UJEMI PEARLS

Zika Virus Infection: A Possible Cause in the Development of Guillain-Barré Syndrome?

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SUMMARY Guillain-Barré syndrome (GBS) is an autoimmune disease that damages the nerves of the peripheral nervous system, causing paralysis in humans. Several infectious agents including dengue virus, Epstein-Barr virus, and herpes virus have been suggested to be possible factors in the development of GBS however the exact cause is yet to be discovered. Recently, a strong temporal and geographical correlation between Zika virus (ZIKV) outbreaks and an increase in GBS cases within the region has implied that ZIKV could possibly portray a key role in the onset of GBS. This *Flaviviridae* virus has recently been causing large epidemics and increasing numbers of neurological complications, such as microcephaly, has been reported following outbreaks within the human population. The Asian strain of ZIKV has been shown to be neurovirulent and therefore capable of infecting nerve cells, providing further support for this connection. This article discusses the current evidence available to support the association between ZIKV and GBS, the molecular determinants that increase the neurotropism of specific ZIKV strains, and the putative molecular mechanism of ZIKV pathogenesis that causes the development of GBS. Determining the role of ZIKV in the onset of GBS can allow for the discovery of novel diagnostic biomarkers, which can aid in the early detection and prevention of GBS. The discovery of a possible mechanism of neurovirulent ZIKV strains can aid in understanding the pathogenesis of the virus in not only GBS, but other associated neurological diseases as well.

INTRODUCTION

Guillain-Barré Syndrome (GBS) is an autoimmune disease that targets the peripheral nervous system (PNS) within the body. More specifically, GBS occurs when there is immune injury at the myelin sheath and related Schwann cell components of the nerve [1]. Approximately 3000-6000 people develop this disease every year in the US, and males are more susceptible than females [2].

The common symptoms include pain in the limbs, and progressive bilateral weakness that typically begins in the lower extremities and leads to paralysis [3]. Although GBS is rare, it is a life-threatening disease as up to 20% of the patients remain severely disabled and about 5% die despite appropriate treatment [4]. This disease was first discovered by French physicians in 1916 and was described by its key diagnostic abnormality: albuminocytological dissociation, which is characterized by elevated protein levels and normal cell counts in the cerebral spinal fluid [5,6]. Currently, physicians continue to rely on this finding for correct diagnosis; however this is not an accurate method as negative test results often do not eliminate the possibility of GBS [1]. Due to the lack of other diagnostic biomarkers there have been no critical advances in the diagnosis of GBS [1].

There are two primary treatments available for GBS: plasma exchange and intravenous immunoglobulin [7,8]. Although these treatments have the potential to reduce the severity of the disease, they are only effective if initiated within the first two weeks after disease onset, which is difficult due to the poor diagnostic tools available [7]. This emphasizes the importance of developing proper diagnostic methods for early detection and proper prevention of GBS. To improve the existing diagnosis, it is necessary to gain a better understanding of the disease etiology. Many infectious agents including Epstein Barr virus,

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dengue virus, West Nile virus and *Campylobacter jejuni* have been suggested to be associated with GBS [9,10]. About 2/3 of GBS patients have reported a respiratory or gastrointestinal tract infection prior to the onset of GBS suggesting that a bacterial infection could also be the cause [9].

Despite all these associations the exact cause of GBS is yet to be determined. Recently a strong association has been made between the Zika virus (ZIKV) and GBS, as increased numbers of GBS cases has been reported in areas with ZIKV outbreaks [11]. ZIKV is an emerging virus from the *Flaviviridae* family containing a positive, single-stranded genomic RNA [11]. Although this virus was first isolated in 1964, it did not begin to cause large epidemics until 2007 [12]. There are currently 2 strains of ZIKV, the African strain and the Asian strain, but it is the Asian strain that is responsible for the recent outbreaks [12]. Historically, this virus initially presented with mild symptoms in 20% of infected patients and was clinically asymptomatic in the remaining 80% [13]. However, the Asian strain has recently been shown to infect neuronal cells causing several neurological complications in humans as well [13]. The pathogenesis of ZIKV in the human nervous system is still unclear and in need of further research [11]. The neurotropism of ZIKV along with the temporal and spatial association between the ZIKV outbreak and increased GBS cases suggests that ZIKV is a potential cause of GBS.

