Without a varicella zoster virus infection, no schizophrenia

Ilija Barukčić[1]

[1] Internist, Horandstrasse, DE-26441 Jever, Germany

Correspondence: Ilija Barukčić, Horandstrasse, DE-26441 Jever, Germany. Tel: 49-4466-333.

E-mail: Barukcic@t-online.de

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Abstract

Objective: Despite decades of research and major efforts, a cause or the cause of schizophrenia is still not identified. Although many studies indicate that infectious agents are related to schizophrenia no definite consensus has been reached on this issue.

Methods: The purpose of this study was to investigate relationship between varicella zoster virus (VZS) and schizophrenia while relying on new statistical methods.

Results: The meta-analysis results provide striking evidence that VZV is a necessary condition of schizophrenia.

Conclusions: There is some weak evidence that VZV infection is the cause of schizophrenia.

Keywords: ***Varicella zoster virus, schizophrenia, causal relationship.***

1. Introduction

Little is known about the etiology of schizophrenia. The herpes simplex family viruses (herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), herpes simplex virus type 3 (HSV-3) or varicella-zoster virus (VZV), herpes simplex virus type 4 (HSV-4) or Epstein-Barr virus (EBV), herpes simplex virus type 5 (HSV-5) or cytomegalovirus (CMV) and human herpes virus type 6 (HHV-6)) and other are often a significant cause of encephalitis and theoretically a possible etiologic agents for schizophrenia. No wonder, the hypothesis that viruses or other infectious agents may cause schizophrenia dates to the 19th century. The French neurologist Jean Esquirol wrote: ''Many authors assure us that mental alienation is epidemic. It is certain that there are years, when, independently of moral causes, insanity seems suddenly to extend to a great number of individuals.'' (Esquirol & Hunt, 1845, p. 33). By time bacteria were becoming known and Theodore Deecke, the pathologist of the New York State Lunatic Asylum, suggested in 1874 in his article ''On the Germ-Theory of Disease'' (Deecke, 1874) by the American Journal of Insanity (now the American Journal of Psychiatry) an infectious hypothesis of schizophrenia too. However, findings from studies including review articles (Yolken & Torrey, 1995) which goes back even decades (Alexander et al., 1992; Delisi et al., 1986; Gotlieb-Stematsky et al., 1981; King et al., 1985) are mixed. As a trial to direct the research on schizophrenia into the correct direction a hypothesis-generating meta- or re-analysis of one case-control study was conducted.

2. Material and methods

Varicella-zoster virus (Arvin, 1996) is a ubiquitous human herpes virus that causes varicella (chicken pox), a common childhood illness, characterized by fever, viremia, and scattered vesicular lesions of the skin and herpes zoster (shingles). Herpes zoster itself is caused by VZV reactivation and is characterized by a localized, painful, vesicular rash involving one or adjacent dermatomes. VZV IgG indicates VZV positivity or latency while changes of VZV IgG during VZV latency might point to recent or frequent VZV reactivation.

2.1. Material

2.1.1. Search Strategy

For the questions addressed in this paper the study of de Witte et al. (de Witte et al., 2015) was re-analyzed.

Table 1. ***The article selection process of the studies analyzed***

1. Identification of records	Size	Total
Records identified by searching in the databases		
PubMed	1	
		1
2. Clean-up of search (Screening)		
Records removed after verifying duplication, excluded by title, excluded due to other reasons		0
3. Eligibility		
Articles evaluated for eligibility		1
Articles excluded for various reasons	0	
4. Included		
Articles included in the meta-analysis (**Table**)		1

Adopted from PRISMA 2009 (Moher, Liberati, Tetzlaff, & Altman, 2009).

2.1.2. VZV IgG-Studies considered for re-analysis

de Witte et al. (de Witte et al., 2015) examined the seroprevalence and titer of IgG antibodies against several herpes simplex viruses in plasma of 368 adult patients with a schizophrenia spectrum disorder. This VZV IgG sero-epidemiological study as presented by **Table 2** was considered for meta-analysis.

Table 2. *VZV* is the cause of schizophrenia.

The study of de Witte et al., 2015.

