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Review article

Prevalence of Guillain-Barré syndrome among Zika virus infected cases: a systematic review and meta-analysis

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ABSTRACT

Zika virus (ZIKV) is an emergent flavivirus transmitted mainly through *Aedes* spp. mosquitoes that is posing challenge to healthcare services in countries experiencing an outbreak. Usually ZIKV infection is mild, but in some cases it has been reported to progress into neurological diseases such as microcephaly in infants and Guillain-Barré syndrome (GBS) in adults. GBS is a debilitating autoimmune disorder that affects peripheral nerves. Since ZIKV caused massive outbreaks in South America in the past few years, we aimed to systematically review the literature and perform a meta-analysis to estimate the prevalence of GBS among ZIKV-infected individuals. We searched PubMed and Cochrane databases and selected three studies for a meta-analysis. We estimated the prevalence of ZIKV-associated GBS to be 1.23% (95% CI = 1.17–1.29%). Limitations include paucity of data regarding previous flavivirus infections and ZIKV-infection confirmation issues. Our estimate seems to be low, but cannot be ignored, since ZIKV outbreaks affects an overwhelming number of individuals and GBS is a life-threatening debilitating condition, especially in pregnant women. ZIKV infection cases must be closely followed to assure prompt care to reduce the impact of GBS associated-sequelae on the quality of life of those affected.

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Introduction

Zika virus (ZIKV) is an arbovirus that belongs to the *Flaviviridae* family, the same of Dengue (DENV) virus.[1] ZIKV is mainly transmitted through *Aedes* spp. mosquitoes' bites, but transmission by blood transfusion and sexual intercourse can also occur.[2] Non-human primates seem to be the reservoir hosts for ZIKV, but the primary species have not yet been identified.[3]

Until 2007, ZIKV was limited to Africa and Asia, and only mild cases were reported.[4] After 2007, ZIKV cases started to increase remarkably, causing outbreaks in many different countries. The first major outbreak of ZIKV infection was recorded in French Polynesia in October 2013.[2] The virus subsequently spread through the Pacific reaching Brazil in mid-2015; the largest outbreak was reported in this country, and up to date the World Health Organization (WHO) has estimated approximately 3–4 million cases of ZIKV.[3]

ZIKV infection is thought to be symptomatic only between 18% and 35% of the cases, resulting in a mild illness with symptoms such as fever, myalgia, maculopapular rash, and arthralgia.[3,5,6] However, there is now growing evidence that ZIKV infection is related to a range of neurologic disorders, such as Guillain-Barré syndrome (GBS) in adults[7] and microcephaly in infants.[2] This link has been hypothesized after the parallel upsurge of Zika cases along cases of GBS and microcephaly, particularly during the Brazilian outbreak. Consequently, the increase in the number of cases led the WHO to declare a public health emergency of international concern. However, it is relevant to mention that some cases of ZIKV have been probably misclassified because of the molecular similarity of the virus with DENV[1] leading to serological cross reactivity in serologic tests employing antibodies for laboratory diagnosis; the RT-PCR based molecular test is more effective but only useful during the first week of infection.

GBS is a rare but serious autoimmune syndrome that attacks the peripheral nerves, causing a progressive paralysis. Typically, an infection eventually triggers autoantibodies targeting gangliosides in the membrane of nervous cells, causing respiratory or gastrointestinal symptoms before more obvious neurologic/motor impairment.[8] It has a mortality rate of approximately 5%, and 20% of the patients affected usually are left with significant disability.[3] This syndrome was already associated with ZIKV infection during the outbreak in French Polynesia. Indeed, the rise and fall of Zika cases was followed by a similar trend in the onset of GBS.[4] However, the mechanisms by which ZIKV infection causes GBS have not yet been established; it has been suggested that the virus could exacerbate the immune response triggering an immunopathogenic process that determines, in turn, the onset of GBS.[3] Some patients "developed neurological symptoms during or immediately after the [ZIKV] infection, suggesting a parainfectious rather than postinfectious pattern that is typically seen in GBS", as noted in a recent review.[9] These symptoms include muscle weakness, inability to walk, facial palsy, and respiratory distress. In 2015, 1708 cases of GBS were reported in Brazil representing a 19% increase in comparison to the previous year.[2]

Therefore, we aimed to systematically review the literature and perform a meta-analysis to estimate the prevalence of GBS among ZIKV-infected individuals and discuss the most recent findings regarding the relation between ZIKV and GBS.

Methods

Literature search and systematic review

Following the recommendations of the PRISMA statement for conducting systematic reviews,[10] we searched for studies published on international journals regarding ZIKV infection and its relationship with GBS. Our inclusion criteria were epidemiological/observational studies, such as case series, epidemiological surveys, cross-sectional or cohort studies, which should have involved adult individuals. Exclusion criteria were review studies, studies written in languages other than English, Portuguese or Spanish and papers without explicit numerical data needed for the calculation of the meta-analysis.

The used keywords were "Zika" and "neurological defects". We searched for papers published anytime until early November 2017 in two databases: PubMed and Cochrane Library. On the PubMed database, 53 abstracts were found. On the Cochrane Library database, the keyword used was only "Zika", retrieving 23 papers, since the combination with "neurological defects" did not result in any paper.

Thus, the initial systematic review strategy found 76 abstracts. Among these, 56 abstracts were not relevant to our objective. The remaining 20 studies full-text were further reviewed. Among those, seven were review studies, two did not report number of individuals affected by GBS, and we could not extract the necessary data from eight studies. Therefore, three studies (totaling nine samples) were selected for further meta-analysis.[11–13]

Two of the authors performed data collection independently and registered studies' data in electronic spreadsheets. Additionally, each author critically reviewed the quality of the studies by answering a CASP checklist[14] and the studies were deemed to have satisfactory quality.

The authors unified the data, resolving any inconsistencies or omissions before further analysis. The data collected from the studies included year of sampling/publication, country where the study was performed, and sample sizes (number of ZIKV infection cases and number of GBS cases). These data were used to calculate the outcome of interest, which was the observed GBS prevalence among ZIKV-infected individuals (in other words, the number of GBS cases divided by the number of ZIKV infected cases). The individual observed GBS prevalence were then included in a meta-analysis for the calculation of a pooled ZIKV infection-associated GBS prevalence.

Meta-analysis

The GBS prevalence estimates (proportions) were log-transformed for the pooled estimation through inverse-variance weighting method[15] and back transformed to simple proportions alongside 95% confidence intervals (95% CI). The meta-analysis was conducted with a fixed effect model assumption.

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