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Current topic

Oropouche virus – another antecedent event for Guillain–Barré syndrome?

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ABSTRACT In May 2024, the Pan American Health Organization issued alerts of increased numbers of cases of Oropouche fever in non-Amazonian regions in Latin America. Following this, an association between Oropouche fever and Guillain–Barré syndrome was reported in three patients in Santiago de Cuba, Cuba. Neurological manifestations have rarely been described in relation to Oropouche virus infection. Previously, encephalitis and meningoencephalitis have been associated with Oropouche virus infection, but now the virus seems also to be associated with Guillain–Barré syndrome. In this article we describe the main factors that could underlie the increased incidence of Oropouche fever and its neurological complications. Oropouche virus should be recognized as a potential pathogen in cases of fever associated with neurological symptoms (meningitis, meningoencephalitis, and Guillain–Barré syndrome). Medical professionals and health systems need to be aware of these complications and the importance of early diagnosis and preparedness, especially during large outbreaks or in patients living in or coming from endemic regions.

Keywords: Guillain Barré syndrome; Bunyaviridae infections; disease outbreaks; neurologic manifestations; Latin America.

Guillain–Barré syndrome is an acute autoimmune disorder affecting the peripheral nervous system. It is one of the most common causes of acute flaccid paralysis worldwide. When treated in appropriate medical settings with standard immunotherapies, most patients have a good prognosis and recovery. Nevertheless, about 5% of people affected die from complications due mainly to respiratory failure, pneumonia, and arrhythmias, and up to 20% have difficulties in walking 1 year after disease onset. Guillain–Barré syndrome is a rare disease, with an incidence of 0.81–1.91 cases per 100 000 person-years in Europe and North America, but lower incidences have been reported in China and Japan (1, 2).

Guillain–Barré syndrome is triggered by infectious and non-infectious environmental agents in genetically susceptible hosts. Several non-infectious agents are recognized as risk factors, such as trauma, surgery, and certain medicines. However, infections are the most common risk factor and these can have occurred up to 4 weeks before developing neurological symptoms. *Campylobacter jejuni* is the most commonly reported pathogen to precede the clinical development of Guillain–Barré syndrome, although other infectious agents have been identified, including cytomegalovirus, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, Epstein–Barr virus, hepatitis E virus, influenza A virus, and Zika virus. Associations with other arboviruses (dengue and chikungunya) have been reported in regions where these infections are endemic or during arbovirus outbreaks (1, 3).

Consequently, the incidence of Guillain–Barré syndrome as well as the most frequent antecedent events are highly dependent on the geographical location and the epidemic situation, especially in tropical regions. For example, in South America,

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before the Zika virus epidemic, the incidence of Guillain–Barré syndrome ranged from 0.4 in Brazil to 2.1 cases per 100 000 person-year in Chile; after Zika virus, the incidence was reported to be as high as 5.6 in Brazil and 7.6 in Colombia (1, 4).

The first report in the scientific literature associating an arbovirus with Guillain–Barré syndrome was in Cuba in 1981, despite the fact that in the preceding 15 years, eight dengue outbreaks had been registered in Caribbean countries. Estrada González described an increase in the incidence of Guillain–Barré syndrome concurring with the first major dengue outbreak which occurred in the island in 1977–1978. He proposed that dengue virus be added to the list of viruses then recognized as antecedent events for Guillain–Barré syndrome (5, 6). Various reports associating Guillain–Barré syndrome with dengue fever followed. However, it was not until the Zika virus outbreak in Latin America in 2015 that this issue received increased attention, and in February 2016, the World Health Organization (WHO) declared Zika virus a public health emergency of international concern (7). To date it is not clear if Zika virus infection makes people more prone to develop Guillain–Barré syndrome than other arbovirus infections. In Brazil, the country with the highest incidence of Zika virus infection, no increased incidence of Guillain–Barré syndrome was found in infected patients, but recent exposure to dengue virus was detected (8). The association between Zika, dengue, and chikungunya virus infections and Guillain–Barré syndrome is complex, because these viruses have short viremia periods that reduce the opportunity for detection, they frequently cocirculate, and the available serological tests are not sufficiently accurate (3).

Now we are facing a new challenge in the region of the Americas, namely Oropouche fever, which was first isolated in 1955 from an infected individual in Vega de Oropouche, Trinidad and Tobago. Since the early 1960s, Oropouche virus has been circulating in the Amazonian region (mainly in Brazil), causing sporadic cases and outbreaks, and it has been implicated in more than 30 epidemics. Outside of Brazil, epidemics have been reported in Panama and Peru (9, 10).