RESEARCH QUESTIONS

Although effective treatment is available to treat GBS, several patients continue to live with severe disabilities due to the lack of diagnostic tools available for early detection [7]. The rapid progression of GBS emphasizes the necessity for discovering new biomarkers that aid in the detection of the disease to allow for early treatment in diagnosed individuals [1]. However, to discover new diagnostic methods, it is crucial to determine the exact cause and pathogenesis of GBS. This could also allow for the identification of new therapeutic targets to control and limit the overall progression of the disease. This article focuses on the possibility of ZIKV being a cause in the development of GBS. First, the current available evidence to support the association between ZIKV and GBS will be addressed. Second, the possible determinants of the Asian strain that increases the neurovirulence of the ZIKV will be elucidated. Finally, a possible mechanism of ZIKV pathogenesis in the onset of GBS will be explored. Exploring these questions will aid in possibly discovering a known cause of GBS.

PROJECT NARRATIVE

The evidence supporting the association between GBS and ZIKV. The correlation between GBS and ZIKV is recent, thus, only two case-control studies and a few case series have been conducted to provide evidence for this association. The first case-control study was performed on GBS patients that were diagnosed during the 2013 outbreak in French Polynesia [14,15]. Prior to 2013, only 3 to 8 cases of GBS on average were reported annually in French Polynesia [14]. However, during the ZIKV outbreak, 42 patients were reported with GBS at local hospitals [14]. Although none of the patients were viremic as they tested negative for the presence of ZIKV in their blood, the presence of ZIKV IgM was detected in 92.9% of the patients indicating a recent ZIKV infection [14]. It is important to note that dengue virus (DENV) 1 and 3 serotypes were co-circulating during the ZIKV outbreak, however analysis of dengue serology did not indicate a recent DENV infection in the patients [14,16]. Furthermore, this study showed negative serological tests for *C. jejuni,* HIV, cytomegalovirus (CMV), EBV and herpes simplex virus, which have all been associated with GBS in the past [14]. This temporal association between ZIKV infection and increased GBS incidences should not be ignored.

The second case-control study was conducted during the 2015-2016 outbreak in Colombia after a 211% increase in GBS incidence over baseline was reported during the ZIKV outbreak [17]. There is a history of DENV and chikungunya virus outbreaks within this region, however the documented increase in GBS is seen during the presence of ZIKV [17]. The study was performed on individuals diagnosed with GBS and 40% of the patients tested positive for ZIKV while all of them tested negative for all four DENV serotypes [17].

