essential foundation of the conditio sine qua non relationship as

$$p\left(A_t \cap B_t\right) = p\left(B_t\right) \tag{7}$$

and equally our starting point of the derivation of chi-square value of the conditio sine qua non relationship. Multiplying equation before by the population or sample/population size N. it is

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

or

$$N \times p\left(A_t \cap B_t\right) - N \times p\left(B_t\right) = 0 \tag{9}$$

The square operation yields

$$\left(N \times p\left(A_t \cap B_t\right) - N \times p\left(B_t\right)\right) \times \left(N \times p\left(A_t \cap B_t\right) - N \times p\left(B_t\right)\right) = 0 \times 0 \tag{10}$$

Dividing by $N \times p(B_t)$ we obtain

$$\frac{\left(N \times p\left(A_t \cap B_t\right) - N \times p\left(B_t\right)\right)^2}{N \times p\left(B_t\right)} = 0 \tag{11}$$

which is equivalent with

$$\frac{\left(a_t - \left(B_t\right)\right)^2}{\left(B_t\right)} = \frac{\left(a_t - \left(a_t + c_t\right)\right)^2}{\left(B_t\right)} = \frac{\left(c_t\right)^2}{\left(B_t\right)} = 0 \tag{12}$$

Adding $((b_t+d_t) - (\underline{B}_t))^2/\underline{B}_t = ((b_t+d_t) - (b_t+d_t))^2/\underline{B}_t = 0$ yields

$$\frac{\left(c_t\right)^2}{\left(B_t\right)} + 0 = 0 + 0 \tag{13}$$

Using *the continuity correction (Yates, 1934),* the chi-square value of a conditio sine qua non distribution before changes to

$$\chi^2\left(SINE\right) \equiv \frac{\left(c_t - \left(\frac{1}{2}\right)\right)^2}{\left(B_t\right)} + 0 = 0 \tag{14}$$

The use of the continuity correction should follow the rules of statistics as established and valid today. This definition of the X^2 distribution of a *conditio sine qua non* distribution (degrees of freedom = 2-1=1) is more precise than already published formulas. In this context, it is not necessary to improve the definition of the X^2 distribution of a *conditio per quam* distribution as already published. The significance of a causal relationship k which is $k > 0$ is supported by a significant conditio sine qua non relationship; otherwise the result of a study should be treated with cautious.

2.2.7 The X² Goodness of Fit Test of the Exclusion Relationship

According to the definition of the exclusion relationship (Barukčć, 2016a; Barukčć, 2017a; Barukčć, 2017b; Barukčć, 2017c; Barukčć, 2018a; Barukčć, 2018b; Barukčć, 2018c) it is

$$p(b_t) + p(c_t) + p(d_t) \equiv +1 \tag{15}$$

Rearranging this equation, we obtain

$$p(b_t) = 1 - p(c_t) - p(d_t) = 1 - \left(p(c_t) + p(d_t)\right) \equiv 1 - p(\underline{A}_t) = p(A_t) \tag{16}$$

and

$$p(c_t) = 1 - p(b_t) - p(d_t) \equiv 1 - \left(p(b_t) + p(d_t)\right) = 1 - p(\underline{B}_t) = p(B_t) \tag{17}$$

The chi square goodness of fit test of the exclusion relationship can be derived as follows.

$$\begin{aligned} N \times p(b_t) &= N \times p(A_t) \\ \left(N \times p(b_t) - N \times p(A_t)\right) &= 0 \\ \left(N \times p(b_t) - N \times p(A_t)\right) \times \left(N \times p(b_t) - N \times p(A_t)\right) &= 0 \times 0 \end{aligned}$$

$$\frac{\left(N \times p(b_t) - N \times p(A_t)\right)^2}{N \times p(A_t)} = \frac{0}{N \times p(A_t)} = 0$$

