ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 11, Issue, 04, pp. 46412-46415, April, 2021
https://doi.org/10.37118/ijdr.21678.04.2021

RESEARCH ARTICLE OPEN ACCESS

IMMUNOLOGICAL RESPONSE AND ZIKA MUTATIONS AS A MECHANISM OF MICROCEPHALY: SYSTEMATIC REVIEW AND META-ANALYSIS

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ARTICLE INFO

Article History:
Received 06th January, 2021
Received in revised form
20th February, 2021
Accepted 26th March, 2021
Published online 28th April, 2021

Key Words:
Microcephaly. Zika Virus.
Immune System. Mutations.

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ABSTRACT

Several circumstances may involve the development of microcephaly in the context of Zika infection. Mutations and the immune response caused by the virus may be part of the theoretical direction in the context. The aim of this study was to analyze the relationship between immune response or zika mutation and the development of microcephaly. A systematic review was conducted with meta-analysis on immunology and zika mutations in the development of microcephaly. A literature search was conducted on PubMed e Scopus online databases, with a search period for the past 5 years. The results of the analysis showed an effect on the immune response of 0.76 and for mutations of the zika virus of 0.60, which represent, in both cases, an average effect with probability of superiority above 63%.These results represent the clinical significance that the immune response and mutations related to zika virus represent in the development of microcephaly. Mutations and the immune response mediated by interferons significantly influence the development of microcephaly.

Citation: ***Willma José de Santana, Dayse Christina Rodrigues Pereira Luz, Natália dos Santos Almeida, José Leonardo Gomes Coelho, Danilo Ferreira de Sousa, Joanacele Gorgonho Ribeiro Nóbrega, Carmelita Maria Silva Sousa, Allex Alves Sobral de Sousa, Micaele Rodrigues Feitosa Melo, Raimunda Aureniza Feitosa, Samyade Araújo Neves and Modesto Leite Rolim Neto,*** **2021.** "Immunological response and zika mutations as a mechanism of microcephaly: systematic review and meta-analysis"*, International Journal of Development Research*, 11, (04), 46412-46415.

INTRODUÇÃO

The Zika virus (ZIKV), an arbovirus whose transmission occurs by mosquitoes, was first isolated in 1947 by a sentinel monkey from Zika forest in Uganda (DICK; KITCHEN; HADDOW, 1952). Between 2015 and 2016, as it spread throughout the Americas, it surpassed more than 500,000 infected people (Pan-american health organization, 2016; Band *et al*, 2017).Zika virus infection has had several national and international consequences. The most evident was the great association between fetal microcephaly and virus infection. There is a probable positive correlation between these two circumstances, but which factors can influence the process are unknown (Yockey*et al*, 2018; Yuan *et al*, 2017).Epidemiological studies showed a high prevalence of ZIKAV antibodies, represented by the YAP epidemic in 2007, presenting a rate of 14.6 per 1000 inhabitants, demonstrating a prevalence in relation to this epidemic of 750/1000 inhabitants who developed the disease. The clinical manifestations of ZICKV are still very unknown, and similar to dengue virus infection.There is a problem to be discussed to elucidate the evidence of this pathology, being caused by the difficulty of more accurate laboratory tests in the diagnosis of this virus (Sousa, 2014; Vasconcelos, 2002; Vasquez, 2016; Viana; Ignotti, 2013; Soares; Bernardo; Netto, 2002).

Due to the significant increase in the number of infected people, the World Health Organization (WHO) declared the ZICKV epidemics a public health emergency at the beginning of 2016, being of international interest, as there was a correlation between the virus and unexpected consequences such as congenital brain anomalies, especially microcephaly, during the gestational period (Organização pan-americana da saúde, 2016; bande *et al*, 2017).Two theories may support the aspect that microcephaly is influenced by zika virus mutations, as well as the immune response to zika itself may influence microcephaly (Yockey *et al*, 2018; Yuan *et al*, 2017).Given the context, the following guiding question arises, based on the acronym PICO: What are the immunological responses and mutations of zika as a mechanism of microcephaly?. Where “P” refers to Zika, “I” Mutations, “C” immune response, “O” microcephaly.Evidence points to the immune response and mutations of the Zika virus as the mechanism of Microcephaly. However, promoting studies and knowledge about the problem related to the Zika vector mosquito, which causes microcephaly in children, becoming a public health problem.Therefore, one may question: is there a relationship between the immune response or mutation of zika and the development of microcephaly?.