Recently, Oropouche fever has attracted more attention from the research community due to the substantial increase in cases. In May 2024, the Pan American Health Organization (PAHO) and WHO issued alerts of increased cases in non-Amazonian regions (11). As of October 15, 2024, PAHO reported 10 275 confirmed cases of Oropouche fever, including two deaths, and possible vertical transmission in the Americas region. Other affected countries include Bolivia (Plurinational State of), Colombia, Cuba, Dominican Republic, Ecuador, and Guyana. Imported Oropouche fever cases have been reported in Canada, the United States, and countries in the European Region (12).

Oropouche fever was first reported in Cuba in May 2024, with 74 confirmed cases from two provinces – 54 cases in Santiago de Cuba and 20 in Cienfuegos (13). Oropouche virus continued to spread and to date it has been detected in all 15 provinces of the country, with 555 confirmed cases until epidemiological week 39. The provinces of Cienfuegos, Havana, Pinar del Rio, and Santiago de Cuba accounted for 58% of confirmed cases (12).

Despite the fact that Oropouche virus has been circulating for decades in the region, it is less known to be associated with neurological manifestations than other arboviruses. The most frequent associated neurological manifestations are aseptic meningitis, meningoencephalitis, and encephalitis (14). In September 2024, three cases of Guillain–Barré syndrome were reported in patients with confirmed Oropouche fever in Santiago de Cuba (15), which was the first time that the virus has been reported in association with this syndrome.

Although neurological complications have rarely been reported to concur with Oropouche fever, the following factors could change this. The geographic distribution of cases has been changing, especially recently. Oropouche virus was initially located in rural and wooded areas, where the climate and forest environment favor the proliferation of its preferred vector – *Culicoides paraensis* midges. However, climate change, the development of human activities leading to deforestation and urbanization, and globalization of human and animal transportation could modify the vector's natural habitats. Mosquitoes such as *Coquillettidia venezuelensis*, *Aedes serratus*, *Culex quinquefasciatus* are also vectors for virus transmission to humans (16).

Environmental changes are not the only factors that can contribute to the epidemic potential of Oropouche virus; virus reassortment has been reported to facilitate adaptation to new vectors or even increase virulence, as suggested with the 2023–2024 Oropouche virus re-emergence in the Brazilian Amazonian region, followed by geographical expansion into previously non-endemic areas (17). Recently, two deaths from Oropouche virus infections were reported for the first time in a non-endemic region of Brazil (18).

Another factor that could contribute to the increased awareness and reporting of Oropouche virus infection is the emergence of other arboviral diseases (e.g., West Nile fever and Zika virus infection) which have attracted and shifted attention to arboviruses in the region of the Americas (16). When the virus was mainly confined to rural or forest regions, we would expect an underdetection of neurological manifestations, owing to the poor access of the population to medical care and to the shortage of available diagnostic tests (14). If a large increase in cases occurs in urban areas, as observed in 2024, more patients will likely present with neurological manifestations, because urban residents have better access to advanced medical care. The occurrence of central nervous system involvement during outbreaks of this virus in Brazil has been documented since 2012, when a short nucleotide RNA genomic segment of Oropouche virus was identified in the cerebrospinal fluid of three patients from the Northern Amazonian region, highlighting its possible neuroinvasive capabilities (19).

Knowledge of the mechanisms underlying the pathophysiology of Guillain–Barré syndrome associated with arboviral infections is very limited. Overall, the development of Guillain–Barré syndrome is not centered on direct neuroinvasive mechanisms of a pathogen; rather it is thought to be caused by an aberrant autoimmune response triggered by a previous infection. Two stages have been recognized: first, an immunological trigger that initiates the mechanism and, second, an immune-mediated attack on axons and/or myelin. Of all the recognized infectious agents involved in triggering Guillain–Barré syndrome, *C. jejuni* is by far the most frequent antecedent infection and the most investigated to date. Autoantibodies generated against *C. jejuni* lipo-oligosaccharides during infection mediate neuronal damage through cross-reaction with various nerve gangliosides (molecular mimicry). However, both humoral and cellular immune responses contribute to the pathophysiology of Guillain–Barré syndrome. Triggering the production of cross-reactive antibodies targeting gangliosides, such as GM1, GD1a, and GQ1b, probably results in axoglial damage. It is thought that a similar process is involved in

the development of Guillain–Barré syndrome associated with viral pathogens, including arboviruses. The understanding of immune-mediated mechanisms underlying axonal damage and demyelination in this condition remains limited (1, 2).

