Nervous System Manifestations of Arboviral Infections

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Accepted: 22 March 2022 / Published online: 15 September 2022 © The Author(s), under exclusive licence to Springer Nature Switzerland AG 2022

Abstract
Purpose of Review Complex environmental factors and human intervention influence the spread of arthropod vectors and the cycle of transmission of arboviruses. The spectrum of clinical manifestations is diverse, ranging from serious presentations like viral hemorrhagic fever (e.g., dengue, yellow fever, rift valley fever) or shock syndromes (e.g., dengue virus) to organ-specific illness like meningoencephalitis.

Recent Findings A spectrum of clinical neurologic syndromes with potential acute devastating consequences or long-term sequelae may result from some arboviral infections.

Summary In this review, we describe some of the most frequent and emerging neuro-invasive arboviral infections, spectrum of neurologic disorders including encephalitis, meningitis, myelitis or poliomyelitis, acute demyelinating encephalomyelitis, Guillain-Barré syndrome, and ocular syndromes.

Keywords Encephalitis · Zika · Chikungunya · Yellow fever · Japanese encephalitis · Meningitis · Guillain-Barre syndrome · Transverse myelitis

Introduction
Arbovirus (arthropod-borne virus) is a broad term to include RNA viruses from different families including Flaviviridae, Phenuviridae, Togaviridae, and Reoviridae which require a life cycle in a host and vector (Table 1). Majority of the arboviral infections are seen in the tropical and sub-tropical regions. However, over the last century, increasing human influence on the environment with activities such as deforestation, industrialization, urbanization, international travel, and population growth has resulted in a change in the environment [1•]. One consequence of these changes is the unprecedented risk of exposure to previously unknown infectious agents or the reemergence of previously known microorganisms including some of the arboviruses. The geospatial distribution and epidemiology of the many members of the arboviral family occurs in complex interactions between hosts, reservoirs, and arthropod vectors [2]. Most arboviruses maintain dynamic enzoonotic or sylvatic transmission cycles between mosquitoes and non-human primates including birds, rodents, horses, or others. In the sylvatic cycle, humans are dead-end hosts. The human host acquires the infection during blood feeding of insects including mosquitoes, ticks, or sandflies. Tick-borne encephalitis may also be transmitted by consumption of raw milk from infected animals like goats and cows [3]. Rare cases of transmission from transfusion and organ donation have been documented [4, 5]. Certain viruses like dengue, chikungunya, Zika, and yellow fever viruses can exist in urban epidemic...
cycle where the virus is fully adapted to the humans who act as the amplifying host without the needs for intermediary animal hosts. Arboviral transmission tends to be seasonal and could be variable depending on local climatic conditions, viral transmission, and vector activity.

Human infection may follow an asymptomatic clinical course or manifest as a spectrum of clinical manifestations ranging from undifferentiated febrile illness to serious presentations like hemorrhagic fever and shock syndromes. Many arboviruses have neurotropic avidity (Table 1) and may produce a spectrum of neurologic disorders due to direct invasion of either the central nervous system (leading to meningoencephalitis, myelitis, retinitis, and/or cerebral vasculitis), or the peripheral nervous system (which can lead to myositis or peripheral neuritis). Importantly, arboviruses are also associated with a variety of post-infectious immune-mediated conditions as well. These can impact the nervous system at any level and lead to a variety of syndromes such as autoimmune encephalitis, acute demyelinating encephalomyelitis (ADEM), acute inflammatory demyelinating polyradiculopathy (AIDP), and its variants [6]. Antibody cross-reactivity across different arboviruses, particularly flaviviruses, may pose challenges for serological diagnosis and serosurveys to assess prevalence or emergence of arboviruses [7–12]. Further advances in accurate point-of-care diagnostics will help not only with patient care but also surveillance of various co-circulating arboviruses in different regions. While new vaccines are being developed for prevention, treatment for most of the arboviral infections is supportive. The objective of this clinical review is to provide a comprehensive review of emerging neurotropic arboviral infections, clinical disorders associated with these infections, prevention, and management.