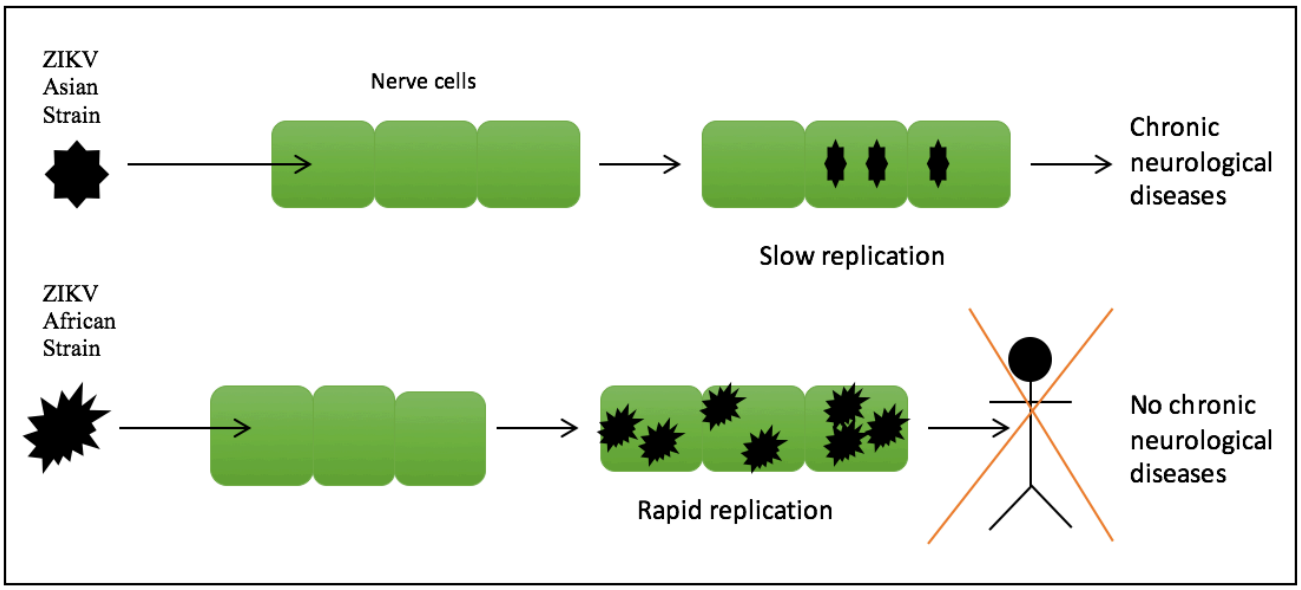

FIG. 1 The effect of the different ZIKV strains on the human population. The ZIKV Asian strain replicates slower allowing for a prolonged and chronic infection. In contrast, the ZIKV African strain replicates much faster causing rapid cell death, this kills infected individuals quickly and prevents the development of a chronic infection.

Immune responses to flaviviruses were also present in most of the patients that were tested and although it is important to consider the possibility of the presence of cross-reactive anti-flavivirus antibodies between DENV and ZIKV, the fact that an increase in GBS within Colombia is only seen during the ZIKV outbreak and not during previous DENV outbreaks lends further support for the involvement of ZIKV in GBS [17].

Additional evidence for the association between ZIKV and GBS has been provided by case reports in areas with ZIKV outbreaks. A case study in Martinique reported 2 GBS patients testing positive for the presence of ZIKV [18]. A multicenter case series reported that 8 GBS patients in an intensive care unit setting tested positive for ZIKV via RT-PCR [19]. Upon emergence of ZIKV, 8 case reports from different regions including French Polynesia, Brazil, Haiti, Netherlands, Spain, Honduras and New Zealand also suggest a link between GBS and ZIKV infection. The presence of ZIKV RNA was found in 4 cases while anti-ZIKV IgM antibodies were detected in the remainder of the patients [20-26]

The confirmation of the suggested association between GBS and ZIKV continues to problematic among researchers [13]. This is because when patients are diagnosed with GBS, ZIKV is likely cleared from the blood and the diagnosis of ZIKV infection is solely based on the detection of antibodies, which holds several limitations [13]. Despite these challenges, the evident temporal and geographical association between the ZIKV outbreaks and GBS cases as presented in these case studies should be further researched.

The determinants of the Asian strain that increases its neurovirulence in comparison to the African strain. ZIKV can be classified into 2 main lineages, the African strain and the Asian strain; however, it is the Asian strain that is responsible for the recent epidemics and neurological disorders [12]. Certain differences between the ZIKV strains could explain the ability of Asian ZIKV strains to be neurotropic [27]. Classifying these differences within the Asian strain will help in understanding how it could potentially lead to the onset of GBS. Certain acquired mutations within the Asian strain have most likely caused it to become more virulent to human neuronal cells [27]. In a recent study, seven ZIKV mutants were constructed based on the clone of the ancestral Asian strain and then used to infect mice and human neural progenitor cells (hNPCs) [28]. It was found that one of the mutants with a specific amino acid change from serine to asparagine on residue 139 (S139N) substantially increased the neurovirulence in mice [28]. The ZIKV strain containing this specific mutation also resulted in an increased viral titer within hNPCs upon infection [28]. As a result, the mutant ZIKV caused more extensive hNPC death in comparison to the wild

