Chikungunya virus–associated encephalitis
A cohort study on La Réunion Island, 2005–2009

ABSTRACT

Objective: To estimate the cumulative incidence rate (CIR) of Chikungunya virus (CHIKV)–associated CNS disease during the La Réunion outbreak, and assess the disease burden and patient outcome after 3 years.

Methods: CHIKV-associated CNS disease was characterized retrospectively in a cohort of patients with positive CHIKV reverse transcriptase PCR or anti-CHIKV immunoglobulin M antibodies in the CSF and fulfilling International Encephalitis Consortium criteria for encephalitis or encephalopathy. Neurologic sequelae were assessed after 3 years.

Results: Between September 2005 and June 2006, 57 patients were diagnosed with CHIKV-associated CNS disease, including 24 with CHIKV-associated encephalitis, the latter corresponding to a CIR of 8.6 per 100,000 persons. Patients with encephalitis were observed at both extremes of age categories. CIR per 100,000 persons were 187 and 37 in patients below 1 year and over 65 years, respectively, both far superior to those of cumulated causes of encephalitis in the United States in these age categories. The case-fatality rate of CHIKV-associated encephalitis was 16.6% and the proportion of children discharged with persistent disabilities estimated between 30% and 45%. Beyond the neonatal period, the clinical presentation and outcomes were less severe in infants than in adults.

Conclusions: In the context of a large outbreak, CHIKV is a significant cause of CNS disease. As with other etiologies, CHIKV-associated encephalitis case distribution by age follows a U-shaped parabolic curve.

GLOSSARY

ADEM = acute disseminated encephalomyelitis; CHIKV = Chikungunya virus; CFR = case-fatality rate; CIR = cumulative incidence rate; DQ = development quotient; DWI = diffusion-weighted imaging; ECSA = East Central South African; IEC = International Encephalitis Consortium; IgM = immunoglobulin M; LP = lumbar puncture; NECACD = nonencephalitic Chikungunya virus-associated CNS disease; WNV = West Nile virus.

Chikungunya virus (CHIKV) is a re-emerging alphavirus.¹ Alphaviruses are divided into arthritogenic viruses (old world) and encephalitogenic viruses (new world) including equine encephalitis viruses.²

Until its reemergence in the Indian Ocean in 2004 and the worldwide spread that followed, beyond the burden of arthritis, known for lasting weeks to years,³ Chikungunya was considered as a nonfatal disease with spontaneous resolution, not causing lifelong disabilities, even though rare cases of CNS disease had been reported.⁴ ⁵

The major outbreaks that have occurred since 2005 in the Indian Ocean islands were attributable to a new Indian Ocean lineage that evolved from the East Central South African (ECSA) lineage and selected the mutation E1-A226V, which favors transmission by Aedes albopictus.⁶ ⁷

¹Deceased.
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Coinvestigators of the Encephalchik Study Group are listed on the Neurology® Web site at Neurology.org.
Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.
Recently, Asian lineage CHIKV emerged in the Caribbean and expanded to the Americas, and recent clinical and experimental data indicate differences in the pathogenicity between Asian and American lineages.8–10

The 2005–2006 epidemic on La Réunion Island affected 300,000 persons and enabled the observation of severe forms of the disease.11 These included rare severe or fatal cases with CNS involvement, in both adults and neonates.12–16

We report the results of an ambispective cohort study aimed at characterizing clinical and biological features of CHIKV-associated CNS disease, disease burden, and 3-year neurologic outcome of patients with this condition.

METHODS We conducted this study in the Groupe Hospitalier Sud Réunion, the largest hospital on the island, which covers a population of 277,602 inhabitants.17

Retrospective cohort study. We considered all patients hospitalized between September 1, 2005, and June 30, 2006, with CHIKV infection and neurologic symptoms that led to lumbar puncture (LP) eligible for the study. Patients with positive CSF for CHIKV RNA or anti-CHIKV immunoglobulin M (IgM) antibodies were studied further.

Anti-CHIKV IgM assay in the CSF was performed by ELISA using the ETIMAX 3000 (Diasorin, Italy). A one-step TaqMan real-time quantitative PCR was performed from CSF samples using the LightCycler 2.0 system (Roche Diagnostics; Basel, Switzerland).