Autoreactive T cell immunity against peripheral nervous system-myelin proteins may be the primary immunopathological mechanism for the demyelinating subtype of Guillain–Barré syndrome (acute inflammatory demyelinating polyneuropathy). On the other hand, autoantibodies against gangliosides of the peripheral nerves are thought to underlie the axonal subtype (acute motor axonal neuropathy). However, differentiation of these two subtypes based on their underlying pathological mechanisms is being challenged, and there is probably a combination of humoral and cellular immune responses in both types of the syndrome. Ganglioside-targeting antibodies, type-1 interferon pathways, together with other immune system players, as well as genetic or epigenetic factors within host and pathogen, are known to determine the susceptibility of an individual to developing Guillain–Barré syndrome (1, 4).

Guillain–Barré syndrome associated with arboviral infections has received much less attention in relation to the pathophysiological mechanisms involved. The few studies that have been conducted are concerned with Zika and dengue infections (3, 20, 21). The immune response evoked by these two viruses could cross-react with peripheral nerve components through sharing of cross-reactive epitopes directed towards the myelin or axon of peripheral nerves. Zika virus has emerged as a possible etiology of acute inflammatory demyelinating polyneuropathy through the production of anti-ganglioside antibodies (autoimmune process) and cross-reacting antibodies to flavivirus antigens (molecular mimicry). On the other hand, the acute motor axonal neuropathy variant of Guillain–Barré syndrome has been frequently reported following Zika virus infection with severe functional impairment and the need for mechanical ventilation. Although there are no reports of typical antiganglioside antibodies in Guillain–Barré syndrome associated with arboviral infection, an antiglycolipid antibody was detected in 30% of patients with acute inflammatory demyelinating polyneuropathy. Additionally, the release of tumor necrosis factor, complement, and interleukins with proinflammatory features that participate in the immune response to dengue and Zika viruses may have an important role in the pathogenesis of Guillain–Barré syndrome (3).

Guillain–Barré syndrome has been reported with other arboviral infections including Chikungunya, West Nile, and Japanese encephalitis viruses (3). Regarding Oropouche fever, very little can be said about its association with Guillain–Barré syndrome and even less about the pathophysiology. A recent integrated genome-wide transcriptome analysis of human primary astrocytes, infected with chikungunya, Mayaro, Oropouche, or Zika viruses, demonstrated that Oropouche virus interferes with ion transport and neuronal synapse regulation and induces down-regulation of type 1 interferon signaling, highlighting genes with antiviral activities (22). Some of these mechanisms could support the neuroinvasive capacities of Oropouche virus in the central nervous system, and these could possibly be extended to the peripheral nervous system, given that astrocytes and Schwann cells could share similar functions. Much more research is needed into the neuropathogenesis of Guillain–Barré syndrome associated with Oropouche virus, but some evidence exists supporting its ability to elicit neuropathogenic mechanisms leading to neurovirulence and neuroimmune interactions.

At present, Latin America is facing a complex epidemiological situation where different arboviruses are circulating, with dengue infection being widespread. It is not clear how some of these pathogens could alter the inflammatory and immunological response and subsequently the clinical manifestations of Oropouche infection, including its neurological manifestations. Until recently, Oropouche fever has been a neglected infectious disease. However, Oropouche virus should be recognized as a potential pathogen in cases of fever associated with neurological symptoms (meningitis, meningoencephalitis, and Guillain–Barré syndrome), especially in patients living in or coming from endemic regions (13). Additionally, more studies are needed to improve the understanding of the neurological manifestations of Oropouche fever, which requires increasing the laboratory diagnostic capacity for Oropouche virus and other arboviruses.

Given the factors described above, the increased incidence of Guillain–Barré syndrome in Santiago de Cuba related to Oropouche virus infection is not unexpected, and we might continue to encounter it in other regions with similar epidemiological characteristics. This is a red flag that medical professionals and health systems must be aware of and which calls for increased surveillance and diagnostics, especially during large outbreaks and in endemic regions.

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REFERENCES

1. Shahrizaila N, Lehmann HC, Kuwabara S. Guillain-Barré syndrome. Lancet. 2021;397(10280):1214–28. https://doi.org/10.1016/S0140-6736(21)00517-1
2. Habib AA, Waheed W. Guillain-Barré syndrome. Continuum (Minneap Minn). 2023;29(5):1327–56. https://doi.org/10.1212/CON.0000000000001289
3. Arriaga-Nieto L, Hernández-Bautista PF, Vallejos-Parás A, Grajales-Muñiz C, Rojas-Mendoza T, Cabrera-Gaytán DA, et al. Predict the incidence of Guillain Barre syndrome and arbovirus infection in Mexico, 2014–2019. PLOS Glob Public Health. 2022;2(3):e0000137. https://doi.org/10.1371/journal.pgph.0000137
4. Ripellino P, Schreiner B, Latorre D. Expanding our understanding of Guillain-Barré syndrome: recent advances and clinical implications. Eur J Immunol. 2024;54(11):e2250336. https://doi.org/10.1002/eji.202250336