### Table 1: Classification of arbovirus

| Arbovirus family | Common viruses |
|------------------|----------------|
| Flaviviridae      | West Nile Virus, Japanese encephalitis virus, St. Louis encephalitis virus, dengue virus, Zika virus, yellow fever virus, tick-borne encephalitis virus, Usutu virus, Kyasanur forest disease |
| Togaviridae       | Eastern equine encephalitis (EEE) virus, Venezuelan equine encephalitis (VEE) virus, Chikungunya virus, O’nyong nyong virus, Ross River virus, Sindbis virus |
| Peribunyaviridae  | Jamestown Canyon, La Crosse, Cache valley |
| Phenuiviridae     | Heartland, Rift Valley fever, Sandfly fever, Toscana |
| Reoviridae        | Colorado tick fever |

### Epidemiology of Arboviruses and Emerging Neuroinvasive Arboviral Infections

About 17% of all infectious diseases are attributed to vector-borne pathogens including parasites, viruses, and bacteria resulting in over 700,000 deaths annually [13]. In the last couple of decades, there have been emergence and re-emergence of a number of viral infections across the world (Fig. 1). Most of the emerging infections are considered to be of zoonotic origin. In addition to spread of endemic arboviruses in a wider geographic region resulting in larger, more frequent outbreaks, new viruses may be introduced in regions with vectors capable of disseminating the infection.

West Nile virus, which was first reported in 1999 in New York, has spread all across North America, Europe, and also parts of South America. In the USA, over 52,000 cases of WNV including 25,849 cases of neuroinvasive WNV have been reported between 1999 and 2020 with a mortality of 8–12% [14]. Increased circulation of West Nile virus has been noted in central and Southern Europe with 300–1000 locally transmitted cases of West Nile virus documented annually [15]. Outbreaks of West Nile virus in Israel and West Asia have occurred since the introduction of the virus in that region in 2000 [16–18].

Zika virus re-emerged in 2007 in the Pacific Islands of Yap and caused pandemic spread in Brazil and the Americas resulting not only in febrile illness but over 3700 cases of congenital microcephaly [19••, 20•, 21]. The chikungunya and Zika virus outbreaks in the Americas in 2013 and 2015 demonstrated how rapidly these diseases could spread with the introduction of a virus in a region with vectors capable for transmission.

Many mosquito-borne viruses are endemic in Africa. Due to lack of disease tracking, the extent of disease caused by various arboviruses is unclear. Recently, there has been reporting of infections from new regions and also discovery of new mosquito-associated viruses [22]. Recent epidemics of yellow fever, Rift Valley fever, dengue, and West Nile viruses highlight the need for ongoing surveillance [23–25].

As in the African subcontinent, many arboviruses are endemic to Asia. There has been a 30-fold rise in incidence of dengue with 50–100 million infections annually, putting over 2.5 billion people at risk for serious illnesses [26]. The last couple of decades have also seen a rise in Japanese encephalitis and chikungunya virus disease cases with potential for widespread disease [27–33]. Along with these highly prevalent infections, outbreaks of other viruses like Rift Valley fever, Kyasanur Forest, Chandipura, and West Nile viruses have occurred and pose additional challenges [34–42].
Pathogenesis

Arboviruses are usually transmitted to human hosts when mosquitoes, ticks, or sandflies attach to the skin for a blood meal. Animal models have suggested that large amounts of virus may be inoculated extravascularly and the level of viral inoculation is proportional to feeding time [43]. The saliva of the arthropods which has anti-inflammatory and anti-hemostatic properties alter host immune response and plays a key role in disease pathogenesis [44]. Following viral inoculation, the initial viral replication occurs in the Langerhans dendritic cells followed by migration to regional lymph nodes. This is followed by a period of transient viremia which results in dissemination of the virus to the reticuloendothelial system [45••, 46•]. The degree and duration of viremia correlates with severity of the disease and neuroinvasion in case of neurotropic viruses [46•, 47–49].

Arboviruses may enter the central nervous system through direct infection of blood brain barrier (BBB), paracellular entry following disruption of BBB, Trojan horse mechanism (migration with infected leukocytes), retrograde transport along peripheral nerves, or by involvement of olfactory neurons with central nervous system entry through cribriform plate [50•, 51–53].