The aim of this study was to analyze the relationship between immune response or zika mutation and the development of microcephaly.

METHOD

This is a systematic review, of exploratory character, followed by meta-analysis. The recommendations of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Liberati *et al*, 2009) (http://www.prisma-statement.org/) were followed. A literature search was conducted on the online databases, covering the articles of the databases: PUBMED and SCOPUS., with publication period of the past 5 years (2015-2020).

The following terms were used in the search on databases using the AND and OR operators:

1) Zika Virus (Medical Subject Headings [MeSH]);
2) Microcephaly (Medical Subject Headings [MeSH]);
3) Immune System (Medical Subject Headings [MeSH]);
4) Mutation (Medical Subject Headings [MeSH]).

(Zika Virus AND Microcephaly) AND (Immune System OR Mutation)

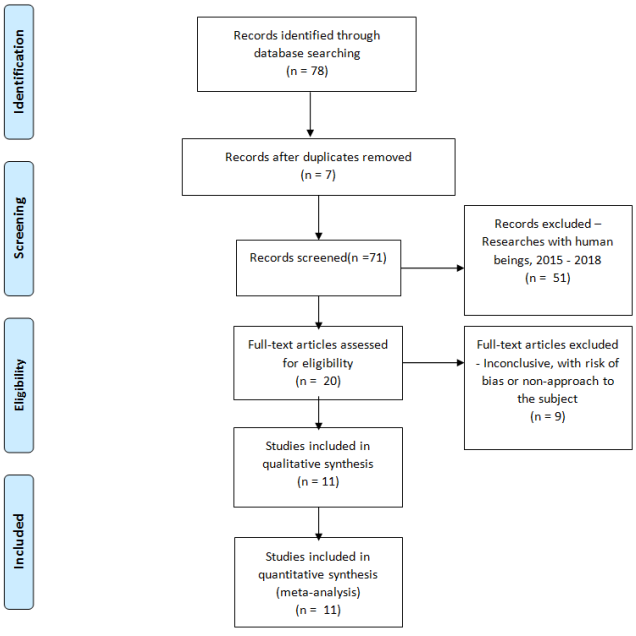
The analysis of the articles followed previously determined eligibility criteria. In the databases, the MeSH terms, title/abstract, publishing dates, free full text and English filters were used. The following eligibility criteria were adopted: (1) publications in any language; (2) studies involving the analysis of immunology and mutations in microcephaly; (3) complete original articles; (4) prospective or retrospective observational, experimental or quasi-experimental study. Exclusion criteria were:(1) studies with other designs, such as literature reviews and comments; (2) non-original studies, including editorials, reviews, prefaces, short communications and letters to the editor. Each article was fully read and the information was used to fill out a spreadsheet that included authors, year of publication, description of study samples, most relevant data and the database. To better analyze the results, the following stages involved the comparison between the articles and the division of the results obtained, from the reading of each one.

The meta-analysis was calculated by effect size with random model. All calculations and graphs were generated in the Stata 14.0 Program. The approach adopted for the development of meta-synthesis involved the following proposed steps: a) elaboration of the research question and problem, b) systematic identification and selection of articles to be analyzed, c) evaluation of articles, d) data extraction and e) elaboration of the synthesis.The risks of bias of the selected studies were analyzed according to the Downs and Black scale (1998), which is composed of the analysis of the study quality (10 items); ability to generalize study results (3 items); study bias (7 items); determination of bias by the sample (6 items) and determination of random findings (1 item). Here, two reviewers also worked independently and studies below 7 points were excluded from the review.

RESULTS

Using mentioned descriptors, 78 studies were found, 45 articles from PubMed and 33 from Scopus. With the application of the inclusion and exclusion criteria, 11 studies were selected, which were included in the systematic review and meta-analysis. Figure 1 represents a flowchart containing the synthesis of the methodological steps of search and selection of studies to reach the final sample.