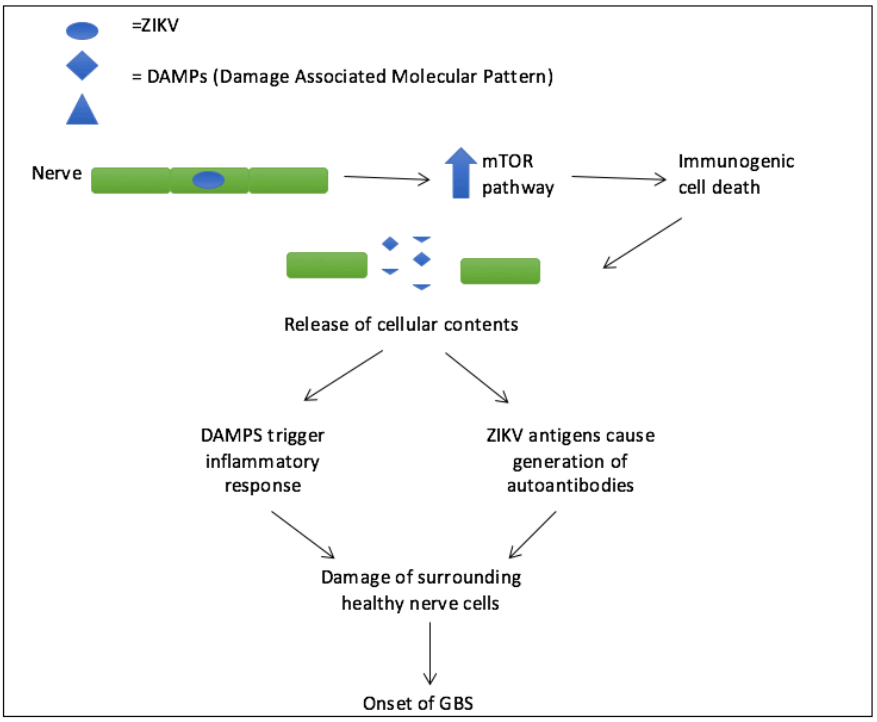

FIG. 2 Model for the proposed mechanism of ZIKV pathogenesis that causes the onset of GBS. ZIKV infection in nerve cells causes the upregulation of the mTOR pathway, which induces immunogenic cell death of infected cells. This can cause one of two things: 1) DAMPs, which are biomolecules, can trigger a local inflammatory response or 2) released ZIKV antigens can cause generation of autoantibodies due to molecular mimicry. Both pathways result in the damage of healthy nerve cells, which leads to the development of GBS.

type ZIKV. Residue 139 is related to the prM protein of ZIKV, which is a surface protein that is required for viral maturation, egress and secretion [29]. The cleavage of the prM protein is required for viral infectivity [29]. Therefore, this specific mutation might alter the maturation process of ZIKV in a way that increases the neurovirulence of the virus.

Notably, the substitution from serine to asparagine in ZIKV only emerged shortly prior to the 2013 ZIKV outbreak in French Polynesia and has been present during subsequent epidemics [28]. The introduction of this mutation in the Asian strain coincides with an increased number of cases reporting neurological disorders, including GBS [28]. In addition to the S139N mutant, three of the other mutants were found to have increased neurovirulence in comparison to the wildtype ZIKV [28]. Although these mutants are not as neurovirulent as the S139N mutant, they may still allow ZIKV to infect hNPCs (Table 1). This emphasizes the importance of studying these mutations in detail to identify the determinants of the Asian strain that promote its neurovirulence.