Spectrum of Neurological Clinical Disorders Associated with Arboviruses

Neurological manifestations of arboviral infections vary based on endemic area, virus serotype, and prior exposure to the virus (e.g., as seen with dengue) and host-viral interactions. Like other infectious pathogens, the classification of neurologic disorders caused by arboviral infections depends on the anatomic location (i.e., meningitis, encephalitis, myelitis, neuritis) and type of involvement-direct viral vs immune-mediated. Neuro-invasive arboviruses may concomitantly affect different anatomic locations and cause a multitude of clinical manifestations including central and peripheral nervous system involvement in the same episode of illness. Some of the arboviruses are thought to be neurotropic viruses like West Nile, Japanese encephalitis, and St. Louis encephalitis viruses. Other arboviruses like dengue, Zika, and chikungunya viruses predominantly cause a systemic syndrome but can also cause direct viral invasion of the brain with serious neurologic manifestations (Table 2). The dengue viruses, which are the most common arboviruses around the world, are associated with neurologic manifestations in 0.5–5% of patients [54, 55].
Syndromes Associated with Direct Viral Invasion

**Encephalitis**

Encephalitis is characterized by inflammation of brain parenchyma and has various causes, infections (predominantly viral), and autoimmune disorders being the most commonly identified.

The etiology of encephalitis varies depending on the geographic region. In eastern Asia, a common cause of encephalitis is Japanese encephalitis virus infection. It is a member of the flavivirus family and causes an estimated 30,000 to 50,000 cases of encephalitis and 10,000 deaths in Asia yearly [56••, 57•]. The classic presentation of Japanese encephalitis includes flat, expressionless facies, tremors, and hypertonia. In the United States (US), encephalitis cases are associated with approximately 19,000 hospitalizations and more than 1000 deaths per year. Most sporadic viral encephalitis cases in the US are attributed to enteroviruses and herpesviruses (HSV, VZV). West Nile virus is the most common cause of epidemic arboviral encephalitis in the US.

Viral infections causing encephalitis produce two distinct clinico-pathological entities: acute viral encephalitis and post-infectious encephalitis which is described below. The pathogenesis of acute viral encephalitis involves direct infection of neurons with associated neuronal destruction, perivascular inflammation, neuronophagia, and tissue necrosis. The clinical features of arboviral encephalitis may vary by causal pathogen, degree of parenchymal involvement, its location (temporal lobe, limbic, brainstem, or other locations), and host factors. Elderly, neonates, and immunocompromised patients may have more severe presentations. Patients may present with fever, headache, nausea, vomiting, and features of neurological dysfunction including altered level of consciousness, gait instability, focal neurologic deficits, seizures, and extrapyramidal signs (hypertonia, tremors).

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tremors). Patients with encephalitis require hospitalization for supportive care, airway management, monitoring for raised ICP, and seizures. A significant proportion of patients can have residual neurological deficits. Approximately, two-thirds of deaths are caused by acute viral encephalitis and one-third attributed to post-infectious syndromes.

Meningitis

Most of the arboviruses which have been implicated in encephalitis may also cause an aseptic meningitis syndrome. Pathogens may cause involvement of both the meninges and the brain parenchyma leading to the term meningoencephalitis. Arboviral meningitis is characterized by fever, headache, and stiff neck and presentation may be indistinguishable from other aseptic meningitis. CSF studies may show lymphocytic pleocytosis with minimal change in CSF protein and glucose [58]. Patients with West Nile meningitis may have significant CSF pleocytosis with neutrophilia unlike typical aseptic meningitis. A strong suspicion for endemic arboviral infection should be maintained when patients present during seasonal periods of viral transmission.

Poliomyelitis/Acute Flaccid Myelitis

West Nile virus has been associated with poliomyelitis due to involvement of anterior horn cells in the spinal cord. In contrast to GBS, WNV poliomyelitis is usually associated with meningitis, and encephalitis, as part of an acute viral process. Pathologic features show motor neuron destruction in anterior horn cells with interstitial and perivascular lymphocytic infiltrate features [59, 60•]. In a population-based study of 32 patients with WNV associated with the clinical syndrome of acute flaccid paralysis, WNV poliomyelitis was the most common cause and occurred in 84% of the patients [61]. Similar anterior horn cell involvement with focal muscle wasting and lower motor neuron signs have also been noted with other flaviviruses including Japanese encephalitis and St. Louis Encephalitis viruses [62].

