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Neurological manifestations of pediatric arboviral infections in the Americas

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ABSTRACT

Dengue, Zika, Chikungunya and yellow fever viruses are arboviruses transmitted by the mosquito *Aedes aegypti*. These viruses exhibit marked neurotropism but have rarely been studied. Here, we conduct an integrative review of the neurological manifestations caused by these arboviruses in the pediatric population. Data on patients under 18 years of age were extracted from literature databases. The most frequently reported neurological manifestations were encephalitis, meningitis, seizures, hypotonia, paresis, and behavioral changes. This review highlights the importance of accurately diagnosing these arboviral infections in children and adolescents with neurological manifestations.

1. Introduction

Arboviruses are viruses transmitted by arthropods, such as mosquitoes. There are four arboviruses of increasing epidemiological importance in the Americas: Zika virus (ZIKV), Dengue virus (DENV), Chikungunya virus (CHIKV) and Yellow fever virus (YFV). All of these can be transmitted by the *Aedes* mosquito [1,2].

Due to accelerated urbanization, climate change and deforestation over the recent decades, outbreaks of arboviral infections transmitted by *Aedes* have become more frequent in the Americas, strongly impacting public health [3].

DENV is among the arboviral infections most frequently affecting humans. It is estimated that 3.9 billion people are at risk of DENV infection [4] and more than 390 million are infected annually [5].

CHIKV was initially detected in the Americas in 2013, responsible for 1 million confirmed cases in the region [6]. The ZIKV epidemic of 2015 caused more than 500,000 suspected and confirmed cases in 40 countries and territories throughout the Americas [3].

YFV is endemic in 47 countries throughout Africa, Central and South America, where localized outbreaks result in 84,000–170,000 severe cases and 29,000–60,000 deaths per year, according to the World Health Organization. [7]

All of these arboviruses cause neurological manifestations in children. Studies evaluating viral etiologies of meningoencephalitis in the Cambodian, Chinese, Indian and Brazilian pediatric populations reported a 4.6–12% prevalence of DENV infection [8–11].

Studies performed during CHIKV outbreaks reported a 4.7–46% prevalence of pediatric neurological manifestations. [12–15] Neurological manifestation prevalence studies have not described children with ZIKV or YFV infections. However, experimental animal studies and well-documented case reports have detailed the neurotropic nature of these viruses [16–19].

Arboviral infections are increasingly important causes of neurological complications worldwide, both in cases of endemic transmission and travel-associated infections. This article analyzes the pediatric neurological complications of four arboviruses that have been reported to exhibit neurotropism.

Here, we conduct an integrative review to systematize the neurological manifestations in children and adolescents infected with clinically important arboviruses that circulate throughout the Americas and are transmitted by *Aedes aegypti* and *Aedes albopictus*.

We extensively searched the PUBMED, EMBASE, LILACS, MedCaribe, IBMCS, and BVS databases. Articles were searched without applying restrictions of language or date of publication. Search strategies used were always as shown in Fig. 1, which depicts a flowchart detailing our article selection and exclusion criteria.

In total, 196 manuscripts describing neurological manifestations resulting from any one of the four arboviral infections were identified;

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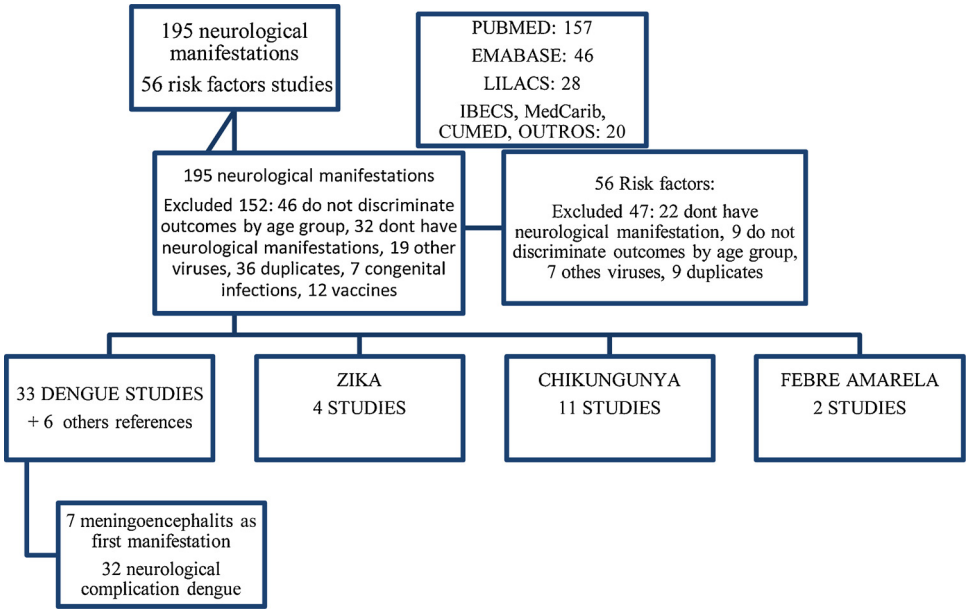