The Asian strain only infects a few cells and replicates slowly in comparison to other viruses, which allows the virus to cause prolonged and chronic infections within the tissues of the nervous system [27], whereas recent *in vitro* studies have shown that African strains replicate faster and cause more rapid death in hNPCs upon infection [27]. Furthermore, no cases of chronic neurological complications have been reported following an infection with the African strain [27]. It is highly unlikely that African strains will cause an endemic or chronic neurological infections as the rapid cell death caused by this strain will inhibit the persistence of the virus (Figure 1).

A possible mechanism of ZIKV that leads to the onset of GBS. Several viruses have been suggested to cause GBS; however, recently ZIKV has been also shown to have a strong association. In a study done on Rhesus monkeys it was found that the persistence of the virus in the nerve cells of the central nervous system (CNS) causes an upregulation of mTOR (the mammalian target of rapamycin) [30]. The functions of the mTOR pathway include maintaining homeostasis, neurodevelopment and regulation of the immune response [30,31]. It was also shown that the virus was able to persist in neurons for up to 42 days, which can explain why the onset of GBS is not seen until 3-4 weeks post ZIKV infection [30]. Furthermore, a mouse model indicated that the inappropriate activation of mTOR signaling in the CNS could disrupt homeostasis within neurons and induce immunogenic cell death [32].

TABLE. 1 The neurovirulence of mutant ZIKV strains in neonatal mice. The survival rate of mice was recorded after ZIKV mutant clones were infected into the brains of the rodents. The listed substitutions of amino acids at specific residues correlate to an increase in the neurovirulence of the mutant ZIKV clones. Adapted from (25)

ZIKV clone of Asian strain	Percent survival 25 days post infection
Wild Type	83%
T106A mutant	80%
S109A mutant	75%
K709R mutant	65%
S139N mutant	25%

Similarities in the molecular pathophysiology of ZIKV in the CNS and peripheral nervous system (PNS) suggest the hypothesis that mTOR signaling will also be upregulated in the nerve cells of the PNS upon ZIKV infection [33]. The increased activity of the mTOR pathway will in turn disturb the homeostasis and cause immunogenic cell death of the infected nerve cells [30,32]. This can possibly result in one of two things. First, upon cell death certain damage-associated molecular patterns that are released into the local area can perpetuate a non-infectious inflammatory response within that region [34,35]. This immune response can damage the myelin sheath of the healthy nerve cells neighboring the infected cell, causing GBS. Second, cell death can release ZIKV antigens, which can be engulfed by immune cells to trigger an adaptive immune response that causes the generation of autoantibodies due to molecular mimicry between ZIKV and PNS antigens. Previous studies have shown that autoantibodies against neural antigens have been found in 60% of GBS patients, suggesting that any existing molecular similarities between ZIKV and PNS antigens can enforce an autoantibody response which will target and damage healthy nerve cells that are not infected with ZIKV causing autoimmunity [36].

As mentioned previously, the mutation from serine to asparagine in the prM protein causes an increase in the neurovirulence of ZIKV [28]. Therefore, the mutated prM protein may play a role in the upregulation of the mTOR pathway upon ZIKV infection. Future studies should focus on relationship between the prM protein and mTOR signaling by infecting PNS nerve cells with the mutated and wildtype forms of the prM protein to monitor the differences in the activity of the mTOR pathway.

Research into this novel mechanism for ZIKV-mediated induction of GBS can aid in providing a greater understanding on the pathogenesis of ZIKV in nerve cells and its relationship to neurological diseases.

CONCLUSIONS

GBS is an autoimmune disease that, although rare, can cause damage to the PNS and cause permanent disabilities [3]. Many viruses have been suggested to be associated with GBS in the past; however, a causal relationship is yet to be determined [9,10]. This article focuses on the recent association that proposes ZIKV to be a possible factor in the onset of GBS. The emergence of neurovirulent ZIKV strains was first observed during the 2013 epidemic and as a result only a limited number of studies are present to support the association between ZIKV and GBS [14]. However, strong temporal and geographical association has been reported through two major case-control studies during ZIKV outbreaks [14,17].