Neuro-Ophthalmologic Syndromes

Arboviruses may cause a multitude of ocular manifestations including conjunctivitis, uveitis, chorioretinitis, and optic neuropathy which may occur in the acute phase due to direct viral involvement or as post-infectious sequelae [63•]. Dengue, Zika, and chikungunya have all been noted to involve the posterior segment of the eye with vascular and neuro-ophthalmic manifestations. Maculopathy characterized by vasculitis and hemorrhages is the most common manifestation in dengue virus infection seen in up to 10% of the patients. Other manifestations include retinal hemorrhages, peripapillary hemorrhages, Roth’s spot, and diffuse retinal edema, choroidal neovascularization but optic neuritis has also been reported [64, 65]. Macular chorioretinal atrophy, optic nerve hypoplasia, and increased cup-to-disc ratio have been noted in infants with congenital Zika virus syndrome [65]. West Nile virus can cause a wide array of ocular manifestations like anterior uveitis, retinal vasculitis, optic neuritis, and sixth cranial nerve palsy [66, 67]. Asymptomatic multifocal chorioretinitis is the most common manifestation [66, 68–71]. Fundoscopic eye exam could be considered during clinical evaluation of neuroinvasive arboviral disease.

Post-Infectious Immune-Mediated Syndromes

Infectious agents are one of the common environmental factors which act as a trigger for autoimmune disorders. Proposed mechanisms include molecular mimicry resulting in altered recognition of self-antigens, epitope spreading which causes non-specific immune response to a wider range of antigens, and bystander activation whereby autoreactive immune cells are triggered following exaggerated inflammatory response to a pathogen [72, 73, 74•].

Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis is an immune-mediated disorder which occurs days to weeks after a viral infection and associated with white matter demyelination [75•]. The histopathologic findings of post-infectious ADEM include widespread perivenular inflammation and demyelination.

ADEM which is classically considered a monophasic illness may present with various neurological signs or symptoms including impaired consciousness, seizures, and/or motor weakness. Acute disseminated encephalomyelitis-like presentation has been described with Zika, dengue, and Japanese encephalitis viruses [76–79]. Patients usually present within 2 weeks after initial onset of infection with headache, vomiting, altered mental status, and seizures and could be mistakenly diagnosed as a meningoencephalitis syndrome.

MRI shows multifocal, asymmetric, white matter hyper-intensities involving cerebral cortex, subcortical white matter, and basal ganglia. These lesions may show a pattern of ring-shaped contrast enhancement. As a consequence of the post-infectious inflammatory process, CSF studies may show pleocytosis and elevated protein. It is important to differentiate ADEM from other demyelinating disorders particularly multiple sclerosis. Monophasic, post-infectious illness with more acute clinical presentation, less pronounced periventricular distribution of lesions on MRI, and inflammatory CSF picture can be helpful. Most of these patients are treated with high dose steroids with a majority of patients recovering in 1–4 weeks. Residual neurological deficits are noted in about one-third of the patients [79].
Autoimmune Encephalitis

Antibodies to neuronal antibodies like N-methyl D-aspartate receptor (NMDA-R) may trigger autoimmune encephalitis. The association of herpes simplex encephalitis with post-infectious autoimmune encephalitis has been well documented. A recent report of three patients who presented with relapsing symptoms like choreoathetosis, sleep disorder, and agitation following proven Japanese encephalitis were found to have positive anti-NMDAR IgG in CSF and improved with immunotherapy [77, 80, 81]. Similar presentation of anti-NMDAR antibody-associated autoimmune encephalitis has been reported with Chikungunya virus as well [82]. Another report describes a patient with West Nile virus infection who developed autoimmune encephalitis with antibodies to anti-glycine receptor and improved with immunomodulatory therapy [83]. As the awareness of autoimmune encephalitis and access to testing improves, it is possible that more cases of arbovirus-associated autoimmune encephalitis may be reported in the future.

Post-Infectious Myelitis

Myelitis can occur as monophasic illness related to direct arboviral infection or as a post-infectious immune-mediated phenomenon. There have been case reports of transverse myelitis following dengue, Zika, chikungunya, and Japanese encephalitis viruses [84–92]. This may present as a monophasic post-infectious inflammatory event. However, acute infectious can also serve as a trigger for underlying autoimmune disorders such as myelin-oligodendrocyte glycoprotein-associated disease (MOGAD) [93•]. Thus, in patients with suspected post-infectious myelitis, a broad inflammatory work-up may be warranted.