Fig. 1. Flowchart of selection of articles.

56 discussed risk factors, yet no descriptions of biomarkers for pediatric neurological complications were noted.

2. Dengue Virus (DENV)

DENV is an RNA virus of the *Flaviviridae* family. Four serotypes (DENV1-5) are transmitted by the *Aedes* mosquito and infection most frequently causes a febrile rash syndrome that lasts for about seven days. [20]

Since 1976, encephalopathy has been described as a complication of severe dengue. [21] However, recent studies have described meningitis, encephalitis, and seizures as neurological manifestations of DENV infection in patients without symptoms of classical or hemorrhagic dengue [8–10].

Murthy et al. [22] and Solbrig et al. [20] classified the neurological complications caused by DENV based on three neuropathogenic mechanisms: (1) invasion of the central (CNS) and peripheral (PNS) nervous systems leading to meningitis, encephalitis, myelitis and paresis; (2) metabolic and vascular disorders leading to encephalopathy, vasculitis and bleeding in the CNS and (3) immune-mediated dengue syndromes including acute disseminated encephalomyelitis (ADEM), neuromyelitis optica, neuritis, myelitis, encephalopathy and Guillain-Barre syndrome [20,22,23].

The neurological manifestations caused by DENV have been described mainly in case reports and series across a rather variable clinical spectrum. Thus, in order to systematize the published literature evaluating pediatric neurological complications of this virus, we classify reports into three groups.

2.1. Neurological symptoms as primary manifestations of infection

For this group, only articles that evaluated primary neurological manifestations without signs or symptoms of dengue prior to manifestations associated with nervous system invasion, at which point DENV was detected in the cerebrospinal fluid (CSF) by (RT)-qPCR, by viral isolation, or by the detection of IgM antibodies in the CSF using an enzyme-linked immunosorbent assay (ELISA) (Table 1) were selected. [8,10,24–27],

DENV mainly infects monocytes and macrophages which can infiltrate the nervous system carrying the virus. Cell culture studies have shown that human neurons are permissive to DENV infection and maintain active viral replication. The detection of RNA or viral antigen in CSF, inflammatory cell infiltrates and intrathecal synthesis of specific antibodies confirm active DENV CNS invasion [20,28,29].

Studies evaluating the detection of CSF DENV antibodies in the setting of DENV CNS infection reported a sensitivity of 46% and specificity of 95–97% for ELISA detection of IgM when compared to the gold standard CSF viral genome detection [29–31].

Of all children evaluated in these seven studies (1672), 3.2% (53) of those with neurological manifestations were diagnosed for dengue by detection of specific CSF IgM antibodies (18.9%) or by PCR of or viral isolation from the CSF (81.1%). The most frequent neurological manifestations in these children during their hospital stay were meningeal signs (18.8%), seizures (27%), signs of intracranial hypertension (10.4%), muscle weakness (6.3%) and encephalitis characterized by a decreased level of consciousness (58.3%). CSF analysis of all children suffering neurological manifestations of DENV revealed discrete pleocytosis with normal protein and glucose levels. Among these children, 5.7% died and 3.8% suffered neurological sequelae at hospital discharge. The most frequently reported sequelae were spasticity, paresis, muscle weakness and difficulty walking (Table 1).

2.2. Neurological manifestations associated with dengue symptoms

In this second group, all 25 publications that described neurological symptoms in patients with signs and symptoms of classical or hemorrhagic DENV were included. In total, 7685 children with dengue symptoms were studied, of which 271 (3.5%) suffered neurological manifestations. Of these patients, 76.7% were diagnosed using serological tests, non -structural protein 1 (NS1) detection or serum sample PCR; 14.2% were diagnosed by CSF PCR or viral isolation from the CSF; 9.2% were found to have CSF positive for DENV IgM (Table 2).