Standard protocol approvals, registrations, and patient consents. Each patient provided oral consent for the use of clinical, biological, and imaging data, in accordance with the recommendations of the local Committee for Clinical Research.18

Case definition. We used positive CSF findings (CHIKV RNA or IgM) to provide the more specific case definition. Additionally, we used International Encephalitis Consortium (IEC) criteria to classify our patients according to an up-to-date definition of encephalitis.19 These combine the major criterion altered mental status (defined as decreased or altered level of consciousness, lethargy, or personality change lasting ≥24 hours with no alternative cause identified) with a set of minor criteria: fever (≥38°C) within the 72 hours before or after presentation; general or partial seizures not fully attributable to epilepsy; new onset of focal neurologic signs; CSF leukocyte count ≥5/mm³; brain parenchyma on neuroimaging suggestive of encephalitis either new from prior studies or appearing acute in onset; EEG consistent with encephalitis and not attributable to another cause.

Exclusion criteria were the main causes of encephalopathy and of noninfectious encephalitis: positive HIV status, pyogenic meningitis, thrombophlebitis, brain abscess, empyema, cerebral malaria, acute disseminated encephalomyelitis, voltage-gated potassium channels, NMDA receptor antibodies, systemic vasculitis, multiple sclerosis, paraneoplastic-related encephalitis, prion disease, encephalopathy of primary tumor, or hematologic, toxic, or metabolic origin.18

Thus, we defined probable CHIKV-associated encephalitis in the presence of the major criterion and at least 3 minor criteria, possible CHIKV-associated encephalitis in the presence of the major criterion and 2 minor criteria,18 and nonencephalitic CHIKV-associated CNS disease (NECACD) in the presence of major criterion alone or with one minor criterion, or in the presence of 2 minor criteria other than fever.

Prospective follow-up study. We followed up each patient with CHIKV CNS disease to search for neurologic sequelae over a 3-year period using the extended Glasgow Outcome Scale (adult and pediatric versions).20 For children, trained psychometrists assured neuropsychological evaluation using the revised neurodevelopmental scale of Brunet-Lézine, a standardized psychometric test routinely used in francophone countries. For adults, neurologists performed clinical and EEG examinations. CT or MRI scans were performed on clinical indication.

Statistical analysis. We compared characteristics of CHIKV-associated encephalitis and NECACD globally and between adults and children using χ² or Fisher exact test for proportions. We compared distributions using Mann-Whitney tests. We tested correlations between CSF and serum viral loads in children, or between CSF and serum IgM levels in adults, using Spearman correlation coefficients.

We provided cumulative incidence rates (CIR) for CHIKV-associated encephalitis (probable, possible, or both), overall and by age groups, applying weights for subpopulation structure using data from the 2006 census.27 We then compared these estimates to US standards.21

We assessed the range of neurologic sequelae in applying the same actual rate or null for the missing observations, this assumption being likely conservative, given the low probability of loss to follow-up due to death or sequelae in our insular population.

We used Stata (v10.0, StatCorp., College Station, TX) for comparisons. Statistical significance was set at p = 0.05.

RESULTS Retrospective cohort study. CHIKV acute patients with neurologic symptoms. Among the 129 CHIKV-infected patients with CNS disease, biological analysis of the CSF was positive for 55 CHIKV RNA or 30 anti-CHIKV IgM in 78 patients and negative in 51 patients (figure 1).

We excluded 9 patients because they exhibited additional conditions, which invalidated CHIKV as a unique cause for the neurologic symptoms. Briefly, these consisted of encephalopathy of primary metabolic origin (n = 3), alcohol-related encephalopathy (n = 3), posterior reversible encephalopathy syndrome in systemic lupus erythematosus (n = 1), Streptococcus pneumoniae meningitis (n = 1), and neurocysticercosis (n = 1). The 69 remaining patients showed at least one IEC encephalitis criterion but 12 of them were excluded because incomplete charts did not allow definite classification. Thus, a total of 57 patients diagnosed with CHIKV-associated CNS disease were enrolled in the study. Among them, 24 (42.1%) patients with altered mental status matched IEC encephalitis definition, whereas 33 (57.9%) others did not and were designated as NECACD in further analysis.
We identified 6 confirmed cases of CHIKV-associated encephalitis (i.e., altered mental status plus at least 3 minor criteria), while 18 patients were classified as possible cases (i.e., 2 minor criteria). Both groups shared the same clinical and biological profiles, which confirmed the appropriateness of the IEC classification that allow these groups to be pooled for case registration (data not shown).