5. Estrada J, Goyenechea A, Herrera C. [Acute polyradiculoneuritis outbreak type Landry-Guillain-Barré-Strohl during a dengue epidemic]. Rev Cub Hig Epid. 1981;19:256–65. [Spanish]
6. González-Quevedo Monteagudo A, Santiesteban Freixas R, Lestayo O'Farrill Z, Machado Curbelo C. The association of Guillain-Barré syndrome with dengue fever was first described in Cuba. An Acad Cienc Cuba. 2024;14(1):e1464.
7. World Health Organization. Fifth meeting of the Emergency Committee under the International Health Regulations (IHR 2005) regarding microcephaly, other neurological disorders and Zika virus 2016. Geneva: WHO; 2016 [cited 2024 Sep 23]. Available from: http://www.who.int/mediacentre/news/statements/2016/zika-fifth-ec/en/
8. Matos LM, Borges AT, Palmeira AB, Lima VM, Maciel EP, Fernández RNM, et al. Frequency of exposure to arboviruses and characterization of Guillain Barré syndrome in a clinical cohort of patients treated at a tertiary referral center in Brasília, Federal District. Rev Soc Bras Med Trop. 2022;55:e03062021. https://doi.org/10.1590/0037-8682-0306-2021
9. Sakkas H, Bozidis P, Franks A, Papadopoulou C. Oropouche fever: a review. Viruses. 2018;10(4):175. https://doi.org/10.3390/v10040175
10. Travassos da Rosa JF, de Souza WM, Pinheiro FP, Figueiredo ML, Cardoso JF, Acrani GO, et al. Oropouche virus: clinical, epidemiological, and molecular aspects of a neglected orthobunyavirus. Am J Trop Med Hyg. 2017;96(5):1019–30. https://doi.org/10.4269/ajtmh.16-0672
11. Pan American Health Organization/World Health Organization. Epidemiological alert: Oropouche in the region of the Americas, 9 May 2024. Washington, DC: PAHO/WHO; 2024 [cited 2024 Sep 23]. Available from: https://www.paho.org/en/documents/epidemiological-alert-oropouche-region-americas-9-may-2024
12. Pan American Health Organization/World Health Organization. Epidemiological alert: Oropouche in the region of the Americas, 15 Oct 2024. Washington, DC: PAHO/WHO; 2024 [cited: 2024 Oct 17]. Available from: https://www.paho.org/en/file/152348/download?token=-0Gi74AQ
13. Benitez AJ, Alvarez M, Perez L, Gravier R, Serrano S, Hernandez DM, et al. Oropouche fever, Cuba, May 2024. Emerg Infect Dis. 2024;30(10):2155–9. https://doi.org/10.3201/eid3010.2409002024
14. Chiang JO, Azevedo RS, Justino MCA, Matos HJ, Cabeça HLS, Silva SP, et al. Neurological disease caused by Oropouche virus in northern Brazil: should it be included in the scope of clinical neurological diseases? J Neurovirol. 2021;27(4):626–30. https://doi.org/10.1007/s13365-021-00987-9
15. de Armas Fernández J, Peña García C, Acosta Herrera B, Betancourt Plaza I, Gutiérrez de la Cruz Y, Resik Aguirre S, et al. Report of an unusual association of Oropouche fever with Guillain-Barré syndrome in Cuba, 2024. Eur J Clin Microbiol Infect Dis. 2024;43(11):2233–7. https://doi.org/10.1007/s10096-024-04941-5
16. Martins-Filho PR, Carvalho TA, Dos Santos CA. Spatiotemporal epidemiology of Oropouche fever, Brazil, 2015–2024. Emerg Infect Dis. 2024;30(10):2196–8. https://doi.org/10.3201/eid3010.241088
17. Naveca FG, Almeida TAP, Souza VS, Nascimento V, Silva D, Nascimento F, et al. Human outbreaks of a novel reassortant Oropouche virus in the Brazilian Amazon region. Nat Med. 2024;30(12):3509–21. https://doi.org/10.1038/s41591-024-03300-3
18. Bandeira AC, Pereira FM, Leal A, Santos SPO, Barbosa AC, Souza MSPL, et al Fatal Oropouche virus infections in nonendemic region, Brazil, 2024. Emerg Infect Dis. 2024;30(11). https://doi.org/10.3201/eid3011.241132
19. Bastos M de S, Figueiredo LT, Naveca FG, Monte RL, Lessa N, Pinto de Figueiredo RM, et al. Identification of Oropouche orthobunyavirus in the cerebrospinal fluid of three patients in the Amazonas, Brazil. Am J Trop Med Hyg. 2012;86(4):732–5. https://doi.org/10.4269/ajtmh.2012.11-0485
20. Lynch RM, Mantus G, Encinales L, Pacheco N, Li G, Porras A, et al. Augmented Zika and dengue neutralizing antibodies are associated with Guillain-Barré syndrome. J Infect Dis. 2019;219(1):26–30. https://doi.org/10.1093/infdis/jiy466
21. Vieira MADCES, Cruz ACR, Barros ANM, Costa DL, Silva EVPD, Batista FMA, et al. Guillain-Barré syndrome and dengue-like disease in 2015: temporal relationship in Piauí state and implications on Zika virus surveillance. Rev Inst Med Trop Sao Paulo. 2017;59:e22. https://doi.org/10.1590/S1678-9946201759022
22. Geddes VEV, Brustolini OJB, Cavalcante LTdF, Moreira FRR, de Castro FL, Guimarães APdC, et al. Common dysregulation of innate immunity pathways in human primary astrocytes infected with Chikungunya, Mayaro, Oropouche, and Zika viruses. Front Cell Infect Microbiol. 2021;11:641261. https://doi.org/10.3389/fcimb.2021.641261