Among children with dengue and neurological symptoms evaluated using CSF PCR (82 children), positivity was found to be 39%. Among children in whom detection of specific CSF IgM antibodies was performed (95), positivity was found to be 26.3%. Methodology, however, differed among these 25 studies. In six studies, CSF was not evaluated in another six, no CSF changes were found. The remainder of the studies described CSF pleocytosis or elevated protein levels.

Computed tomography (CT) or magnetic resonance imaging (MRI) was performed in 12 studies; the most commonly reported finding was cerebral edema in 33 children. [33–37] Signal hyper intensity was also

Table 1
Neurological manifestations associated with CNS invasion by DENV in children*.

Neurological manifestations	Liquor**	Diagnostic method	Number + dengue / children number with neurological manifestation	Outcomes/ complications	Reference / Country
Meningitis, encephalitis, signs of intracranial hypertension	Leuk < 200 PMN 40-80% Gluc e Prot normais	PCR	5 / 70	All recovered at discharge	Oliveira et al, 2017 [10] Brasil
Meningitis, seizure	Leuk: 1-176 PMN:1-86 Glu: 45-75 Prot: 11-97	PCR	7/ 22	Not rated complications at discharge	Marinho et al, 2017 [24] Brasil
Encephalitis	Leuk > 4 Prot > 40	13 PCR + 5 IgM +	18 / 1160	Not rated complications by etiological agents	Horwood et al, 2017 [8] Cambodja
Meningitis or encephalitis	pleocytosis	IgM +	3/ 24	Not rated complications at discharge	Bermúdez et al, 2011 [32] Venezuela
Seizure, glasgow < 9, meningitis muscle weakness	No alteration	PCR	9 / 194	11% death and 11% serious complication	Le van Tan et al, 2010 [25] Vietnã
Encephalitis, myelitis, seizure	Prot > 45	2 viral isolation, 3 PCR e 2 IgM +	7 /150	14% paresis and spasticity at discharge	Soloman et al, 2000 [26] Vietnã
Encephalitis	Leuc: 14-140	PCR	4 / 52	2 deaths	Srey et al, 2002 Cambodja [27]

* Proven by DENV-specific IgM antibody detection, RT-PCR, or CSF virus isolation.
** Leuk: leukocytes, PMN: polymorphonuclear, Gluc: glucose (mg / dl), Prot: protein (mg / dl).

reported in the temporal lobes, corpus callosum or globus pallidus in four patients, subarachnoid hemorrhage in two children and laminar cortical necrosis in one [38–42]. Studies that included autopsy findings reported moderate cerebral edema and subarachnoid hemorrhages [43,44].

Electroencephalographic findings of children with seizures subsequent to DENV infection were evaluated in five studies which reported the onset of slow theta and delta waves with complete resolution 15–30 days later. [33,37,42,45,46]The most frequent neurological manifestations with which patients presented during hospitalization, as shown in Table 2, were encephalitis or encephalopathy (56.5%), generalized or focal seizures (42.8%), coma (12.2%), meningitis (7.4%), motor alterations, hyporeflexia (7%) and cranial nerve palsies (3.3%).

Of all patients suffering neurological manifestations of DENV infection in these studies, 17.3% died and 3.3% continued to suffer neurological sequelae at discharge or even months after initial symptoms. Patients with systemic dengue symptoms associated with neurological complications were found likely to mount a more exacerbated inflammatory response to viral infections and have a higher probability of death [29,31].

As the inflammatory response exacerbated by DENV infection triggers a cascade of cytokines and inflicts marked vascular, metabolic and hepatic damage, neurological manifestations in this group of patients may be due to both the neurotropism of this virus, which results in direct neuronal injury, as well as secondary to metabolic disturbances subsequent to vasculitis or CNS bleeding [29,31,47].

2.3. Immunologically-mediated neurological manifestations subsequent to dengue infection

Acute disseminated encephalomyelitis, Guillain-Barre syndrome and transverse myelitis are neurological manifestations described after DENV infections that are immune-mediated. Nonspecific activation of auto reactive T cells leads to the destruction of the myelin sheath subsequent to molecular mimicry mechanisms of DENV infection in some patients. Neuropathogenic mechanisms involved in such neuroimmune disorders are complex and include activation of the inflammatory cascade [33].