Country: **The Netherlands**		Schizophrenia YES	NO	
VZV IgG	YES	352	16	**368**
	NO	16	784	800
		368	800	**1168**

PMID: 27336045

Statistical analysis

Causal relationship k =	**0,937**	95 % CI (k) :	(0,871	to	1,002)
P value (k | HGD) =	**0,0000000000**	Chi Sq.(k) =	1024,421		
p(IOI) =	**0,000**	**p(IOU) =**	**0,370**	**p(IOU) + p(IOI) =**	**0,370**
p (SINE) =	**0,986**	**X^2(SINE|Bt) =**	**0,696**	X^2(SINE|At) =	0,320
P likely (SINE)=	0,986	P Value (SINE)=	0,014		
p (IMP) =	**0,986**	X^2(IMP| At)) =	0,696	X^2(IMP|Bt) =	0,320
P likely (IMP) =	0,986	P Value (IMP) =	0,014		
p (SINE ^ IMP) =	**0,973**	X^2(SINE^IMP|At) =	1,016	X^2(SINE^IMP|Bt) =	1,016
p likely (SINE^IMP)=	0,973	p Value (SINE^IMP)=	0,027		
p (EXCL) =	**0,699**	X^2(EXCL| At)=	336,696	X^2(EXCL|Bt)=	336,696
P (Likely EXCL)=	0,740	P Value (EXCL)=	0,260		
Odds ratio (OR) =	1078,000	95 % CI (OR) :	(533,031	to	2180,142)

Remark/Critique: **Fictive Control Group.**

2.1.3. Fictive control group

The *control group* used by de Witte et al. (de Witte et al., 2015) was very inappropriate. Both, the index of independence (IOI) and the index of unfairness (IOU) indicate highly biased data (p(IOI)=0,405; p(IOU) = 0,537; p(IOU)+p(IOI) =0,942). Therefore, it was not possible to consider the control group of de Witte et al. (de Witte et al., 2015) for this purposes. In point of fact, it is not very probable that newborn children suffer from schizophrenia. However, a re-infection with varicella zoster virus (VZV) in pregnancy of the mother may lead to a VZV infection of the newborn too. The estimated risk of congenital varicella syndrome (CVS) has been reported at 0.8 per 100,000 live births (Khandaker et al., 2011), while CVS as a severe condition may affect about 2% (Mirinaviciute, Barlinn, Gjeruldsen Dudman, & Flem, 2019). With this background information, we constructed the following **"fictive" control group** and analyzed the data. To achieve an optimal p(IOI) it is appropriate and necessary that **c = b**. Since c = 16 it follows that b = 16, while b denotes the number of VZV positive newborn which do not suffer from schizophrenia. The number 16 is equal to 2 % of the control group or 16/(control group) = 2/100. It follows that the control group should be (100*16/2) = 800.

2.2. Methods

2.2.1. Definitions

Definition 1. (The 2x2 Table)

Karl Pearson (K. Pearson, 1904) introduced in 1904 the notion of a contingency table (I. Barukčić, 2019a, 2019d) or two by two table. Especially the relationships between Bernoulli (i. e. Binomial) distributed random variables can be examined by contingency tables. Thus far, let a Bernoulli distributed random variable A_t occur/exist et cetera with the probability $p(A_t)$ at the Bernoulli trial (period of time) t. Furthermore, let another Bernoulli distributed random variable B_t occur/exist et cetera with the probability $p(B_t)$ at the <u>same</u> Bernoulli trial (period of time) t. Let $p(a_t)= p(A_t \cap B_t)$ denote the joint probability distribution of A_t and B_t at the <u>same</u> Bernoulli trial (period of time) t. The following table (**Table 7**) may show the relationships in more details.

Table 3. The probabitlities of a contingency table

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

In this context, it is *per definitionem*

$$
\begin{array}{ccccc}
p(A_t) & \equiv & p(a_t) + p(b_t) & = & 1 - p(\underline{A}_t) \\
p(B_t) & \equiv & p(a_t) + p(c_t) & = & 1 - p(\underline{B}_t) \\
p(a_t) & \equiv & p(A_t \cap B_t) & = & 1 - p(b_t) - p(c_t) - p(a \\
+1 & \equiv & p(A_t) + p(\underline{A}_t) & = & p(B_t) + p(\underline{B}_t) \\
+1 & \equiv & p(a_t) + p(b_t) & + & p(c_t) + p(d_t) \\
p(B_t) + p(\Lambda_t) & \equiv & p(A_t) & = & 1 - p(\underline{B}_t) + p(\Lambda_t) \\
p(\underline{A}_t) & = & 1 - \left(1 - p(\underline{B}_t) + p(\Lambda_t)\right) & = & p(\underline{B}_t) - p(\Lambda_t) \\
p(\Lambda_t) & = & p(A_t) - p(B_t) & = & p(b_t) - p(c_t) \\
p(b_t) + p(c_t) & = & \left(2 \times p(c_t)\right) + p(\Lambda_t) & = & 1 - p(a_t) - p(d_t)
\end{array}
\quad (1 \;)
$$