Acute inflammatory Demyelinating Polyradiculopathy

AIDP is the most common cause of acute flaccid paralysis and is characterized by acute, progressive, bilateral, flaccid weakness, and sensory changes. It is commonly associated with albumin-cytologic dissociation in CSF studies. AIDP can be broadly classified into demyelinating and axonal subtypes, which have variable presentations. The main demyelinating forms include the classic Guillain-Barre syndrome (GBS), as well as Miller Fisher syndrome, characterized by ataxia, ophthalmoplegia, and areflexia [94••]. The main axonal variants include acute motor axonal neuropathy (AMAN), which may be clinically indistinguishable from acute flaccid myelitis (AFM) as they both typically present with flaccid weakness, areflexia, and preserved sensation, and acute motor and sensory axonal neuropathy (AMSAN) which presents similarly to GBS. Autoimmune processes (anti-ganglioside antibody) and molecular mimicry (cross-reacting antibodies to flavivirus antigens) have been thought to be the etiology for AIDP [94••]. Various AIDP variants have been described mostly following dengue infection but there are rare reports of AIDP presenting during acute febrile dengue illness [95–99]. Zika virus has emerged as an important cause of AIDP in regions with recent outbreaks particularly in South America [76, 100, 101, 102•, 103–105, 106•]. The prevalence of AIDP among Zika-infected individuals has been estimated to be about 1.2% however, in one study, antiglycolipid antibody was present in about 30% of patients with AIDP [101, 107]. In regions with high prevalence of multiple arboviral infections, AIDP has been being reported in arboviral co-infections [101, 103, 107, 108]. Similarly, AIDP has been reported with other arboviral infections including chikungunya, West Nile, and Japanese encephalitis viruses [109–117].

Differential Diagnosis of Arboviral Neurological Syndromes

A major consideration in the differential diagnosis of viral neuro-infections is to exclude other infectious agents that can mimic viral meningoencephalitis like bacterial, mycobacterial, fungal, rickettsial, or parasitic infections. Aseptic meningitis due to other viruses like herpes virus, varicella zoster, and enterovirus may be similar in presentation to arboviral meningitis. Acute flaccid weakness has a broad infectious differential and may be seen in non-arboviral poliomyelitis syndromes (as seen with enterovirus D68), infectious myeloradiculitis (which can be seen with various herpesviruses, or rarely parasites like schistosomiasis), or with other neuromuscular pathology that may be unrelated to other viral pathogens (AIDP due to other triggers such as Campylobacter jejuni, other infectious myositis).

Non-infectious Mimics of Arboviral Encephalitis

In addition to ruling out other infectious entities, non-infectious causes of these syndromes must be considered. Over the past decade, an increasing number of non-infectious, mainly autoimmune, encephalitis cases, have been identified and many do not meet the traditional existing criteria for encephalitis. Therefore, newly identified criteria, focusing on
neurological and psychiatric manifestations without fever or CSF pleocytosis, have been proposed [118•]. The diagnosis of autoimmune encephalitis can be challenging due to the myriad manifestations. Autoimmune encephalitis is often associated with antibodies against neuronal cell surface or synaptic proteins; however, the absence of autoantibodies does not exclude the possibility that a disorder is immune-mediated [119, 120].

Acute flaccid weakness also has a broad non-infectious differential including some demyelinating syndromes such as MOGAD or neuromyelitis optica spectrum disorder, other inflammatory syndromes (sarcoidosis, antibody-mediated, or paraneoplastic syndromes), and malignancies such as lymphoma. Acute flaccid weakness may also be seen with non-infectious myopathies and neuropathies, motor neuron disease, neuromuscular junction disorders like myasthenia gravis, botulism, and tick paralysis which is a neurotoxin-mediated condition.