$$\begin{aligned} \chi^2(b_t) = \frac{\left(N \times p(b_t) - N \times p(A_t)\right)^2}{N \times p(A_t)} = \frac{\left(b_t - (a_t + b_t)\right)^2}{A_t} = \frac{\left(-(a_t)\right)^2}{A_t} &= 0 \\ \chi^2(b_t) = \frac{\left(-(a_t) - 0{,}5\right)^2}{A_t} &= 0 \end{aligned} \tag{18}$$

and as

$$\begin{aligned} N \times p(c_t) &= N \times p(B_t) \\ \left(N \times p(c_t) - N \times p(B_t)\right) &= 0 \\ \left(N \times p(c_t) - N \times p(B_t)\right) \times \left(N \times p(c_t) - N \times p(B_t)\right) &= 0 \times 0 \end{aligned}$$

$$\frac{\left(N \times p(c_t) - N \times p(B_t)\right)^2}{N \times p(B_t)} = \frac{0}{N \times p(B_t)} = 0 \tag{19}$$

$$\chi^2(b_t) = \frac{\left(N \times p(c_t) - N \times p(B_t)\right)^2}{N \times p(B_t)} = \frac{\left(c_t - (a_t + c_t)\right)^2}{B_t} = \frac{\left(-(a_t)\right)^2}{B_t} = 0$$

$$\chi^2(c_t) = \frac{\left(-(a_t) - 0{,}5\right)^2}{B_t} = 0$$

The chi square value with degree of freedom 2-1=1of the exclusion relationship with a *continuity correction* (Yates, 1934) can be calculated as

$$\chi^2(\mathrm{EXCL}) = \frac{\left(-(a_t) - 0{,}5\right)^2}{A_t} + \frac{\left(-(a_t) - 0{,}5\right)^2}{B_t} \tag{20}$$

A significant causal relationship k which is **$k < 0$** is supported by an exclusion relationship otherwise the results of a study can be interpreted with some cautious. It would be a mistake not to consider all aspects of the relationship between cause and effect. Finally, it should be noted that the fundamental concepts of necessary and sufficient conditions is one of the handy tools which can help us to proof causal claims too.

2.2.8 The Mathematical Formula of the Causal Relationship k

The mathematical formula of the causal relationship k (Barukčć, 2016a; Barukčć, 2017a; Barukčć, 2017b; Barukčć, 2017c; Barukčć, 2018a; Barukčć, 2018b; Barukčć, 2018c; Barukčć, 2018d; Barukčć, 2018e; Barukčć, 2018f; Barukčć, 2018g) is defined *at every single event, at every single Bernoulli trial t,* as

$$k\left(A_t,B_t\right) \equiv \frac{\left(p\left(A_t \cap B_t\right)-\left(p\left(A_t\right)\times p\left(B_t\right)\right)\right)}{\sqrt[2]{\left(p\left(A_t\right)\times p\left(\underline{A}_t\right)\right)\times\left(p\left(B_t\right)\times p\left(\underline{B}_t\right)\right)}} \tag{21}$$

where A_t denotes the cause and B_t denotes the effect. The chi-square distribution can be applied to determine the significance of causal relationship k. Pearson's concept of correlation (Pearson, 1896) is not identical with causation, causation (Heisenberg, 1927; Einstein & Podolsky & Rosen, 1935; Bohr, 1937; Einstein, 1948) is not identical with correlation. In particular, the relationship between correlation and causation has already been discussed in many publications (Wright, 1921; Sober, 2001). Thus far, repeating itself over and over again on this topic is only a waste of time and will not contribute anything new to further scientific progress.

2.2.9 The 95% Confidence Interval of the Causal Relationship k

A confidence interval (CI) of the causal relationship k calculated from the statistics of the observed data can help to estimate the true value of an unknown population parameter with a certain probability. Let the sample mean S be

$$S = \overline{k\left(A_t,B_t\right)} = \frac{k\left(A_1,B_1\right)+k\left(A_2,B_2\right)+\ldots+k\left(A_n,B_n\right)}{n} = \frac{\sum_{t=+1}^{n} k\left(A_t,B_t\right)}{n} \tag{22}$$

