Parvovirus B19 infection is the cause of acute myeloid leukaemia

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Abstract

Objectives.

Identifying a cause or the cause of acute myeloid leukaemia (AML) could be of help for the survival of patients while accelerating the diagnosis and therapy of AML.

Methods.

As known, a contingency table is defined by the fields a, b, c, d while a+b =U, c+d=$\underline{U}$, a+c=W, b+d=$\underline{W}$ and a+b+c+d = U+ $\underline{U}$ = W+$\underline{W}$ = N. Appropriate statistical methods like the necessary condition relationship, defined as p(without U_t no W_t) = (a+b+d)/N, the sufficient condition relationship, defined as p(if U_t then W_t) =(a+c+d)/N, the necessary and sufficient condition relationship, defined as p(U_t is necessary and sufficient for W_t)=(a+d)/N, the exclusion relationship, defined as p(U_t excludes W_t) = (a)/N, and the causal relationship k, defined as $k(U_t,W_t)=\sigma(U_t,W_t)/(\sigma U_t) \times \sigma W_t))$, were used for causal data analysis. A p-value of less than 0.05 has been treated as significant.

Results.

Without parvovirus B19 infection, no acute myeloid leukaemia (P value = 0.0108). If parvovirus B19 infection then acute myeloid leukaemia (Chi-square = 1.35 < 3.84). Parvovirus B19 infection is a necessary and sufficient condition of acute myeloid leukaemia (Chi-square = 1.381 < 3.84). The causal relationship k between a parvovirus B19 infection and acute myeloid leukaemia is highly significant (k = +0.7866, p Value right tailed = 2.55351E-15).

Conclusion.

Thus far, until contrary evidence, according to this study it is justified to consider that parvovirus B19 is the cause of acute myeloid leukaemia (p Value = 2.55351E-15).

Keywords — ***Cause, effect, causal relationship. parvovirus B19 infection, acute myeloid leukaemia.***

I. Introduction

A high relapse rate(see Chen et al. 2020) is one feature of acute myeloid leukaemia (AML), a biologically and clinically very heterogeneous disease and equally one of the most common (see Yamamoto and Goodman 2008) acute leukaemia in adults. Despite the unknown pathogenesis, acute myeloid leukaemia involves the abnormal differentiation and proliferation of a clonal population of human myeloid stem cells. Most of the clinical manifestations of AML reflect an accumulation of malignant, poorly differentiated myeloid cells within the peripheral blood, the bone marrow and in other organs. Individual genetic mutations, large chromosomal rearrangements, molecular changes et cetera have often been implicated in the development of AML. Studies examined the potential role of risk factors like benzene (see Goldstein 2010), tobacco (see Chunxia et al. 2019) and other risk factors including car exhaust fumes, pesticides, anti epileptic drugs, chemical contamination in

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drinking water, both viral and bacterial infections, and parental cigarette smoking, and so on (see Belson et al. 2007) in relation to leukaemia. However, the results reported in different scientific publications seem contradictory in relation to this topic and much remains to be discovered on the exact contribution of these factors in particular in the aetiology of AML. The incidence of AML increases with age with an U.S. incidence of AML which ranges from three to five cases per 100000 US-inhabitants. Although advances in the treatment of AML have led to significant improvements in outcomes for younger patients, the overall long-term survival and prognosis in the elderly remains poor (see Shah et al. 2013). In the year 2015 about 20830 new US-AML cases were diagnosed (see Siegel et al. 2015) while over 10000 patients (ca. 50 %) died from this disease. It is a matter of concern that 70% of AML patients 65 years or older (see De Kouchkovsky and Abdul-Hay 2016) die of AML within 1 year of diagnosis. However, haematological malignancies such as leukaemia (30%), lymphoma (12%) including acute myeloid leukaemia (15-20%) are common (see De Renzo et al. 1994) among children too. There are strong reasons for considering that viral infections like the single stranded DNA human parvovirus B19 (B19) are a risk factor for leukaemia too and are involved in the pathogenesis of acute leukaemia (see Heegaard et al. 2001). Various studies investigated the relationship between an acute parvovirus B19 infection and leukaemia. Several of these studies found the frequency of B19 infection in leukaemia cases increased (see Kerr et al. 2003; El-Mahallawy et al. 2004; Lindblom et al. 2008). Despite of obvious advances in the treatment of (childhood) leukaemia and novel agents (see De Kouchkovsky and Abdul-Hay 2016) like sorafenib (tyrosine kinase inhibitors), midostaurin, quizartinib, crenolanib, clofarabine and other, a cause or the cause of AML remain unclear. Lastly, regardless of unknown AML aetiology identifying a cause or the cause of AML is an important step in the reduction of the overall burden of this disease.