Seven reports of cases concerning immune-mediated conditions subsequent to DENV infections were identified. All patients described suffered dengue symptoms days before any neurological manifestations and were diagnosed by serological tests. None of these cases resulted in death. Although all of these patients received treatment (e.g. immunoglobulin or corticosteroid therapy), all manifested with neurological sequelae on discharge or months after initial clinical assessment. The most commonly reported sequel was muscle weakness with difficulty walking (Table 3).

One of the limitations of this review was that most studies included were case reports or case series describing neurological manifestations noted in patients infected with DENV. The 11 studies described 24 children with neurological complications who were identified weeks or months after discharge. However, 10 of these studies were solely descriptive and it was not possible to infer if the neurological complications after DENV were significant when compared to other viral encephalitis. Only the study by Chokepharkbuilt[55] that compared children suffering different viral encephalitis and followed them for six months described a better prognosis in patients with dengue encephalitis; all children recovered completely within two weeks.

Laboratory results and clinical symptoms were evaluated in three publications that described the risk factors for neurological complications in children suffering DENV. Cam et al. (2001) [36] compared 27 children infected with DENV that suffered neurological symptoms with a control group matched for age and symptom severity but without these complications. Transaminase, bilirubin, alkaline phosphatase, and D dimer elevation, as well as a reduction of prothrombin activity, were statistically significant in relation to the control group.

Table 2
Neurological manifestations in children with signs and symptoms of dengue*.

Dengue symptoms	Neurological manifestation	Líquor**	Diagnostic method	Number children with neurological manifestation/ Number dengue	Outcomes/ Complications	Reference; Country
Leukopenia Thrombocytopenia, increased transaminases and fever	Encephalitis with cortical laminar necrosis	No alteration	+ serum IgM	1 case report	Recovered at discharge	Garg et al, 2017 [38] Índia
Dengue shock	Hemiconvulsion-hemiplegia and epilepsy (HHE)	Not described	+ serum NS1	1 case report	Focal seizures for 1 year	Saini et al, 2017 [33] Índia
Dengue fever (DF) or hemorrha-gic dengue fever (DHF)	Encephalitis, motor weakness, transverse myelitis, ADEM and Guillain-Barré	pleocytosis, Prot > 45	+ serum IgM or NS1 + CSF IgM in 2 children	20 / 71	25% death in the group with neurological symptoms	Sil et al, 2016 [34] Índia
DF	Encephalopathy, delirium, ophthalmoplegia	Not described	+ serum PCR, IgM or NS1 + CSF PCR	1 case report	Recovered at discharge	Choong Yi Fong et al, 2016 [39] Malaysia
Fever and headache	Meningitis, oculomotor nerve palsy, diplopia	No alteration	+ sérum IgM	1 case report	After 2 weeks partial ptosis	Biswas et al, 2014 [40]
Fever, headache, arthralgia	Meningitis and encephalopathy	Leuk 133-460 Prot:45-53	+ CSF IgM e Ns1	4 cases reports	50% óbito	Araujo et al, 2012 [30]Brasil
Fever, headache and thrombocytopenia	Meningitis	Leuk: 86 Glic: 72 Prot: 116	+ CSF and serum IgM, + serum NS1	1 case report	All recovered at discharge	Goswami et al, 2011 [48] Índia
Rash, bleeding, thrombocytopenia, edema and hepatomegaly	Convulsion, meningitis, cranial nerve palsy, neurological deficts,	pleocytosis, Prot > 40	21 + CSF PCR, 9 + sérum PCR, 10 + serum IgM or HI	39 children	23% death in the group with neurological symptoms	Kumar et al, 2008 [49] Índia
All DF or DHF	Encephalopathy: change in level of consciousness and mental confusion	No alteration	+ CSF PCR	4 cases report	Sequelae not reported	Domingues et al, 2008 [50]Brasil
DHF	Encephalopathy, ADEM, subarachnoid hemorrhage	Pleocytosis	+ serum IgG or IgM	24/109	3 deaths, 2 evolved with permanent neurological sequelae	Kamath et al, 2006 [51]Índia
Fever, headache, myalgia and thrombocytopenia	Encephalitis with ptosis and ataxia	Leuk:10 Prot 11 Gluc: 60	Serum and CSF IgM	1 case report	Recovered at discharge	Muzaffar et al, 2006 [41]Índia
All with dengue fever (DF) or hemorrhagic dengue fever (DHF)	Seizures and hyporeflexia	Leuk: 0-350 Prot: 24-128	+ serum IgM	4 cases report	25% partially recovered	Misra et al, 2006 [42] Índia
Febre e plaqueto-penia	Encephalitis and seizures	Leuk:0 Prot:744 Gluc:120	+ serum and CSF IgM	1 case report	death	Witayathawornwong P et al,2005 [52]Tailândia
DHF	Flaccid paralysis	Not done	+ sérum IgM	2 cases report	After 3 months a child can not walk	Kalita et al, 2005 [53]Índia
DHF	Coma, seizures hemiplegia	No alteration	14 + CSF IgM, only one children + PCR	27/ 5400	22% death in the group with neurological symptoms	Cam et al, 2001 [36]Vietnã
DHF or dengue shock	Encephalitis, convulsion, spasticity, hemiplegia	Leuk:0-40	+ sérum IgM	80/1493	5% death, 1 patient with spasticity and permanent muscular weakness	Pancharoen C et al, 2001 [54]
DHF	Encephalitis, meningitis	No alteration	+ serum IgM or PCR, 2 blood viral isolation	8 cases report	All recovered at discharge	Chokephar-bulkit et al, 2001 [55]Tailândia
Hemoconcentration, leukopenia thrombocytopenia	seizure, cranial nerve palsy, meningism, papilledema	Prot > 40	4 + serum PCR, 2 blood viral isolation, 2 + serum IgM	8 /44	All recovered at discharge	Kankirawatana et al, 2000 [56]Tailândia
DHF	Encephalopathy, encephalitis, hepatic encephalopathy	Leuk > 5 Prot > 45	1 + CSF IgM, 1 + serum IgM, 1 blood viral isolation	3 cases report	33% febril seizure 20 months after encephalitis	Solomon et al, 2000 [26]Vietnã
DHF	Seizure and coma	Not done	+ PCR brain tissue	1 case report	death	Ramos et al, 1998 [43]México
DHF	Encephalitis	Not done	Monoclonal antibody in brain tissue	3 cases report	deaths	Bhoopat L et al,1996 [57]Tailândia
Dengue schock	Seizure and meningitis	Pleocytosis	CSF Viral isolation	6 cases report	16,7% death 16,7% residual palsy	Lum et al, 1996 [37]Malasya
DHF	Focal seizure, fever and headache	pleocytosis	blood viral isolation	1 case report	Recovered at discharge	Systayana-rian et al, 1996 [58]Tailândia
Dengue shock	Encephalitis, convulsion	Not done	IgM + sangue	12/ 505	25% death	Thisyakorn et al, 1994 [59]Tailandia