Since $k(A_t,B_t)$ is Bernoulli(p) distributed with $E(k(A_t,B_t)) = (1\times p(k(A_t,B_t))) + (0\times(1- p(k(A_t,B_t))) = p(k(A_t,B_t))$ where $E(k(A_t,B_t))$ denotes the expected value of $k(A_t,B_t)$ it is

$$E\left(S\right) = p\left(k\left(A_t,B_t\right)\right) \text{ and } \sigma\left(S\right)^2 = \frac{p\left(k\left(A_t,B_t\right)\right)\times\left(1-p\left(k\left(A_t,B_t\right)\right)\right)}{n} \tag{23}$$

where $\sigma(S)^2$ denotes the variance of the sampling distribution of $p(k(A_t,B_t))$. When the sample size is not too small, the central limit theorem based normal approximation can be used to estimate the confidence interval (CI) as

$$p\left(k\left(A_t,B_t\right)\right) \pm\left(Z\times\sqrt[2]{\frac{p\left(k\left(A_t,B_t\right)\right)\times\left(1-p\left(k\left(A_t,B_t\right)\right)\right)}{n}}\right) = p\left(k\left(A_t,B_t\right)\right) \pm\left(\sqrt[2]{\frac{Z^2}{n}\times p\left(k\left(A_t,B_t\right)\right)\times\left(1-p\left(k\left(A_t,B_t\right)\right)\right)}\right) \tag{24}$$

where $p(k(A_t,B_t))$ denotes the proportion of successes in a Bernoulli trial process and Z is the $(1–(\alpha/2))$ quantile of a standard normal distribution. For a 95% confidence level $Z \sim 1.96$, For an unknown standard deviation the Student's t distribution t can be used as the critical value. Still, it is known that $\sigma(S)^2$ has the maximum value $(1/(4\times n))$ when $p=1/2$ and we have

$$p\left(k\left(A_t,B_t\right)\right) \pm\left(\sqrt[2]{\frac{Z^2}{4\times n}}\right) \Leftrightarrow p\left(k\left(A_t,B_t\right)\right) \pm\left(\sqrt[2]{\frac{1.96}{4\times n}}\right) \approx p\left(k\left(A_t,B_t\right)\right) \pm\left(\sqrt[2]{\frac{1}{2\times n}}\right) \tag{25}$$

The proposed approximation is of use even under circumstances where $p(\ldots) = 0.9999 \ldots 999 \sim p=1$. In this context, we obtain the critical value $p_{critical}$ approximately as $p_{critical} = 1 - (1/(2n))^{1/2}$. In particular, the concept of Chebyshev's inequality (Tchébychef, 1867) is profound because the same inequality is true for every distribution even if the distribution isn't normal. Thus far, Chebyshev's inequality allows calculating the 95% confidence of the causal relationship k and so by the Chebyshev inequality it is

$$p\left\{p\left(k\left(A_t,B_t\right)\right)-c\times\sqrt[2]{\sigma\left(S\right)^2}<S<p\left(k\left(A_t,B_t\right)\right)+c\times\sqrt[2]{\sigma\left(S\right)^2}\right\}\geq 1-\frac{1}{c^2} \tag{26}$$

were the right side has the value 0.95 when $c=(20)^{1/2}$. This is the case since $(1-(1/c^2))=0.95$ or $0.05=(1/c^2)$ or $c^2=(1/0.05)$ or $c^2=(100/5)$ or $c^2=20$ or $c=(20)^{1/2}$. Thus far, if S does lie in the interval

$$\left\{p\left(k\left(A_t,B_t\right)\right)-\sqrt[2]{20\times\sigma\left(S\right)^2},p\left(k\left(A_t,B_t\right)\right)+\sqrt[2]{20\times\sigma\left(S\right)^2}\right\} \tag{27}$$

then $p(k(A_t,B_t))$ itself must be in the interval

$$\left\{S-\sqrt[2]{20\times\sigma\left(S\right)^2},S+\sqrt[2]{20\times\sigma\left(S\right)^2}\right\} \tag{28}$$

which is equally the 95% confidence interval for an unknown parameter $p(k(A_t,B_t))$. Again, $\sigma(S)^2$ has the maximum value $(1/(4\times n))$ when $p=1/2$, so we have

$$\left\{S-\sqrt[2]{\frac{20\times 1}{4\times n}},S+\sqrt[2]{\frac{20\times 1}{4\times n}}\right\} \tag{29}$$

or **the 95% interval for the causal relationship k** as

$$\left\{k\left(A_t,B_t\right)-\sqrt[2]{\frac{5}{n}},k\left(A_t,B_t\right)+\sqrt[2]{\frac{5}{n}}\right\} \tag{30}$$