II. Material and methods

Since this study is a meta-analysis of the data of previously published data, the ethical approval and patient consent are not required.

2.1 Material

2.1.1 Literature search

The PubMed database was systematically searched for relevant studies until December 18, 2020. The following keywords were used not individually but in combination: "acute myeloid leukaemia" and "parvovirus b19" and "case control". Reporting in adherence to Preferred Reporting Items for Systematic Reviews and Meta-analysis(see Moher et al. 2009; Liberati et al. 2009) was assured.

Table 1: *Systematic Reviews and Meta-analysis*

Identification:		
	PubMed	3
Screening:		
	Articles excluded	2
Eligibility:		
	Articles eligible for analysis	1
Inclusion:		
	Studies included (meta-analysis)	1

2.1.2 Inclusion and exclusion criteria

Original studies using a case–control study design with an assessment of B19 and AML were considered for a re-analysis. The following studies were excluded: letters, reviews, case reports, conference abstracts, or expert opinions.

2.1.3 Study selection and characteristics

The literature search was re-conducted on December 12, 2020. The search yielded 3 potentially eligible titles. After reviewing the abstracts and removing inappropriate articles, the full text of 1 article, the polymerase-chain reaction (PCR) study of Noha Tharwat Abou El-Khier et al.(see Tharwat Abou El-Khier et al. 2018), were obtained and compared to the inclusion criteria. Two articles were excluded. This resulted in 1 eligible article for meta-analyses.

2.1.4 Data extraction and assessment of study quality

The investigators independently extracted data that met our inclusion and exclusion criteria. The index of independence (see Barukčić 2019b) (IOI) and the index of unfairness (see Barukčić 2019c) (IOU) was used to evaluate the methodological quality of the data of the study included. The data of the study of Noha Tharwat Abou El-Khier et al.(see Tharwat Abou El-Khier et al. 2018) were the following (see Table 2).

Table 2: Parvovirus B19 infection and AML.

		AML		
		YES	NO	
Parvovirus B19 infection	YES	31	9	40
	NO	1	51	52
		32	60	92

Causal relationship k =	+0,7866
p Value right tailed (HGD) =	0,000000000000003
p (SINE) =	0,9891
$\tilde{\chi}^2$ (SINE | B_t) =	0,0313
$\tilde{\chi}^2$ (SINE | $\underline{A}_t$) =	0,0192
p (IMP) =	0,9022
$\tilde{\chi}^2$ (IMP | A_t) =	2,0250
$\tilde{\chi}^2$ (IMP | $\underline{B}_t$) =	1,3500
p (SINE∩IMP) =	0,8913
$\tilde{\chi}^2$ $(SINE \cap IMP)_1$ =	2,0442
$\tilde{\chi}^2$ $(SINE \cap IMP)_2$ =	1,3813
p(IOI)=	0,0870
p(IOU)=	0,2174
RR (nc) =	40,3000
RR (sc) =	6,4583
OR =	175,6667
IOR =	1,2281

Just for the sake of the argument, RR (nc), the relative risk of a necessary(see Barukčić 2021b) condition, RR (sc), the relative risk of a sufficient(see Barukčić 2021b) condition, the odds ratio(see Cornfield 1951; Sadowsky et al. 1953) and the index (see Barukčić 2021a) of relationship (IOR) are calculated. There is a misprint in the study of El-Khier et al.(see Tharwat Abou El-Khier et al. 2018) with respect to the data inside Table 2 on page 339. However, this misprint is without an effect on the final statistical results and the conclusion drawn.

2.2 Methods

2.2.1 Independence

Definition 2.1 (**Independence**).

In general, an event A_t at the Bernoulli trial t need not but can be independent of the existence or of the occurrence of another event B_t *at the same* Bernoulli trial t. Mathematically, independence (see Moivre 1718; Kolmogoroff 1950) in terms of probability theory is defined at the same (period of) time t (i.e. Bernoulli trial t) as

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

2.2.2 Two by two table of Binomial random variables

Definition 2.2 (**Two by two table of Binomial random variables**).

Table 3: The two by two table of Binomial random variables

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

The two by two or contingency table between two binomial random variables has been introduced by Karl Pearson(see Pearson 1904) in 1904.