(*continued on next page*)

Table 2 (*continued*)

Dengue symptoms	Neurological manifestation	Líquor**	Diagnostic method	Number children with neurological manifestation/ Number dengue	Outcomes/ Complications	Reference; Country
DHF	Encephalitis, convulsion, coma, spasticity	No alteration in five children	IgM + sangue, 4 isolamentos virais tecidos	18 children	55,5% death	Nimmany-ta et al 1987, [44]Tailândia

* diagnosis made by RT-PCR, viral isolation or serology in blood or CSF.

** Leuk: leukocytes, PMN: polymorphonuclear, Gluc: glucose (mg / dl), Prot: protein (mg / dl).

Table 3
Neurological manifestations in children post DENV infection.

Neurological manifestation/ Age	Líquor**	Time between dengue and neuro symptoms	Treatment	Outcomes/ complications	Reference/ Country
Transverse myelitis 12 years	Not done	8 days	Methylprednisolone, immunoglobulin and plasmapheres	Muscle weakness with walking difficulty for 6 months	Fong et al, 2016 [39]Malasia
Encephalitis with Parkinsonism 6 years	No alterations	11 days	3d Methylprednisolone dexamethasone 7d	No neurological deficits after 7 weeks	Fong et al, 2014 [45]Malasia
seizures and difficulty of ambulation12 years	High leukocitos and proteins	No reported	Risperidone 1 mg/dia	Persistent behavioral change 60 days later	Baldaçara et al, 2013 [60] Brasil
ADEM 13 years	Prot: 80	5 days	3d Methylprednisolone dexamethasone 2wks + prednisolone 6 wks	At discharge he still had ataxia and dysarthria	Chowdhury et al 2011 [61] Índia
Guillain-Barre 6 years	Leuk: 60 Prot: 360 Gluc: 45	20 days	immunoglobulin 400 mg/kg for 5 days	5 months later still had tetraparesis, sensorial alterations and hyporeflexia	Gonçalves et al, 2011 [62] Brasil
tetraparesis, dysphagia, behavioral change + optic atrophy 10 years	Pleocytose	1 week	No reported	4 months still dependent on walker and maintained behavioral change	Palma da Mata et al, 2004 [63]Brasil
Guillain-Barré 14 years	Leuk: 2 Prot: 56	10 days	No reported	8 months after wandering without support, but remained with deep arreflexia	Palma da Mata et al, 2004 [63] Brasil