2.2.10 Odds Ratio

The odds ratio (OR) is given (Cornfield, 1951; Edwards, 1963; Mosteller, 1968) by

$$OR\left(A_t,B_t\right)\equiv\frac{a_t/b_t}{c_t/d_t}=\frac{a_t\times d_t}{c_t\times b_t} \tag{31}$$

Under conditions were $c_t=0$ we have a conditio sine qua non relationship while the odds ratio collapses. Under conditions were $b_t=0$ we have a conditio per quam relationship but the odds ratio collapses again, since to date it is not generally accepted (Barukčić & Barukčić, 2016b; Barukčić, 2018d) to divide by zero. To avoid confusion on this issue, 0.5 is added to the cells a_t, b_t, c_t, d_t (Pagano & Gauvreau, 2018), if zero causes some problems with the calculation of the odds ratio or its standard error which is often very misleading. In point of fact, the odds ratio (OR) is nothing more but *Yule's coefficient of association Q* (Yule, 1900) re-written (Warrens, 2008) in a non-normalized form and given by

$$Q\left(A_t,B_t\right)\equiv\frac{OR\left(A_t,B_t\right)-1}{OR\left(A_t,B_t\right)+1}=\frac{\frac{\left(a_t\times d_t\right)}{\left(b_t\times c_t\right)}-1}{\frac{\left(a_t\times d_t\right)}{\left(b_t\times c_t\right)}+1}=\frac{\frac{\left(a_t\times d_t\right)-\left(b_t\times c_t\right)}{\left(b_t\times c_t\right)}}{\frac{\left(a_t\times d_t\right)+\left(b_t\times c_t\right)}{\left(b_t\times c_t\right)}}=\frac{\left(a_t\times d_t\right)-\left(b_t\times c_t\right)}{\left(a_t\times d_t\right)-\left(b_t\times c_t\right)} \tag{32}$$

If Q = 0 then there is no association. Yule's coefficient of association, Q, and thus far Odds ratio itself, has been severely criticized by Karl Pearson (1857–1925), the long-time and rarely challenged leader of statistical science and by Heron (Pearson & Heron, 1913). The standard error and 95% confidence interval of the odds ratio (OR) can be calculated according to Altman (Altman, 1991). The standard error of the log odds ratio is given by

$$SE\left(\ln\left(OR\left(A_t,B_t\right)\right)\right)\equiv\sqrt[1]{\frac{1}{a_t}+\frac{1}{b_t}+\frac{1}{c_t}+\frac{1}{d_t}} \tag{33}$$

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

$$95\%\,\mathrm{CI} = \exp\left(\ln\left(\mathrm{OR}\left(\mathrm{A_t},\mathrm{B_t}\right)\right) - \left(1.96 \times \mathrm{SE}\left(\ln\left(\mathrm{OR}\left(\mathrm{A_t},\mathrm{B_t}\right)\right)\right)\right)\right) \text{ to } \exp\left(\ln\left(\mathrm{OR}\left(\mathrm{A_t},\mathrm{B_t}\right)\right) + \left(1.96 \times \mathrm{SE}\left(\ln\left(\mathrm{OR}\left(\mathrm{A_t},\mathrm{B_t}\right)\right)\right)\right)\right) \quad (34)$$

2.2.11 The Chi Square Distribution

The following critical values of the chi square distribution as visualized by **Table 5** are used in this publication.

Table 5. 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 a Human Cytomegalovirus Infection no Glioblastoma Multiforme.

Claims.