Under conditions where *the probability of an event, an outcome, a success et cetera is* ***constant*** *from Bernoulli trial (see Uspensky 1937) to Bernoulli trial t*, it is

$$\begin{aligned} A &= a+b \\ &\equiv N-\underline{A} \end{aligned} \tag{2}$$

and

$$\begin{aligned} \underline{A} &= c+d \\ &\equiv N-A \end{aligned} \tag{3}$$

and

$$\begin{aligned} B &= a+c \\ &\equiv N-\underline{B} \end{aligned} \tag{4}$$

and

$$\begin{aligned} \underline{B} &= b+d \\ &\equiv N-B \end{aligned} \tag{5}$$

and

$$a+b+c+d \equiv A+\underline{A} \equiv B+\underline{B} \equiv N \tag{6}$$

2.2.3 Necessary condition

Definition 2.3 (Necessary condition [*Conditio sine qua non*]).

Mathematically, the necessary condition (SINE) relationship, denoted by $p(A_t \leftarrow B_t)$ in terms of statistics and probability theory, is defined (see also Barukčić 2011; Barukčić 1989; Barukčić 1997; Barukčić 1997; Barukčić 2005; Barukčić 2017a; Barukčić 2017b; Barukčić 2019a; Barukčić 2020a; Barukčić 2016a; Barukčić 2018; Barukčić 2016b; Barukčić 2017c; Barukčić 2020b; Barukčić 2021c; Barukčić 2019d) as

$$\begin{aligned} p(A_t \leftarrow B_t) \equiv p(A_t \vee \underline{B}_t) &\equiv \frac{\sum_{t=1}^{N} (A_t \vee \underline{B}_t)}{N} \\ &\equiv p(a_t)+p(b_t)+p(d_t) \\ &\equiv \frac{N \times (p(a_t)+p(b_t)+p(d_t))}{N} \\ &\equiv \frac{a+b+d}{N} \\ &\equiv +1 \end{aligned} \tag{7}$$

It is $p(A_t - < B_t) \equiv 1 - p(A_t \leftarrow B_t)$ (see Table 4).

Table 4: Necessary condition.

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

2.2.4 Sufficient condition

Definition 2.4 (**Sufficient condition [*Conditio per quam*]).**

Mathematically, the sufficient condition (IMP) relationship, denoted by $p(A_t \rightarrow B_t)$ in terms of statistics and probability theory, is defined(see also Barukčić 2011; Barukčić 1989; Barukčić 1997; Barukčić 1997; Barukčić 2005; Barukčić 2017a; Barukčić 2017b; Barukčić 2019a; Barukčić 2020a; Barukčić 2016a; Barukčić 2018; Barukčić 2016b; Barukčić 2017c; Barukčić 2020b; Barukčić 2021c; Barukčić 2019d) as

$$\begin{aligned} p(A_t \rightarrow B_t) \equiv p(\underline{A}_t \vee B_t) \equiv & \frac{\sum_{t=1}^{N} (\underline{A}_t \vee B_t)}{N} \\ & \equiv p(a_t) + p(c_t) + p(d_t) \\ & \frac{N \times (p(a_t) + p(c_t) + p(d_t))}{N} \\ & \equiv \frac{a+c+d}{N} \\ & \equiv +1 \end{aligned} \tag{8}$$

It is $p(A_t > -B_t) \equiv 1 - p(A_t \rightarrow B_t)$ (see Table 5).

Table 5: Sufficient condition.

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

2.2.5 Causal relationship k

Definition 2.5 (**Causal relationship k).**

Nonetheless, mathematically, the causal relationship (see also Barukčić 2011; Barukčić 1989; Barukčić 1997; Barukčić 1997; Barukčić 2005; Barukčić 2017a; Barukčić 2017b; Barukčić 2019a; Barukčić 2020a; Barukčić 2016a; Barukčić 2018; Barukčić 2016b; Barukčić 2017c; Barukčić 2020b; Barukčić 2021c; Barukčić 2019d) between a cause U_t (German: Ursache) and an effect W_t (German: Wirkung), denoted by $k(U_t, W_t)$, is defined *at each single Bernoulli trial t* in terms of statistics and probability theory as

$$\begin{aligned} k(U_t, W_t) \equiv & \frac{\sigma(U_t, W_t)}{\sigma(U_t) \times \sigma(W_t)} \\ \equiv & \frac{p(U_t \wedge W_t) - p(U_t) \times p(W_t)}{\sqrt[2]{(p(U_t) \times (1 - p(U_t))) \times (p(W_t) \times (1 - p(W_t)))}} \end{aligned} \tag{9}$$