** Leuk: number of leukocytes, Gluc: glucose (mg / dl), Prot: protein (mg / dl).

However, the cross-sectional study by Sil et al. (2016) [34] found no statistically significant difference between 20 children with dengue who suffered neurological symptoms and 51 children with dengue who did not in relation to thrombocytopenia, hemorrhage, elevated transaminase levels, hepatomegaly and jaundice.

Kumar et al. (2008) [49] compared 39 children admitted with dengue and neurological complications to 130 children with acute febrile encephalopathy but without dengue symptoms. Rash, gastric and other bleeding, edema, hepatomegaly, hypoalbuminemia, elevated prothrombin time and pleural effusion were significantly more prevalent in the dengue group.

Such conflicting results indicate that a greater number of studies are needed to accurately compare cases with control-matched neurological outcomes and better define risk factors as well as biomarkers for neurological complications in DENV patients. In addition, prospective studies are necessary to evaluate the prognosis of neurological manifestations. Studies that evaluated infants exposed to perinatal mother-to-child dengue virus infection did not report neurological manifestations in these children. Perinatal dengue infection was associated with increased maternal and perinatal mortality, prematurity, low birth weight, thrombocytopenia and sepsis symptoms in the newborns [64–68].

3. Zika virus (ZIKV)

ZIKV is a single-stranded RNA virus of the Flavivirus genus and the Flaviviridae family. ZIKV was first isolated from the Zika forest of Uganda in 1947. As early a 1952, experimental inoculation of rats with the virus revealed its neurotropism as evidenced by cerebral edema and neuronal degeneration [69].

ZIKV infection during pregnancy has been associated with fetal loss, microcephaly, subcortical calcifications, cerebellar hypoplasia, congenital contractures, arthrogryposis and retinal changes [70]. However, there are few reports of neurological manifestations secondary to ZIKV infection acquired among pediatric patients.

An extensive search of the literature identified only four reports of cases concerning pediatric ZIKV acquired infection with neurological manifestations [71–74]. Although reports were scarce and described few cases, the diversity of neurological manifestations was remarkable and included hemiparesis, myelitis, Guillain-Barre syndrome, cortical infarction and behavioral changesCSF analysis revealed pleocytosis with normal protein and glucose levels in three of the four cases.

ZIKV was detected by PCR in the CSF of only one patient, yet all suffered persistent neurological symptoms for at least one month after initial manifestations. In other cases, diagnoses were made with PCR analyses of other specimens (i.e. blood and urine) or positive IgM. None of the children infected with ZIKV died (Table 4).

4. Chikungunya virus (CHIKV)

CHIKV is a single-stranded RNA virus of the *Alphavirus* genus and the *Togaviridae* family [75]. The pathophysiology of the neurological complications caused by CHIKV is not fully understood. Studies evaluating the histopathology of neuronal lesions have reported cerebral edema; frontal, occipital and internal capsule ischemia; hemorrhages; demyelination and periventricular cavitation [76,77]. Minimal microgliosis was reported to occur in cortical gray matter and the diencephalon along with periventricular lymphocytic infiltrate [15,76–78].

The 11 studies that assessed children with neurological manifestations subsequent to CHIKV infection were found to have applied varying methodologies. Of these studies, six were retrospective and five cross-sectional. In nine of these publications the studied children presented with clinical symptoms of CHIKV infection and those that manifested neurological features were evaluated. Only six studies evaluated neurological sequel; one evaluated children 3 years after discharge. Of the 554 children treated for CHIKV infection 24% were

Table 4
Neurologic manifestations in children associated with ZIKV infection.