Null hypothesis:

A cytomegalovirus infection is a necessary condition (a conditio sine qua non) of glioblastoma multiforme. In other words, the sample distribution of the study analyzed agrees with the hypothetical (theoretical) distribution of a necessary condition.

Alternative Hypothesis:

A cytomegalovirus infection is not a necessary condition (a conditio sine qua non) of glioblastoma multiforme. In other words, the sample distribution of the study analyzed 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 results of the re-analyses of the data reviewed by this article (**Table 2**) which investigated the relationship between a cytomegalovirus infection and glioblastoma multiforme are viewed by the table (**Table 2**). Altogether, 16 studies were meta-analyzed while the level of significance was alpha = 0.05. In toto, 16 out of 16 studies provide significant evidence of a conditio sine qua non relationship between a cytomegalovirus infection and glioblastoma multiforme. The study of Dziurzynski et al. (2011) was significant according to the rule of three. *Some of the studies were performed without a control group which had no mathematical effect on the calculation of the chi square value of the conditio sine qua non relationship*. The most of the studies analyzed were able to provide evidence of a significant, positive cause effect relationship. In other words, the data analyzed support the Null-hypothesis: *without* a cytomegalovirus infection *no* glioblastoma multiforme (X^2 Calculated (SINE) = 16.19 and is less than X^2 Critical (SINE) = 24.996). **Q. e. d.**

3.2 HCMV is a Necessary and Sufficient Condition of Glioblastoma Multiforme

Null Hypothesis:

A cytomegalovirus infection is a *necessary and sufficient condition* of glioblastoma multiforme. In other words, the sample distribution of the study analyzed agrees with the hypothetical (theoretical) distribution of a necessary and sufficient condition.

Alternative Hypothesis:

A cytomegalovirus infection is not a *necessary and sufficient condition* of glioblastoma multiforme. In other words, the sample distribution of the study analyzed does not agree with the hypothetical (theoretical) distribution of a necessary and sufficient condition.

The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0.05.

Proof.

The results of the re-analyses of the data reviewed by this article (**Table 2**) which investigated the necessary and sufficient condition relationship between a cytomegalovirus infection and glioblastoma multiforme are viewed by the table (**Table 3**). Altogether, it was possible to consider 11 studies with a sample size of N=718 for a meta-analyzed while the level of significance was alpha = 0.05. In toto, 11 out of 11 studies provide significant evidence (**Table 3**) of a necessary and sufficient conditions relationship (X^2 Calculated (SINE^IMP) = 8.3689 is less than X^2 Critical (SINE^IMP) = 16.918) while the causal relationship between a cytomegalovirus infection and glioblastoma multiforme was positive and significant. The studies of Dziurzynski et al. (Dziurzynski et al., 2011) and Stangherlin et al. (Stangherlin et al., 2016) were smaller than N = 30 and were analyzed according to the rule or three. Especially, the study of Rahbar et al. (Rahbar et al., 2012) detected HCMV-IEA in 79 (99%) of 80 GBM tumor cells *but not in surrounding non-tumor cells*. In general, a cytomegalovirus infection is a necessary and sufficient condition of glioblastoma multiforme (**Table 3**). **Q. e. d.**

3.3 HCMV is the Cause of Glioblastoma Multiforme

Several studies presented *missed an appropriate control groups* and were not considered for the analyses of the causal relationship between HCMV and GBM (**Table 2**).

Claims.

Null Hypothesis:

A cytomegalovirus infection is not the cause of glioblastoma multiforme. In other words. $k = 0$.

Alternative Hypothesis:

A cytomegalovirus infection is the cause of glioblastoma multiforme. In other words. $k \neq 0$. .

The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0.05.

Proof.