where $p(U_t)$ is the probability of a cause at a single Bernoulli trial t, $p(W_t)$ is the probability of an effect at a single Bernoulli trial t, $p(U_t \wedge W_t)$ is the joint probability of a cause and an effect at same single Bernoulli trial t, $\sigma(U_t, W_t)$ denotes the co-variance between a cause U_t and an effect W_t *at every single Bernoulli trial t*, $\sigma(U_t)$ denotes the standard deviation of a cause U_t at the same single Bernoulli trial t, $\sigma(W_t)$ denotes the standard deviation of an effect W_t at same single Bernoulli trial t.

2.3 Statistical methods

The necessary (see also Barukčić 2011; Barukčić 1989; Barukčić 1997; Barukčić 1997; Barukčić 2005; Barukčić 2017a; Barukčić 2017b; Barukčić 2019a; Barukčić 2020a; Barukčić 2016a; Barukčić 2018; Barukčić 2016b; Barukčić 2017c; Barukčić 2020b; Barukčić 2021c; Barukčić 2019d) condition relationship, the sufficient (see also Barukčić 2011; Barukčić 1989; Barukčić 1997; Barukčić 1997; Barukčić 2005; Barukčić 2017a; Barukčić 2017b; Barukčić 2019a; Barukčić 2020a; Barukčić 2016a; Barukčić 2018; Barukčić 2016b; Barukčić 2017c; Barukčić 2020b; Barukčić 2021c; Barukčić 2019d) condition relationship and the causal relationship k (see also Barukčić 2011; Barukčić 1989; Barukčić 1997; Barukčić 1997; Barukčić 2005; Barukčić 2017a; Barukčić 2017b; Barukčić 2019a; Barukčić 2020a; Barukčić 2016a; Barukčić 2018; Barukčić 2016b; Barukčić 2017c; Barukčić 2020b; Barukčić 2021c; Barukčić 2019d) were used to evaluate the possible causal relationship between B19 and AML. The chi-square goodness of fit test with one degree of freedom has been used to test whether the sample data of the study of Noha Tharwat Abou El-Khier et al.(see Tharwat Abou El-Khier et al. 2018) fits a necessary condition distribution, a sufficient condition distribution, a necessary and sufficient condition distribution from a certain population. The sample size was sufficient enough in order for the chi-square approximation to be used. The hyper-geometric distribution has been used to test the one-sided significance of the causal relationship k. All statistical analyses were performed using MS Excel (Microsoft Corporation, USA). A P-value $<.05$ were considered statistically significant.

III. Results

3.4 Necessary condition: Without B19 infection no AML

El-Khier et al. provided data about the relationship between Parvovirus B19 infection and AML. The data available and the statistical analysis of these data are illustrated in detail by Table 2. The index of independence (see Barukčić 2019b) of the study of El-Khier et al. is p(IOI) = 0,087 and not greater than 0,25. In other words, the data of El-Khier et al. can be considered for a re-analysis of causal relationships and for a re-analysis of an exclusion relationship. The index of unfairness (see Barukčić 2019c) of the study of El-Khier et al. study is p(IOU) = 0,217 and is less than 0,25 too. The index of unfairness of this study does not indicate potentially biased data. The data of El-Khier et al. can be considered for a re-analysis of necessary and sufficient conditions and of causal relationships too. Altogether, the data as published by the study of El-Khier et al. are more or less not biased. The causal relationship k is (k = +0,787, P-value right tailed (HGD) = 2,55351E-15) positive and statistically highly significant. The relative frequency or the probability of the conditio sine qua non relationship between a Parvovirus B19 infection and AML is calculated as p (SINE) = 0,989130 (necessary condition). The approximate P-value (see Barukčić 2019d) can be calculated as P-value (SINE) = 0,010811. The significance of these data tested by the Chi-square goodness of fit test (sample size n = 92) yields the following results while the X^2critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data of the study of El-Khier et al. yields a calculated $X^2(\text{SINE}| B_t)$ of $X^2(\text{SINE}|B_t)$ = (((1)*(1))/ 32) + 0 = 0,031. Secondly. The same data lead to the calculated $X^2(\text{SINE}|A_t)$ of $X^2(\text{SINE}|A_t)$ = (((1)*(1))/ 52) + 0 =0,019. Furthermore, causal relationship is positive and highly significant. Thus far and independent of the point of view, the data of the study of El-Khier et al. do support the null-hypothesis that Parvovirus B19 infection is a necessary condition of AML. In other words, **without** Parvovirus B19 infection **no** AML (P-value (SINE) = 0,010810705).