while +1 may denote *the normalized sample space* of A_t and B_t. Under circumstances were *the probability of an event is* ***constant*** *from trial to trial* (i. e. Binomial distribution), the relationships above simplifies. It is *per definitionem*

$$
\begin{array}{lclcl}
A & \equiv & n \times p(a_t) + n \times p(b_t) & = & n \times p(A_t) \\
B & \equiv & n \times p(a_t) + n \times p(c_t) & = & n \times p(B_t) \\
a & \equiv & n \times p(a_t) & = & n \times p(A_t \cap B_t) \\
b & & n \times p(b_t) & & \\
c & & n \times p(c_t) & & \\
d & & n \times p(d_t) & & \\
n & \equiv & n \times p(a_t) + n \times p(b_t) & + & n \times p(c_t) + n \times p(d_t) \\
n & \equiv & n \times p(A_t) + n \times p(\underline{A}_t) & = & n \times p(B_t) + n \times p(\underline{B}_t)
\end{array}
\tag{2}
$$

The meaning of the abbreviations a, b, c, d, n et cetera are explained by following 2 by 2-table (**Table 8**). The relationships are valid even under conditions where n = 1.

Table 4. The sample space of a contingency table

		Conditioned B (Outcome)		
		Yes = +1	**No = +0**	**Total**
Condition A	Yes =+1	a	b	A
(risk factor)	No = +0	c	d	$\underline{A}$
	Total	B	$\underline{B}$	*n*

Definition 2. (Index of unfairness)

The index of unfairness (IOU) is defined (I. Barukčić, 2019c) as

$$
IOU \equiv \left(\left(\frac{A + B}{n} \right) - 1 \right) \tag{3}
$$

The range of A is $0 \leq A \leq n$, while the range of B is $0 \leq B \leq n$. A study design based on A=B=0 leads to an index of unfairness of IOU = (((0+0)/n)-1) = -1. A study design which demands that A=B=n leads to an index of unfairness of IOU = (((n+n)/n)-1) = +1. In particular, the range of the index of unfairness is [-1;+1].

Definition 3. (The probability of an index of unfairness)

The probability of an unfairness p(IOU) is defined as

$$p(IOU) \equiv Absolute\left(\left(\frac{A \quad + B}{n}\right) - 1\right) \tag{4}$$

Definition 4. Index of independence (IOI)

The index of independence (IOI) is defined (I. Barukčić, 2019b) as

$$IOI \equiv \left(\left(\frac{A \quad + \underline{B}}{n}\right) - 1\right) \tag{5}$$

Definition 5. (The probability of an index of independence)

The probability of an index of independence p(IOI) is defined (I. Barukčić, 2019b) as

$$p(IOI) \equiv Absolute\left(\left(\frac{A \quad + \underline{B}}{n}\right) - 1\right) \tag{6}$$

Definition 6. Sufficient Condition (Conditio per Quam)

The *sufficient* condition (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (*conditio per quam*) of a population is defined (I. Barukčić, 2019a, 2019d) as

$$\begin{aligned} p(A_t \rightarrow B_t) &\equiv \frac{(a_t) + (c_t) + (d_t)}{N_t} = 1 \\ &\equiv p(a_t) + p(c_t) + p(d_t) \\ &\equiv p(B_t) + p(d_t) \\ &\equiv p(a_t) + p(\underline{A}_t) \\ &\equiv +1. \end{aligned} \tag{7}$$

and is used to prove the hypothesis: *if* A_t *then* B_t or is taken to express that *the occurrence of an event A_t is a sufficient condition for existence or occurrence of an event B_t*. Sufficient and necessary conditions are converse relations (I. Barukčić, 2019a, 2019d).

Definition 7. The X² Test of Goodness of Fit of a Sufficient Condition

Under certain circumstances, the X^2 test of goodness-of-fit is an appropriate method for testing the null hypothesis that a random sample of observations comes from a specific distribution (i.e. the distribution of a sufficient condition) against the alternative hypothesis that the data have some other distribution (I. Barukčić, 2019a, 2019d). The additive property of X^2 distribution is of special importance in this context. The applicability of using the Pearson chi-squared statistic including Yate's continuity correction (I. Barukčić, 2019a, 2019d) are widely discussed in literature. Especially, the need of incorporating Yate's continuity correction into the calculation of the X^2 value is very controversial. Thus far, only due to formal reasons, in the following, the use of *the continuity correction* is assured. The chi-square value of a conditio per quam relationship is derived (I. Barukčić, 2019a, 2019d) as

$$X^2\left(\left(A \quad \rightarrow B \quad\right)|A \quad\right) \quad \equiv \quad \frac{\left(\left(b \quad\right)-\left({}^{1}/_{2}\right)\right)^2}{A}+0=0 \tag{8}$$

or alternatively as

$$X^2\left(\left(A \quad \rightarrow B \quad\right)|\underline{B} \quad\right) \quad \equiv \quad \frac{\left(\left(b \quad\right)-\left({}^{1}/_{2}\right)\right)^2}{\underline{B}}+0=0 \tag{9}$$