The results of the re-analyses of the data reviewed by this article (**Table 2**) which investigated the causal relationship between a cytomegalovirus infection and glioblastoma multiforme are viewed by the table (**Table 3**). Altogether, 11 studies were meta-analyzed while the level of significance was alpha = 0.05. In toto, 11 from 11 studies provided significant evidence of a causal relationship between a cytomegalovirus infection and glioblastoma multiforme. The studies of Dziurzynski et al. (2011) and Stangherlin et al. (Stangherlin et al., 2016) were smaller than N = 30. In the same respect, a cytomegalovirus infection is a necessary (**Table 2**) and a necessary and sufficient condition of glioblastoma multiforme (**Table 3**). In other words, *without* a HCVM infection *no* GBM. Thus far, the conclusion is inescapable. Human cytomegalovirus is the cause of glioblastoma multiforme ($k \sim 0.8608$, X^2 Calculated (k) =532.06 and is greater than X^2 Critical (k) =19.6751). **Q. e. d.**

4. Discussion

Due to the conflicting reports concerning the presence of the human cytomegalovirus in glioma tissue the association between human cytomegalovirus (HCMV) infection and glioblastoma is still a source of debate. While some studies detected HCMV DNA, RNA and proteins et cetera in GBM tissues others studies (Taha et al., 2016) have not. In most of the previous studies, only a very restricted number of HCMV viral targets with different sensitive techniques (Immunoglobulin G antibodies. immunohistochemical analysis, PCR, in situ hybridization, immunohistochemistry, real-time PCR et cetera) accompanied by a very different personal skill were analysed.

Thus, the question is justified to which extent was the (entire) viral genome detected at all when present. Furthermore, complicating issues are creating uncertainty about the results of the studies above which detected a strong relationship between HCMV with GBM tumours due to the relatively limited study population and non-randomization. In particular, sample quality (age or method of preservation) and primer selection has substantial effects on the outcome of a study. All these factors may have contributed to the few studies which were not able (Taha et al., 2016) to detect HCMV in GBMs tissues. In contrast to results like these, HCMV presence has been found in about 90-100% (Cobbs et al., 2002; Mitchell et al., 2008; Rahbar et al., 2012; Söderberg-Nauclér et al., 2013) of GBM tumors. Söderberg-Nauclér et al. (Söderberg-Nauclér et al., 2013) examined more than 250

cases of glioblastoma while only one of these patients was CMV-negative. Due to the missing control group, the very convincing data of the study of Söderberg-Nauclér et al. (2013) were not considered for causal analysis while the conditio sine qua non relationship is highly significant. Rahbar et al. (2012) detected HCMV infection in 79 of 80 patients (99%) GBM tumor samples. The surrounding non-tumor cells of the same patient served as the control group. Rahbar et al. (2012) were not able to detect HCMV in any of the controls i. e. HCMV was not detected in surrounding non-tumor cells. The results of the study of Rahbar et al. (2012) are viewed by **Table 6**. The single study of Rahbar et al. (2012) has provided striking evidence that HCMV infection is a necessary, a sufficient and a necessary and sufficient condition of GBM while the cause effect relationship between HCMV and GBM is highly significant. Thus far and ultimately, according to the study of Rahbar et al. (2012) HCMV is the cause of GBM and much more than this. The evidence of the studies presented cannot be ignored too. In point of fact, several studies did not present a suitable control group (**Table 2**). Thus far, it was not possible to consider these studies to calculate the causal relationship k between HCVM and GBM. Besides of this limitation, the missed control group had no mathematical influence on the calculation of the chi square value of the necessary condition distribution. All but the study of Lucas et al. (2011) underdetermine empirically the Null-hypothesis: *without* HCVM *no* GBM. In other words, GBM cannot develop without a HCVM infection. It is obvious that the evidence of the relationship between HCVM *and* GBM is much stronger then outlined just before. In toto, 11 studies with a sample size of n=718 (**Table 3**) support the Null-hypothesis that HCMV is a necessary and sufficient condition of GBM while the cause effect relationship k between HCMV and GBM is highly significant (**Table 3**). Ultimately, the evidence documented is extensive, solid and sufficient to justify the hypotheses that HCMV is the cause of GBM.