3.5 Sufficient condition: If B19 infection then AML

The data of the study of El-Khier et al. (see Tharwat Abou El-Khier et al. 2018) support the null-hypothesis too that Parvovirus B19 infection is a sufficient condition of AML (see X^2 values of Table 2).

3.6 A B19 infection is the cause of AML

El-Khier et al. (see Tharwat Abou El-Khier et al. 2018) support the null-hypothesis too that Parvovirus B19 infection is a necessary and sufficient condition of AML (see X^2 values of Table 2). In general, the data of El-Khier et al. (see Tharwat Abou El-Khier et al. 2018) support the null-hypothesis that Parvovirus B19 infection is a necessary, a sufficient and a necessary and sufficient condition of acute myeloid leukaemia. Equally, the causal relationship k itself is positive and calculated as k = +0,787 (P-value right tailed (HGD) = 2,55351E-15). El-Khier et al. (see Tharwat Abou El-Khier et al. 2018) support the hypothesis that **B19 is the cause of AML**.

IV. Discussion

The support for a cause effect relationship between B19 and AML by the data of Noha Tharwat Abou El-Khier et al. (see Tharwat Abou El-Khier et al. 2018) is indeed more or less only of preliminary nature. **Firstly.** Additional investigations like bone marrow puncture to investigate the relationship between B19 and AML have not been carried out by the authors. **Secondly.** The sample size of the study of El-Khier et al. (see Tharwat Abou El-Khier et al. 2018) is more or less small. A small trial sample size (random error) may induce bias of different kind. However, the study of El-Khier et al.(see Tharwat Abou El-Khier et al. 2018) can be compared with a kind of a small Pilot (see Arain et al. 2010) study carried out as an essential precursor study in preparation for larger high-quality investigations. Despite their possible importance, the reality is that pilot studies receive little or no attention in scientific research. Although not all studies need to be preceded by pilot investigations, Pilot studies (see Thabane et al. 2010), even if designed to provide preliminary evidence or answers with respect to a certain research question, need not to obtain only preliminary answers to primary research questions and need not imply unjustified and potentially misleading conclusions. The conclusions drawn from a small (Pilot) study depend to a very great extent on the study design of a study and the quality of the data obtained by the same study. Nonetheless, it should be emphasised that the data of the study of El-Khier et al.(see Tharwat Abou El-Khier et al. 2018) were not extremely biased. The index of independence (see Barukčić 2019b) has been p(IOI) = 0,087 which indicates that the data of El-Khier et al. (see Tharwat Abou El-Khier et al. 2018) can be used for re-analyses of causal relationships and for exclusion relationships. The index of unfairness (see Barukčić 2019c) has been p(IOU) = 0,217 and indicates equally that the data of the study of El-Khier et al.(see Tharwat Abou El-Khier et al. 2018) can be re-analysed for conditions and potentially for causal relationships too. Therefore, the data of the study of El-Khier et al. (see Tharwat Abou El-Khier et al. 2018) highlights in a very impressive manner and not only preliminary that a B19 infection is a necessary condition of AML. In other words, without a B19 infection no AML (P-value = 0,010811) and much more than this. The data of the study of El-Khier et al.(see Tharwat Abou El-Khier et al. 2018) provided highly significant statistical evidence of a cause effect relationship between a B19 infection and AML (k = +0,787, P-value = 2,55351E-15). This study provided direct supporting evidence of a cause-effect relationship between a B19 infection and AML and indicates that B19 is the cause AML. Further carefully designed studies considering the AML classification (see Vardiman et al. 2009; Arber et al. 2016) system in greater detail are required and will be needed in order to re-evaluate and determine the relationship between B19 and AML definitely.

V. Conclusion

Until contrary evidence, the findings of this study provide direct and striking support for the hypothesis that a parvovirus B19 infection is the cause of AML.

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VII. Patient consent for publication

Not required.

VIII. Conflict of interest statement

No conflict of interest to declare.

IX. Important note

Before reading this article note can be taken that it was not possible to publish the content of this paper by a Web of Science, EBSCO, Scopus, PubMed/Medline et cetera indexed journal in our times. Ultimately it is the responsibility of each individual reader her/himself to decide which theoretical, practical and other conclusions should and need to be drawn from this.

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