Definition 8. Necessary Condition (Conditio Sine Qua Non)

The self-organization of matter is governed by view basic natural laws among those is the necessary condition (conditio sine qua non) too. An event A_t which is necessary (or an essential) for some other event B_t to occur must be satisfied in order to obtain B_t (I. Barukčić, 2019a, 2019d). In this respect, let an event A_t with its own probability $p(A_t)$ at the (period of) time *t* be a necessary condition for another event B_t with its own probability $p(B_t)$. This is equivalent to say that it is impossible to have B_t without A_t. In other words, *without* A_t *no* B_t or the absence of A_t must guarantee the absence of B_t. The mathematical formula of the *necessary* condition (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (conditio sine qua non) of a population is defined (I. Barukčić, 2019a, 2019d) as

$$
\begin{aligned}
p(A_t \leftarrow B_t) &\equiv \frac{(a_t) + (b_t) + (d_t)}{N_t} = 1 \\
&\equiv p(a_t) + p(b_t) + p(d_t) \\
&\equiv p(A_t) + p(d_t) \\
&\equiv p(a_t) + p(\underline{B_t}) = p(a_t) + (1 - p(B_t)) \\
&\equiv +1.
\end{aligned}
\tag{10}
$$

Definition 9. The X^2 Test of Goodness of Fit of a Necessary Condition

The chi-square value of a *conditio sine qua non* distribution (I. Barukčić, 2019a, 2019d) before changes to

$$
X^2((A \leftarrow B)|B) \equiv \frac{((c) - (1/2))^2}{B} + 0 = 0 \tag{11}
$$

Depending upon the study design, another alternative and equivalent method to calculate the chi-square value of a *conditio sine qua non* distribution (while using *the continuity correction*) is defined as

$$
X^2((A \leftarrow B)|\underline{A}) \equiv \frac{((c) - (1/2))^2}{\underline{A}} + 0 = 0 \tag{12}
$$

Definition 10. Exclusion (A_t Excludes B_t and Vice Versa Relationship)

The mathematical formula of the *exclusion* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (A_t excludes B_t and vice versa) of a population is defined (I. Barukčić, 2019a, 2019d) as

$$
\begin{aligned}
p(A_t \mid B_t) &\equiv \frac{(b_t) + (c_t) + (d_t)}{N_t} = 1 \\
&\equiv p(b_t) + p(c_t) + p(d_t) \\
&\equiv p(b_t) + p(\underline{A}_t) = p(b_t) + (1 - p(A_t)) \\
&\equiv p(c_t) + p(\underline{B}_t) = p(c_t) + (1 - p(B_t)) \\
&\equiv +1.
\end{aligned} \tag{13}
$$

and used to prove the hypothesis: A_t *excludes* B_t and vice versa. Under which conditions does A_t exclude B_t and vice versa and what are the consequences? The relationship A_t excludes B_t and vice versa is of outstanding importance especially in human medicine because the same relationship allows researchers to identify among other an *antidote against a certain factor*.

Definition 11. The X^2 Test of Goodness of Fit of the Exclusion Relationship

The chi square value with degree of freedom 2-1=1of the exclusion relationship with a *continuity correction* can be calculated (I. Barukčić, 2019a, 2019d) as

$$
X^2\left((A \mid B) \mid A\right) \equiv \frac{\left((a) - (1/2)\right)^2}{A} + 0 = 0 \tag{14}
$$

Another equivalent method to calculate the chi-square value of a *conditio sine qua non* distribution is defined (I. Barukčić, 2019a, 2019d) as

$$
X^2\left((A \mid B) \mid B\right) \equiv \frac{\left((a) - (1/2)\right)^2}{B} + 0 = 0 \tag{15}
$$

In particular, the chi square Goodness of Fit Test of the exclusion relationship provides evidence how well observed data compare with the expected theoretical distribution of an exclusion relationship (I. Barukčić, 2019a, 2019d).