Table 6. The Study of Rahbar et al. (Rahbar et al., 2012)

		GBM <B>		
		Yes	No	Total
HCMV-IEA <A>	Yes	79	0	79
	No	1	80	81
	Total	80	80	160
			k =**0.98757716**	
			p value (k) =**8.258E-36**	
			WITHOUT <A> NO <B>.	
			p (SINE) =0.99375	
			X^2(SINE) =**0.003125**	
			IF <A> THEN <B>	
			p (IMP)=1	
			X^2 (IMP)=**0.00316456**	
			<A> is SINE and IMP of <B>	
			p(SINE ^ IMP) =0.99375	
			X^2(SINE ^ IMP) =**0.00628956**	

To date, aggressive treatment (Stupp et al., 2005) of glioblastoma multiforme with surgery, radiation therapy and chemotherapy are relatively ineffective due to the known aggressive nature of GBM and provides only a very limited overall survival benefit for these patients. In fact, there is no effective therapy or cure for glioblastoma multiforme while the life of the patients suffering from this disease is extremely (Smoll et al., 2013) endangered. New therapeutic strategies should be offered to counteract the poor prognosis of GBM. HCMV is the cause of GBM and has a major impact on morbidity, mortality and survival of GBM patients too. In this context, it is necessary to consider a highly effective and simple to practice anti-HCMV therapeutic strategy. HCMV appears to control the PGE 2 synthesis and the expression of COX-2 (Baryawno et al., 2011) in medulloblastomas. Valganciclovir and specific COX-2 inhibitors (Etoricoxib, Celecoxib) are able to prevent HCMV replication and to reduce medulloblastoma tumor cell growth in vitro and in vivo (Baryawno et al., 2011). Anti-CMV treatment has already reduced the growth of medulloblastoma by 72% in animal model (Baryawno et al., 2011). The double-blind Valcyte Treatment of Glioblastoma Patients in Sweden (VIGAS) clinical trial of valganciclovir (Söderberg-Nauclér et al., 2013) found that cases receiving at least 6 months of antiviral therapy had an significantly increased rate of 2-year survival (50% vs. 20.6%, P<0.001) compared with controls. In fact, an optimal treatment of CMV can help to improve the outcome of GBM patient and may focus additionally and primarily on ganciclovir or valganciclovir (Söderberg-Nauclér et al., 2013) and other similar drugs. In particular, drugs like etanercept, etoricoxib (Hung et al., 2017) and leflunomide (John et al., 2004; Suissa et al., 2006) are

simple to work with and are to some extent effective against human cytomegalovirus too. Ganciclovir, valganciclovir (Söderberg-Nauclér et al., 2013), etanercept, etoricoxib (Hung et al., 2017) and leflunomide (John et al., 2004; Suissa et al., 2006) is of strategic importance at least as an add-on therapy in patients suffering from glioblastoma multiforme. Thus far, it is useful to point out that John et al. (John et al., 2004) documented the efficacy of leflunomide in humans with CMV disease who received loading dose of 100 mg of leflunomide once daily on days 1–3 and then 20 mg once daily for three months. To date and for preliminary purposes, Etanercept, etoricoxib and leflunomide should become additionally one part of an effective intervention against glioblastoma multiforme. We see the bright colors and the beauty of galaxies so far away from our earth and listen very carefully to the heartbeat of deep space. I stubbornly refuse to accept the conclusions that we are unable to develop a low cost and highly effective vaccine (Inoue et al., 2018) against a CMV infection and even an appropriate DNA CMV therapeutic vaccine too. Historically this hope arises out of the experience that together we have achieved what divided was impossible. In addition, such an undertaking is an urgent and major public health duty too.

5. Conclusion

The studies presented in this publication provided a very impressive evidence of a cause effect relationship between HCMV and GBM. In any case, this publication invites us in an overwhelmingly plausible manner to leave aside any doubts and any uncertainty we might have about whether there is a cause effect relationship between HCMV and GBM. For a different view, until a contrary and more convincing experimental objections have been raised against the causal relationship between HCMV and GBM, according to this analysis it is necessary and justified to accept in agreement with the majority of studies presented that human cytomegalovirus is the cause of glioblastoma multiforme.

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Dedicated to Celina.

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