PRISMA 2009 Flow Diagram



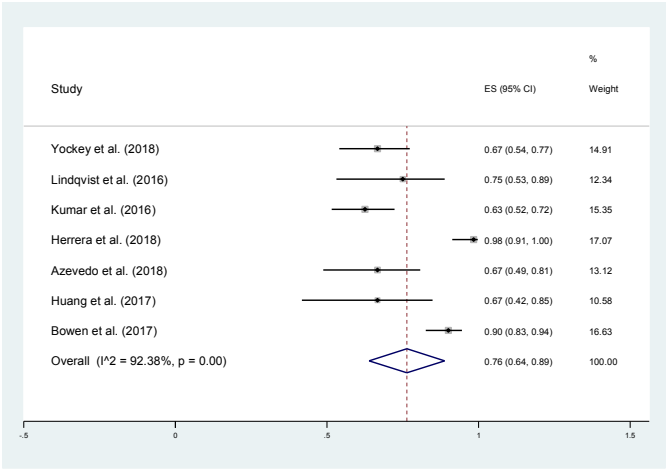
In the following table, the parameters extracted from the selected articles were synthesized for the analysis of the risk of bias, containing the following information: author and year; microcephaly attribution and score on the Downs and Black scale.

Table 1. Risk of bias of the study, based on the selected studies

Author and year	Attribution of microcephaly	Score on Downs and Black scale
Yockey et al (2018)	Immune response	22
Yuan et al (2017)	Mutation	22
Lindqvist et al (2016)	Immune response	22
Kumar et al (2016)	Immune response	24
Herrera et al (2018)	Immune response	20
Azevedo et al (2018)	Immune response	24
Huang et al (2017)	Immune response	24
Bowen et al (2017)	Immune response	20
Tiwari et al (2017)	Mutation	20
Wang et al (2017)	Mutation	24
Ridler et al (2018)	Mutation	24

Based on the selected articles, the meta-analysis was elaborated to assess the impact in the analyzed context. In Figure 1, 7 articles were selected for the meta-analysis addressing the effect of immune response when associated with microcephaly. Figure 2 meta-analyzed the effect of the mutations with 4 selected articles.

Figure 1. Meta-analysis of the effect of immune response



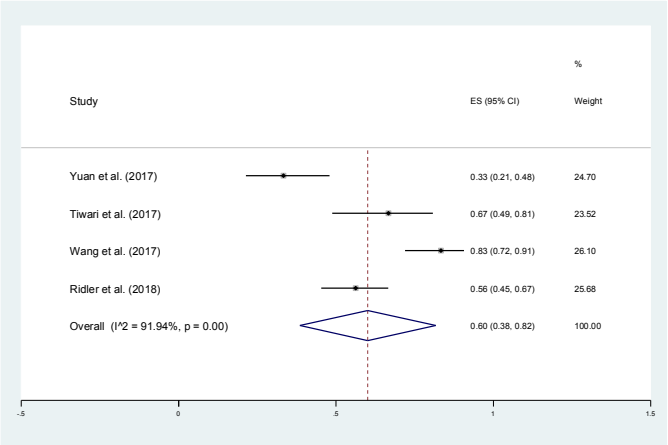
Study	ES	[95% Conf.	Interval]	% Weight
Yockey et al. (2018)	0.67	0.54	0.77	14.91
Lindqvist et al. (20	0.75	0.53	0.89	12.34
Kumar et al. (2016)	0.63	0.52	0.72	15.35
Herrera et al. (2018	0.98	0.91	1.00	17.07
Azevedo et al. (2018	0.67	0.49	0.81	13.12
Huang et al. (2017)	0.67	0.42	0.85	10.58
Bowen et al. (2017)	0.90	0.83	0.94	16.63
Random pooled ES	0.76	0.64	0.89	100.00

Heterogeneity chi^2 = 78.79 (d.f. = 6) p = 0.00
I^2 (variation in ES attributable to heterogeneity) = 92.38%
Estimate of between-study variance Tau^2 = 0.02

Test of ES=0 : z= 12.00 p = 0.00

DISCUSSION

The results of the analysis showed an effect on the immune response of 0.76 and for mutations of the zika virus of 0.60, which represent, in both cases, an average effect with probability of superiority above 63%. Therefore, the study demonstrates results that indicate a significant association between mutations and immune response in the development of zika-mediated microcephaly.The zika virus (ZIKV) has evolved into a major and worrying threat to global health, caused by the unexpected causal relationship with the development of microcephaly. After studies conducted with animal models and clinical materials, there was evidence that zika virus has a direct relationship with neural progenitor cells (NPCs), causing severe pathological consequences, such as microcephaly (Li et al, 2016; Rasmussen et al, 2016).