Although treatments are available for GBS, they are only shown to be effective when implemented during the early stages of the disease [7]. However, early detection of this disease poses several difficulties due to the lack of efficient diagnostic methods [7]. Diagnosis currently relies on the combination of clinical features, which is problematic because the initial symptoms are usually similar to several other neurological diseases [8]. Discovering reliable biomarkers of GBS can aid in early detection and treatment of the

disease. As mentioned previously, the presence of autoantibodies that target the PNS can be a useful diagnostic marker for the detection of GBS, as these autoantibodies are present in approximately 60% of GBS patients [36].

The presence of autoantibodies against neural antigens, gangliosides in particular, were found in GBS patients and associated with damage to healthy nerves [36]. Therefore, determining any molecular similarities between ZIKV antigens and existing gangliosides on nerve cells can aid in understanding the mechanism whereby ZIKV is responsible for eliciting the generation of autoantibodies. These discoveries will not only aid in providing evidence for the association between ZIKV and GBS but can also further explain the pathogenesis of ZIKV in GBS patients.

ZIKV is still present in many countries around the world and it can cause severe neurological complications, therefore, the development of a successful vaccine would be very beneficial [37]. Since GBS is potentially life threatening and a difficult disease to treat, determining an association between ZIKV and GBS could lead to more intense efforts made towards vaccine development. Future studies should focus on the proposed pathological mechanisms in the article to prove the association between ZIKV and GBS. Moreover, since GBS is prevalent in male adults, investigating the molecular differences, such as the presence and absence of certain gangliosides, between the neurons in males and females may also be a valuable area of research to gain more insight on the relationship between ZIKV and GBS [2].

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REFERENCES

1. Willison HJ, Jacobs BC, vanDoorn PA. 2017. Guillain-Barré syndrome. The Lancet 388:717-727.
2. Winer JB. Guillain-Barré syndrome. 2001. Molecular Pathology 54:381-385.
3. Hughes R, Léger JM. 2013. The discovery of the Guillain-Barré syndrome and related disorders. Quartley Medical Review 42:177-179.
4. Yuki N, Hartung HP. 2012. Guillain-Barré syndrome. The New England Journal of Medicine 366:2294-2304.
5. Guillain G, Barré JA, Strohl A. 1916. Sur un syndrome de radiculonévrite avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire: remarques sur les caractères cliniques et graphiques des réflexes tendineux. Bulletins et mémoires de la Société des Médecins des Hôpitaux de Paris 40:1462-70.
6. Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R, Burwen DR, Cornblath DR, Cleerbout J, Edwards KM, Heininger U, Hughes R, Khuri-Bulos N, Korinthenberg R, Law BJ, Munro U, Maltezou HC, Nell P, Oleske J, Sparks R, Velentgas P, Vermeer P, Wiznitzer M. 2011. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 29:599-612.
7. The Guillain-Barre Syndrome Study Group. 1985. Plasmapheresis and acute Guillain-Barré syndrome. Neurology 35:1096-1104
8. van der Meche FGA, Schmitz PIM, Dutch Guillain-Barre Study Group. 1992. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. The New England Journal of Medicine 326:1123-1129.
9. Jacobs BC, Rothbarth PH, van der Meché FG, Hebrink P, Schmitz PI, de Klerk MA, van Doorn PA. 1998. The spectrum of antecedent infections in Guillain-Barré syndrome: a case-control study. Neurology 51:1110-1115.
10. Poropatich KO, Walker CL, Black RE. 2010. Quantifying the association between Campylobacter infection and Guillain-Barré syndrome: a systematic review. Journal of Health, Population and Nutrition 28:545-552
11. Massey TH, Robertson NP. 2016. Zika virus and neurology: proving cause and effect. Journal of Neurology 263:1255-1257.
12. Malone RW, Homan J, Callahan MV, Glasspool-Malone J, Damodaran L, De Bernardi Schneider A, Zimler R, Talton J, Cobb RR, Ruzic I, Smith-Gagen J, Janies D, Wilson J, Zika Response Working Group. 2016. Zika Virus: Medical countermeasure development challenges. PLOS Neglected Tropical Diseases 10: e0004530.
13. Munoz LS, Parra B, Pardo CA.2017. Neurological implications of Zika virus infection in adults. The Journal of Infectious Diseases 216:S897-S905.