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El virus del Oropouche, ¿otro antecedente del síndrome de Guillain-Barré?

RESUMEN En mayo del 2024, la Organización Panamericana de la Salud emitió una alerta sobre el aumento del número de casos de fiebre del Oropouche en zonas no amazónicas de América Latina. Posteriormente, se notificó una asociación entre la fiebre del Oropouche y el síndrome de Guillain-Barré en tres pacientes en Santiago de Cuba (Cuba). Solo en contadas ocasiones se han descrito algunas manifestaciones neurológicas asociadas a la infección por el virus del Oropouche. La encefalitis y la meningoencefalitis han sido asociadas anteriormente a la infección por este virus, pero al parecer esta infección podría ahora también estar asociada al síndrome de Guillain-Barré. El propósito de este artículo es describir los principales factores subyacentes que podrían explicar el aumento de la incidencia de la fiebre del Oropouche y sus complicaciones neurológicas. En los casos de infección por el virus del Oropouche asociada a síntomas neurológicos (como meningitis, meningoencefalitis y síndrome de Guillain-Barré), se recomienda reconocer al virus del Oropouche como un posible agente patógeno. Es imperativo que los profesionales médicos y los sistemas de salud tengan en cuenta estas complicaciones, así como la importancia del diagnóstico temprano y la preparación, especialmente durante los grandes brotes o en pacientes residentes o provenientes de zonas con endemicidad.

Palabras clave: Síndrome de Guillain-Barré; infecciones por Bunyaviridae; brotes de enfermedades; manifestaciones neurológicas; América Latina.

Seria o vírus Oropouche mais um evento antecedente da síndrome de Guillain-Barré?

RESUMO Em maio de 2024, a Organização Pan-Americana da Saúde emitiu alertas sobre o aumento no número de casos de febre do Oropouche em regiões não amazônicas da América Latina. Posteriormente, foi relatada uma associação entre a febre do Oropouche e a síndrome de Guillain-Barré em três pacientes em Santiago de Cuba, Cuba. Relatos de manifestações neurológicas relacionadas à infecção pelo vírus Oropouche são raros. No passado, tanto encefalite quanto meningoencefalite foram associadas à infecção pelo vírus Oropouche. Agora, acredita-se que o vírus esteja associado também à síndrome de Guillain-Barré. Neste artigo, descrevemos os principais fatores que podem estar por trás do aumento na incidência da febre do Oropouche e suas complicações neurológicas. O vírus Oropouche deve ser considerado um possível patógeno em casos de febre associada a sintomas neurológicos (meningite, meningoencefalite e síndrome de Guillain-Barré). Os profissionais de saúde e os sistemas de saúde precisam estar cientes dessas complicações e da importância do diagnóstico precoce e da preparação, sobretudo durante grandes surtos ou em pacientes que morem em regiões endêmicas ou que tenham visitado essas regiões.

Palavras-chave: Síndrome de Guillain-Barré; infecções por Bunyaviridae; surtos de doenças; manifestaciones neurológicas; América Latina.