Study	ES	[95% Conf.	Interval]	% Weight
Yuan et al. (2017)	0.33	0.21	0.48	24.70
Tiwari et al. (2017)	0.67	0.49	0.81	23.52
Wang et al. (2017)	0.83	0.72	0.91	26.10
Ridler et al. (2018)	0.56	0.45	0.67	25.68
Random pooled ES	0.60	0.38	0.82	100.00

Heterogeneity chi^2 = 37.24 (d.f. = 3) p = 0.00
I^2 (variation in ES attributable to heterogeneity) = 91.94%
Estimate of between-study variance Tau^2 = 0.04

Test of ES=0 : z= 5.45 p = 0.00

Figure 2. Meta-analysis of the effect of mutations

The strains that are considered epidemic have emerged in the contemporary world with new varieties in relation to those of origin. The substitution of asparagine (S139N) in viral polyprotein substantially increased zika infectivity in human neural progenitor cells, leading to the development of microcephaly (yuan et al, 2017; Tiwari et al, 2017; Wany et al, 2017; Ridler, 2017).Evolutionary analysis indicates that S139N substitution occurred before the 2013 outbreak in French Polynesia and remained stable during subsequent spread to the Americas (Yuan et al, 2017; Tiwari et al, 2017; Wany et al, 2017; Ridler, 2017).When associated with the gestational period, Zika virus infection is associated with adverse fetal outcomes, including microcephaly, growth restriction, and fetal death. Type I interferons (IFNs) are essential for host resistance against zika, and IFN-α/β receptors (IFNAR) are highly susceptible to infection.Severe fetal growth restriction with placental damage and fetal resorption is observed after zika infection (Yockey et al, 2018; Lindqvist et al, 2016; Kumar et al, 2016).The role of type I IFNs in limiting or mediating zika disease within this model of congenital infection remains unknown. Fetal and placental analyses revealed that, after Zika infection, IFNAR signaling in the conceptus inhibits the development of placental labyrinth, resulting in abnormal maternal-fetal barrier architecture (Yockey et al, 2018; Lindqvist et al, 2016; Kumar et al, 2016).Exposure of mid-aged human chorionic explants to type I IFN, but not to type III IFN, induces altered placenta morphology and induced cytoskeletal rearrangement in the villus nucleus (Herrera et al, 2018; Azevedo et al, 2018; Huany et al, 2017; Bowen et al, 2017).

CONCLUSION

Mutations and interferon-mediated immune response significantly influence the development of microcephaly.Phylogenetic and Evolutionary analyses indicate that there is an increase in the proliferation of zika virus before the contemporary population.Studies indicate that mutations and immune response of Zika virus are significant in the development of microcephaly. Nevertheless, public policies should be implemented in the fight against the Zika virus, bringing a new perspective of immunological and genetic tests that can diagnose the immune response and mutations of the Zika virus in the fight against microcephaly.

REFERENCES

Azevedo, R.S.S. et al. In situ immune response and mechanisms of cell damage in central nervous system of fatal cases microcephaly by Zika virus. Sci Rep [Internet]; v.8, n.1, p.1, 2018. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29311619

Baud, D. et al. Uma atualização sobre a infecção pelo vírus Zik. Lancet, v. 390, p.2099 - 2109, 2017.

Bowen, J.R. et al. Zika Virus Antagonizes Type I Interferon Responses during Infection of Human Dendritic Cells. Pierson TC, editor. PLOS Pathog [Internet]; v.13, n.2, p,e1006164, 2017. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28152048

Dick, G.W. et al. Vírus Zika. I. Isolamentos e especificidade sorológica . Trans. R. Soc. Trop. Med. Hyg., v. 46, p. 509-520, 1952. Doi: 10.1016/0035-9203.

Downs, S.H.; Black N. The feasibility of creating a checklist forthe assessment of the methodological quality both of randomi-sed and non-randomised studies of health care interventions. J Epidemiol Community Heal. 1998.