14. Cao-Lormeau VM, Blake A, Mons S, Lastere S, Roche C, Vanhomwegen J, Dub T, Baudouin L, Teissier A, Larre P, Vial AL, DEcarn C, Choumet V, Halstead SK, Willison HJ, Musset L, Manuguerra JC, Despres P, Fournier E, Mallet HP, Musso D, Fontanet A, Neil J, Ghawché F. 2016. Guillain-Barré syndrome outbreak caused by ZIKA virus infection in French Polynesia. The Lancet. 387:1531-1539.
15. Krauer F, Riesen M, Reveiz L, Oladapo OT, Martinez-Vega R, Porgo TV, Haefliger A, Broutet NJ, Low N. 2017. Zika virus infection as a cause of congenital brain abnormalities and Guillain-Barré syndrome: systematic review. PLOS Medicine 14:e1002203.
16. Roth A, Mercier A, Lepers C, Hoy D, Duituturaga S, Benyon E, Guillaumot L. 2014. Concurrent outbreaks of dengue, chikungunya and Zika virus infections - an unprecedented epidemic wave of mosquito-borne viruses in the Pacific 2012-2014. Europe Surveillance 19: 20929.
17. Parra B, Lizarazo J, Jimenez-Arango JA, Zea-Vera AF, Gonzalez-Manrique G, Vargas J, Angarita JA, Zuniga G, Lopez-Gonzalez R, Beltran CL, Rizcala KH, Morales MT, Pacheco O, Ospina ML, Kumar A, Cornblath DR, Munoz, LS, Osorio L, Barreras P, Pardo CA. 2016. Guillain-Barré syndrome associated with Zika virus infection in Colombia. The New England Journal of Medicine 375:1513-1523.
18. Rozé B, Najioullah F, Fergé JL, Apetse K, Brouste Y, Cesaire R, Fagour C, Fagour L, Hochedez P, Jeannin S, Joux J, Mehdaoui H, Valentino R, Signate A, Cabié A. 2016. Zika virus detection in urine from patients with Guillain-Barré syndrome on Martinique, January 2016. Euro Surveillance 21:30154.
19. Sebastián UU, Ricardo AVA, Alvarez BC, Cubides A, Luna AF, Arroyo-Parejo M, Acuña CE, Quintero AV, Villareal OC, Pinillos OS, Vieda E, Bello M, Peña S, Dueñas-Castell C, Rodriguez GMV, Ranero JLM, López RLM, Olaya SG, Vergara JC, Tandazo A, Ospina JPS, Leyton Soto IM, Fowler RA, Marshall JC. 2017. Zika virus-induced neurological critical illness in Latin America: severe Guillain-Barré syndrome and encephalitis. Journal of Critical Care 42:275-281.
20. Oehler E, Watrin L, Larre P, Leparc-Goffart I, Lastere S, Valour F, Baudouin L, Mallet H, Musso D, Ghawche F. 2014. Zika virus infection complicated by Guillain-Barré syndrome—case report, French Polynesia, December 2013. Euro Surveillance 19:20720.
21. Fontes CA, Dos Santos AA, Marchiori E. 2016. Magnetic resonance imaging findings in Guillain-Barré syndrome caused by ZIka virus infection. Neuroradiology 58:837-838.
22. Kassavetis P, Joseph JM, Francois R, Perloff MD, Berkowitz AL. 2016. Zika virus-associated Guillain-Barré syndrome variant in Haiti. Neurology 87:336-337.
23. van den Berg B1, van den Beukel JC, Alsma J, van der Eijk AA, Ruts L, van Doorn PA, Jacobs BC, Simon CC. 2016. Guillain-Barré syndrome following infection with the Zika virus. Ned Tijdschr Geneeskd 160:D155.