Zika symptoms	Neurological Manifestations/ Age	Liquor**	Diagnostic method	Outcomes/ complication	Reference/ Country
Fever, rash, conjunctivitis	Hemiparesis, cortical infarction 10 months	Leuk: 8 Prot:18 Gluc: 61	+ PCR serum	Arm weakness after 3 months, walked at 1 year and 3 months	Landais et al, 2017 [71] Guadalupe Island
No symptoms	Guillain-Barre 9 years	High leukocytosis and protein in CSF	+ serum IgM, + PRNT CSF	No sequelae after 4 months	Raboni et al, 2017 [72] Brazil
Sore throat, headache, rash, arthralgia	Recent memory loss, slowed speech, impulsivity, regression 13 years	Leuk: 8 Prot:30 Gluc: 55	+ urine PCR, + CSF IgM	15 weeks after symptoms still persisted	Zucker et al, 2016 [73] United States
Headache, arthralgia and conjunctivitis	Hemiparesis, myelitis 15 years	No alterations	+ PCR CSF, blood and urine	1 month afterwards maintained moderate weakness in the legs	Mécharles et al, 2016 [74] Guadalupe Island

** Leuk: number of leukocytes, Gluc: glucose (mg / dl), Prot: protein (mg / dl).

found to suffer neurological complications. Two other studies that together evaluated 1118 children with meningoencephalitis reported a CHIKV prevalence of 2.8% as the etiological agent. The prevalence of pediatric neurological manifestations subsequent to CHIKV infection varied according to the methodology used in the study.

All studies were performed during epidemic periods of infection and 90% of children were diagnosed by PCR. Among the studies that utilized CSF analysis, leukocytosis and high protein levels were reported in 48.7% of cases.

Electroencephalography was performed in 45 children and revealed changes such as slowing waves and paroxysmal peaks in 68.9%. [12–15] Cranial CT was performed in 51 children and cranial MRI was performed in 45 children. CT and MRI changes were found to be present in 23.5% and 20% of children, respectively. The most commonly described changes on imaging were cerebral edema and T2-weighted white matter and limbic area signal intensity [12–15,79,80].

The most common neurological manifestations found in these children were seizures (56.3%), encephalitis (41.7%), meningism (19.4%) and behavioral changes (8.7%). Of these children, 5.6% died and 8.5% developed neuronal sequelae. The commonest sequelae were seizures, hypertonia, hypotonia, behavioral disturbances, developmental delay and finger gangrene (Table 5).The CHIMERE Cohort Study on Reunion Island compared the cognitive development of 33 chikungunya-infected children during the perinatal period with 135 uninfected pairs [81]. They found that 51% of infected children had cognitive developmental delay at 2 years of age, compared to only 15% of uninfected children. In the multivariate analysis, perinatal CHIKV infection was an independent factor for delayed child development, increasing by about three times the risk of delay, after controlling for microcephaly, maternal social status and restricted intrauterine growth [81]. Children who at birth had severe encephalopathy evolved with more significant developmental delays. Among the 12 cases of children with neonatal encephalopathy, five evolved with microcephaly and four with cerebral palsy. The main developmental delays detected in children with perinatal chikungunya virus infection were language and coordination (57%), sociability (36%) and movement / posture (27%) [81].

5. Yellow fever virus (YFV)

YFV is an RNA virus of the *Flavivirus genus* and the *Flaviviridae* family that causes a highly lethal febrile illness. This virus is endemic in the tropical regions of Africa and South America. [2] We identified only two studies that included children and reported neurological complications subsequent to wild-type YFV infection.

Over the course of a 1969 yellow fever outbreak in Nigeria, 103 patients were evaluated. Of these, 14 were aged less than 19 years old. Signs of CNS involvement were described in 25% of the patients during the epidemic and 8 were reported to have suffered generalized seizures [17].

A descriptive, cross-sectional, multicenter study conducted in Sudan during the 2012–2013 outbreak evaluated a total of 844 hospitalized patients and detailed patients suspected of suffering from yellow fever, including 181 patients younger than 15 years of age. This study did not discriminate outcomes by age group, but described that 15.6% of all patients suffered seizures [There is one case of perinatal infection by the sylvatic virus of yellow fever. The 22-year-old mother with no prior immunization history was admitted to the intensive care unit with symptoms of severe yellow fever at 38 weeks' gestation and the cesarean section was taken. The 6-day-old infant evolved with jaundice, hemodynamic instability, encephalopathy, and seizures. Mother and baby were diagnosed by PCR in the blood and unfortunately they evolved to death in a few days [85].

6. Limitations

Although the main limitation of this review is that most studies

Table 5
Neurological manifestations in children associated with CHIKV infection.