Long-Term Sequelae of Arboviral Neurological Syndromes

Though a majority of neurotropic arboviral infections are asymptomatic, residual long-term physical, mental, neurocognitive deficits have been noted in a significant proportion of recovered patients. West Nile, Japanese encephalitis, and eastern equine encephalitis viral disease have been associated with long-term sequelae in 50–75% of neuroinvasive cases, with symptoms lasting years after the onset of illness [121–127]. The common physical sequelae involve fatigue, myalgias, arthralgias, and generalized weakness and the cognitive/psychological sequelae involve memory loss, depression, difficulty concentrating, and anxiety. Other serious sequelae associated with West Nile virus also included paralysis, movement disorders, ataxia, and visual impairment [123, 124, 128]. Chikungunya infection has been associated with arthralgia, myalgia, and generalized weakness [129, 130, 131•]. Congenital Zika syndrome due to direct neuronal injury of the developing fetal brain during maternal Zika virus infection may cause severe microcephaly, brain atrophy, contractures, ocular abnormalities, and hypertonia [132, 133•, 134, 135].

Diagnosis

The diagnosis of neuroinvasive arboviral infection is established using serological or sometimes nucleic acid amplification tests (NAAT) in the serum and CSF. For dengue, chikungunya and Zika, NAAT, for detection of viral genome may be helpful when performed within 5–7 days of symptom onset, following which IgM should be considered [136••, 137••]. Immunoassay for nonstructural protein 1 can be used as an alternate test for dengue virus infection. IgM for the flaviviruses particularly dengue, Zika, and chikungunya may cross-react dengue, Zika, and chikungunya may cross-react causing diagnostic uncertainties [7]. Plaque reduction neutralization tests (PRNTs) with > fourfold higher titers can sometimes be used for confirmation. However, PRNTs are labor- and time-intensive, limiting utility for high-volume and resource-limited settings. Also, in endemic areas with high prevalence of dengue and Zika, PRNTs may not be able to distinguish between the infecting virus and may not be able to confirm positive IgM results.

For most neurotropic arboviral infections, use of NAAT is limited by low viral loads and decreased sensitivity except in immunocompromised hosts who may have prolonged viral RT-PCR positivity in serum and CSF. In most clinical situations, serum and CSF IgM is used for diagnosis. IgM is detectable in the serum about 5–10 days from symptom onset. If initial IgM test is negative, repeat IgM testing should be performed around 10 days from symptom onset. Presence of IgM in the CSF is indicative of intrathecal synthesis and implies neuroinvasive infection. IgM antibodies may persist for 30–90 days but prolonged persistence has been documented [138, 139].

IgG detection in a single serum may not be helpful since it indicates prior infection but a fourfold rise in IgG titers between acute and convalescent serum can be used for diagnosis.

Prevention and Treatment

There are currently no human vaccines available for prevention for a majority of the arboviruses except for Japanese encephalitis virus, yellow fever virus, and tick borne encephalitis virus. The first licensed live attenuated dengue vaccine, Dengvaxia, has been approved by the FDA in the USA and being considered as part of vaccination strategy in various countries with high burden of dengue infection [140•, 141, 142]. This vaccine is recommended only for individuals who have been previously exposed to dengue virus and are seropositive due to the risk of severe infection in seronegative individuals who experience their first natural dengue infection.

Personal protection by decreasing exposed body surfaces while outdoors, minimizing outdoor time during dusk and dawn, and applying insect repellants like DEET and picardin in high transmission areas are recommended to decrease exposures to mosquitoes and ticks [143, 144]. One of the other major foci of prevention is vector control which requires a coordinated effort from health departments. Entomological surveys, early identification of virus in mosquitoes, ticks, elimination of standing water sources to decrease breeding of mosquitoes, and insecticide spraying are some of the strategies but could be expensive.
Treatment for neuroinvasive arboviral infections is largely supportive. Innovative therapies like monoclonal antibodies and antiviral compounds are being investigated [145–151].

Conclusions

Emerging and re-emerging arboviral infections will continue to pose a major challenge to human health in the coming decades. Most arboviral infections cause asymptomatic infections and undifferentiated acute febrile illness. Hence, the large majority may be undiagnosed and the burden of disease in the community may be difficult to assess. The “One Health approach” which promotes a collaborative, multidisciplinary framework linking human health to animals, plants, and the shared environment is crucial to understand and manage the emerging viral infections. Advances in accurate, rapid, point-of-care diagnostics, effective vaccine candidates, and new therapeutic strategies can herald a new era in the control and management of arboviral diseases.

Declarations

Conflicts of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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