24. Reyna-Villasmil E, Lopez-Sanchez G, Santos-Bolivar J. 2016. Guillain-Barré syndrome due to Zika virus during pregnancy. Medicina Clinica 146:331-332.
25. Medina MT, England JD, Lorenzana I, Medina-Montoya M, Alvarado D, De Bastos M, Fontiveros S, Sierra M, Contreras F. 2016. Zika virus associated with sensory polyneuropathy. Journal of the Neurological Sciences 369:271-272.
26. Siu R, Bukhari W, Todd A, Gunn W, Huang QS, Timmings P. 2016. Acute Zika infection with concurrent onset of Guillain-Barré Syndrome. Neurology 87:1623-1624.
27. Simonin Y, van Riel D, Van de Perre P, Rockx B, Salinas S. 2017. Diffrential virulence between Asian and African lineages of Zika virus. PLOS Neglected Tropical Diseases 11:e0005821.
28. Yuan L, Huang XY, Liu ZY, Zhang F, Zhu XL, Yu JY, Xu YP, Li G, Li C, Wang HJ, Deng YQ, Wu M, Cheng ML, Ye Q, Xie DY, Li XF, Wang X, Shi W, Hu B, Shi PY, Xu Z, Q CF. 2017. A single mutation in the prM protein of Zika virus contributes to fetal microcephaly. Science. DOI: 10.1126/science.aam7120.
29. Li L, Lok SM, Yu IM, Zhang Y, Khun RJ, Chen J, Rossmann MG. 2008. The flavivirus precursor membrane-envelope protein complex: structure and maturation. Science 319:1830–1834.
30. Malika A, Abbink P, Larocca RA, Boyd M, Nityanadam R, Nanayakkara O, Martinot AJ, Moseley ET, Blass E, Borducchi EN, Chandrashekar A, Brinkman AL, Molloy K, Jetton D, Tartaglia LJ, Liu J, Best K, Pereison AS, De La Barrera RA, Lewis MG, Barouch DH. 2017. Zika Virus persistence in the central nervous system and lymph nodes of Rhesus monkeys. Cell 169:610-620.
31. Wong M. 2013. Mammalian Target of Rapamycin (mTOR) Pathways in Neurological Diseases. Biomedical Journa 36:10.4103/2319-4170.110365.
32. Kassai H, Sugaya Y, Noda S, Nakao K, Maeda T, Kano M, Aiba A. 2014. Selective activation of mTORC1 signaling recapitulates microcephaly, tuberous sclerosis, and neurodegenerative diseases. Cell Reports 7:1626-1639.
33. Oh Y, Zhang F, Wang Y, Lee EM, Choi IY, Lim H, Mirakhori F, Li R, Huang L, Xu T, Wu H, Li C, Quin CF, Wen Z, Wu QF, Tang H, Xu Z, Jin P, Song H, Ming GI, Lee G. 2017. Zika virus directly infects peripheral neurons and induces cell death. Nature Neuroscience 20:1209-1212.
34. Land WG. 2015. The role of damage-associated molecular patterns (DAMPs) in human diseases: Part II: DAMPs as diagnostics, prognostics and therapeutics in clinical medicine. Sultan Qaboos University Medical Journal 15:e157-e170.
35. Chiu IM, von Hehn CA, Woolf CJ. 2012. Neurogenic Inflammation – The peripheral nervous system's role in host defense and immunopathology. Nature neuroscience. 15:1063-1067.

36. Tsunoda I, Omura S, Sato F, Kusunoki S, Fujita M, Park Am, Hasanovic F, Yanagihara R, Nagata S. 2017. Neuropathogenesis of Zika virus infection: potential roles of antibody-mediated pathology. Acta medica Kinki University 41:37-52.
37. Morabito KM, Graham BS. 2017. Zika virus vaccine development. The Journal of Infectious Diseases 216:S957-963