CHIKV symptoms	Neurological Manifestations/ Number children	Liquor**	Diagnostic method	Outcomes/ complication	Reference/ Country
Fever, rash	Convulsions, encephalitis, bulging fontanelle 11 of 235 (4,7%)	Pleocytosis and high protein	+ PCR serum	EEG and CT alteration in 7 children. RMI alteration in 5. 1 death	Samra et al, 2017 [12] Honduras
Fever, rash and arthralgia	Menigoencephalitis, behavioral changes and seizures 5 of 48 (104%)	No reported	4+ PCR serum, 1 + IgM serum	1 death 1 child remained with behavioral change for 4 weeks	Singh et al, 2017 [80] India
Fever, rash, arthralgia, vomiting, headache	Convulsive crisis, diffuse cerebral edema 1 child 5 years	Not done	+ IgM serum	death	Sá et al, 2017 [78] Brazil
1160 children with encephalitis	23 children encephalitis by CHKV	Leuk > 4 Prot > 40	11 + PCR serum 6 + IgM CSF 6 + IgM serum	Not reported	Horwood et al, 2017 [8] Cambodja
Fever, rash	Encephalitis with seizures in 3 infants	Leuk: 12-70	IgM sérico +. Mães negativas	Not reported	Gupta et al, 2015 [82] India
Fever and vomiting for 2 days	Encephalitis, seizures, hyporeflexia, coma and death in children 12 years	No reported	+ PCR CSF and blood	Death	Shaikh et al, 2015 [79] India
Fever, rash and hepatomegaly	Baby 4 months with irritability, bulging fontanelle and seizure	No alterations	+ PCR and IgM serum	Withouth complications	Lee et al, 2010 [83] Singapura
58 children with neurological symptoms	8 children with encephalitis, meningitis, or seizures	Pleocytosis only in 2 cases	+ PCR CSF and serum	Aphasia, tardiness at school, hearing loss, gangrene fingers	Lewthwait et al, 2009 [84] India
Fever, rash and severe pain	Hypotonia, meningitis, seizures 23 of 50 (46%)	No alterations or only high protein	+ PCR CSF and serum	2 deaths and 1 child maintained eye sequelae	Bonin et al, 2008 [13] Mayotte Island
Fever, arthralgia and rash	Seizure, behavioral disorders meningism 23 of 86 (27%)	Pleocytosis with moderate protein	+ PCR or IgM 8 children with + PCR CSF	1 death	Ernould et al, 2008 [14] La Reunion Island
Fever, arthralgia and rash	Encephalitis, seizures, encephalopathy, meningitis 26 of 103 (25%)	1 CSF with leukocytosis e 1 CSF with high protein	+ PCR serum or CSF	2 deaths 3 children with neurological sequelae at discharge	Robin et al, 2008 [15] La Reunion Island

** Leuk: number of leukocytes, Gluc: glucose (mg / dl), Prot: protein (mg / dl), CSF: liquor.

included were case reports, case series and retrospective studies, several studies reported viral detection in the CSF either by viral isolation or RT-PCR, underscoring the neurological effects these viruses produce in the pediatric population. Further studies concerning etiological detection of different viral agents that cause neurological manifestations in children, case-control studies assessing risk factors and biomarkers, and prospective studies evaluating long-term neurological sequel are required.

7. Conclusion

No specific antiviral therapies are available for any of the arboviral infections discussed in this review. Only the yellow fever vaccine, available since 1939, has a 92–95% efficacy in protecting against severe forms of this infection [86]. The commercially available DENV vaccine has a low effectiveness of around 60%, with a greater effectiveness for severe forms of the secondary infection at 83.7% vs. 43.2%. A phase 3 study in children younger than 9 years of age revealed a higher risk of hospitalization for severe dengue in vaccinated children when compared to the control group (RR = 7.45, 95% CI, 1.15–313.8). Therefore, World Health Organization (WHO) has recommended vaccination only in patients with previous dengue infection [87,88].

Vaccines for ZIKV [89,90] and CHIKV [91,92] are in the pre-clinical stages of development with the eventual aim of preventing the severe complications of these infections via immune modulation. Arboviruses are major public health issues worldwide. Recent studies have increased our understanding of the neurological complications caused by these infections. Epidemiological factors, population displacements and increasingly alarming climate changes highlight how necessary it is for pediatricians and neurologists to readily recognize neurological manifestations caused by these viruses and provide accurate and timely diagnoses that will, in turn, result in effective infection management and patient treatment.

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