Definition 12. Independence

In the case of independence (Kolmogoroff, 1933; Moivre, 1718) of A_t and B_t it is generally valid that

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \tag{16}$$

Definition 13. The Mathematical Formula of the Causal Relationship k

The causal relationship k (I. Barukčić, 2016a, 2018b, 2018a, 2019d; K. Barukčić & Barukčić, 2016; K. Barukčić, Barukčić, & Barukčić, 2018) is defined *at every single event, at every single Bernoulli trial t,* as

$$k(A_t, B_t) \equiv \frac{p(A_t \cap B_t) - (p(A_t) \times p(B_t))}{\sqrt[2]{p(A_t) \times (1 - p(A_t)) \times p(B_t) \times (1 - p(B_t))}} \tag{17}$$

where A_t denotes the cause and B_t denotes the effect. The significance of causal relationship k can be tested by several methods. Under some certain circumstances, the chi-square distribution can be applied too. However, it is necessary to point out again that the mathematical formula of the causal relationship k has nothing to do *neither* with Pearson's concept of correlation *nor* with Pearson's concept of ϕ. Pearson's correlation methods are not identical with causation or correlation and causation must be distinguished, this has been proved (Sober, 2001) many times by different publications.

Definition 14. The 95% Confidence Interval of the Causal Relationship k

The approximate 95% interval for the causal relationship k can be estimated by the formula

$$\left\{ k(A_t, B_t) - \sqrt[2]{\frac{5}{n}} \quad ; \quad k(A_t, B_t) + \sqrt[2]{\frac{5}{n}} \right\} \tag{18}$$

2.2.2. Data analysis

The causal relationship k (I. Barukčić, 1989, 1997, 2016a, 2016b, 2017, 2018a, 2019d; K. Barukčić & Barukčić, 2016; Hessen, 1928; Korch, 1965) was used to proof the data for a causal relationship while the significance was tested by the hypergeometric distribution (HGD) and the chi-square distribution (Karl Pearson, 1900). The *conditio sine qua non* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (SINE) was used to proof the hypothesis, *without* VZV infection *no* Shizophrenia. The *conditio per quam* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (IMP) was used to proof the hypothesis, *if* VZV infection *then* Shizophrenia. The *necessary and sufficient condition* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (SINE) was used to proof the hypothesis, (*without* VZV infection *no* Shizophrenia) **and** (*if* VZV infection *then* Shizophrenia). The index of independence (I. Barukčić, 2019b) and the index of unfairness (I. Barukčić, 2019c) was used to control publication bias. All statistical analyses were performed with Microsoft® Excel® for Mac® version 16.2 (181208) software (© 2018, Microsoft GmbH, Munich, Germany). The level of significance was set to 0.05.

3. Results

THEOREM 1. VARICELLA ZOSTER VIRUS IS A NECESSARY CONDITION, A SUFFICIENT CONDITION, A NECESSARY AND SUFFICIENT CONDITION OF SCHIZOPHRENIA AND EQUALLY THE CAUSE OF SCHIZOPHRENIA

CLAIM.

Null-Hypothesis: VZV is not the cause of Schizophrenia ($k = 0$).

Alternative Hypothesis: VZV is the cause of Schizophrenia ($k \neq 0$).

PROOF.

The data (**Table 2**) of study of de Witte et al. (de Witte et al., 2015) provided that the control group reflect fair and realistic conditions indicates that VZV is the cause of schizophrenia (**Table 2**).

QUOD ERAT DEMONSTRANDUM.

4. Discussion

This study aimed to assess the relationship between VZV and schizophrenia. However, there are several limitations associated with the present study. First, what characterizes a good and fair control group? Is a fictive control group of any use at all? Moreover, limitation of the study is the assumption (without a proof) that newborn children do not suffer from schizophrenia. In addition, how can we be sure that newborn children do not suffer from schizophrenia? Therefore, the relationship between VZV and schizophrenia is not ultimately cleared by the present study. More studies with a very fair control group are needed to confirm the relationship between VZV and schizophrenia. Athough this hypothesis-generating study does not resolve the issue of VZV and schizophrenia, this study has advantages over other studies. In point of fact, study of de Witte et al. (de Witte et al., 2015) supports clearly the hypothesis that VZV is a necessary condition of schizophrenia ($\mathbf{X^2(SINE \mid B_t) = 0{,}696}$, according to equation 11) which cannot be ignored.

5. Conclusion

In conclusion, **without** VZV seropositivity **no** schizophrenia. A fair study design assured, VZV is the cause of schizophrenia.

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Author Contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of Interest Statement

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. There are no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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