Herrera, B.B. et al. Sustained specific and cross-reactive T cell responses to Zika and Dengue viruses NS3 in West Africa. J Virol [Internet], 2018. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29321308

Huang, H. et al. CD8 $^{+}$ T Cell Immune Response in Immunocompetent Mice during Zika Virus Infection. Diamond MS, editor. J Virol [Internet]; v.91, n.22, p.e00900-17, 2017. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28835502

Kumar, A. et al. Zika virus inhibits type□I interferon production and downstream signaling. EMBO Rep [Internet]; v.17, n.12, p.1766–75, 2016. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27797853

Li, C. et al. O vírus zika interrompe o desenvolvimento de progenitores neurais e leva à microcefalia em camundongos. Cell Stem Cell, v. 19, p.120 – 126, 2016. DOI: 10.1016 / j.stem.2016.04.017 PMID: 27179424.

Liberati, A. et al. A declaração do PRISMA por relatar revisões sistemáticas e meta-análises de estudos que avaliam intervenções em saúde: explicação e elaboração. J Clin Epidemiol; v.62, p.e1-34, 2009.

Lindqvist, R. et al. Fast type I interferon response protects astrocytes from flavivirus infection and virus-induced cytopathic effects. J Neuroinflammation [Internet].; v.13, n.1, p.277, 2016. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27776548

Organização Pan-Americana da saúde / Organização Mundial da Saúde. Casos suspeitos e confirmados de zika relatados por países e territórios nas Américas Casos cumulativos, 2015-2016. Washington, DC, 2016.

Rasmussen, S.A.et al. Vírus zika e defeitos congênitos - Revendo as evidências de causalidade. N. Engl. J. Med., v.374, p.1981 – 1987, 2016. Doi: 10.1056 / NEJMsr1604338 pmid: 27074377.

Ridler, C. CNS infections: Zika virus mutation associated with increased infectivity, mortality and severe microcephaly. Nat Rev Neurol [Internet]; v.14, n.1, p.:3–3, 2017. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29192259

Soares, S. R. A; Bernardes, R.S; Netto, O.M.C. Relações entre saneamento, saúde pública e meio ambiente: elementos para formulação de um modelo deplanejamento em saneamento. Cad. Saúde Pública, Rio de Janeiro, V. 18, n.6, p.1713-1724, 2002.

Sousa, J. A. Estudo comparado da relação entre saneamento básico e indicadores epidemiológicos entre o Brasil e a América Latina. Juiz de Fora ,2014. 56 f. Monografia (Graduação em Engenharia Sanitaria e Ambiental) - Faculdade de Engenharia da Universidade Federal de Juiz de Fora.

Tiwari, S.K. et al. Zika virus infection reprograms global transcription of host cells to allow sustained infection. Emerg Microbes Infect [Internet]; v.6, n.4, p.e24, 2017. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28442752

Vasconcelos, P. F. C. Febre amarela: Reflexões sobre a doença, as perspectivas para o século XXI e o risco da reurbanização. Revi. Bras. Epidimiol, v. 5, n. 3, p. 244 – 258, 2002.

Vasquez, M. A. *"*Informe de Médicos de Povos Fumigados sobre Dengue-Zika e fumigações com venenos químicos*"*, 2016.

Viana, D. V; IGNOTTI,E. A ocorrência da dengue e variações meteorológicas no Brasil: Revisão sistemática. RevBrasEpidemiol, Cuiabá, MT, v. 16 n. 2, p. 240 – 56, 2013.

Wang, D. et al. A Mutation Identified in Neonatal Microcephaly Destabilizes Zika Virus NS1 Assembly in Vitro. Sci Rep [Internet]; v.7, p.42580, 2017. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28198446

Yockey, L.J. et al. Type I interferons instigate fetal demise after Zika virus infection. Sci Immunol [Internet], v. 3, n.19, p.eaao1680, 2018. Available from: http://www.ncbi.nlm.nih.gov/ pubmed/29305462

Yuan, L. et al. A single mutation in the prM protein of Zika virus contributes to fetal microcephaly. Science [Internet], v. 358, n.6365, p.933-936, 2017 Sep 17. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28971967

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