CHIKV encephalitic cases were more likely to exhibit severe CNS disease than were cases of NECACD, which consisted almost exclusively of mild to moderate behavioral changes (table 1). Two
### Table 1: Clinical features of CHIKV-associated CNS disease in La Réunion Island (2005–2006)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Probable or possible encephalitis (n = 24), n (%)</th>
<th>NECACDa (n = 33), n (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>9 (37.5)</td>
<td>27 (81.8)</td>
<td>0.003ab</td>
</tr>
<tr>
<td>1–19</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>20–44</td>
<td>2 (8.3)</td>
<td>1 (3.0)</td>
<td></td>
</tr>
<tr>
<td>45–64</td>
<td>4 (16.7)</td>
<td>1 (3.0)</td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>9 (37.5)</td>
<td>4 (12.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
<td></td>
<td></td>
<td>0.843</td>
</tr>
<tr>
<td>History of fever (≥ 38°C)</td>
<td>24 (100)</td>
<td>33 (100)</td>
<td>1</td>
</tr>
<tr>
<td>Onset of fever ≥7 d</td>
<td>12 (60.0)</td>
<td>18 (58.5)</td>
<td>0.063</td>
</tr>
<tr>
<td><strong>Altered mental status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased consciousness</td>
<td>8 (33.3)</td>
<td>2 (6.1)</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>Coma</strong></td>
<td>4 (16.7)</td>
<td>1 (3.0)</td>
<td>0.151</td>
</tr>
<tr>
<td>General or partial seizures</td>
<td>3 (12.5)</td>
<td>1 (3.0)</td>
<td>0.300</td>
</tr>
<tr>
<td><strong>Focal neurologic signs</strong></td>
<td>5 (20.8)</td>
<td>0 (0)</td>
<td>0.010</td>
</tr>
<tr>
<td><strong>Other behavioral changes</strong></td>
<td>15 (62.5)</td>
<td>32 (97.0)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Skin rash</strong></td>
<td>8 (33.3)</td>
<td>17 (51.5)</td>
<td>0.190</td>
</tr>
<tr>
<td><strong>Intensive care support</strong></td>
<td>10 (41.7)</td>
<td>3 (9.1)</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>Length of stay &gt;4 d</strong></td>
<td>14 (58.3)</td>
<td>13 (39.4)</td>
<td>0.187</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td>4 (16.7)</td>
<td>3 (9.1)</td>
<td>0.439</td>
</tr>
</tbody>
</table>

Abbreviations: CHIKV = Chikungunya virus; IgM = immunoglobulin M; NECACD = nonencephalitic Chikungunya virus-associated CNS disease.

aUnless stated, the data were available for 24 encephalitic cases and 33 cases of NECACD. The onset of fever was available for 20 encephalitic cases and 21 cases of NECACD.

bFisher exact overall p value testing the 5 age categories.

cDecreased or altered level of consciousness, lethargy, or personality change (disorientation, agitation).

dGlasgow Coma Scale score <15.

eGlasgow Coma Scale score ≥9.

fAttention disorders, memory troubles, excessive pain feeling (irritability).

focal neurologic signs, seizures, or a fatal issue (table e-1 on the *Neurology*® Web site at Neurology.org).

Protein, glucose, and chloride CSF levels were higher in adults than infants (table e-2). CHIKV loads in the CSF or serum were higher in infants than adults, whereas it was the opposite for IgM. These results are in line with the fact that adults were observed later than infants in the course of the CHIKV-associated CNS disease. CHIKV loads in the CSF and serum for infants and between IgM levels in the CSF and serum for adults were positively correlated (data not shown).

In infants, CHIKV loads in serum negatively correlated with age, while in adults IgM levels in serum positively correlated with age (data not shown).

Except for one neonate exhibiting cerebral edema MRI features, no early (<7 days) diffusion-weighted imaging (DWI) MRI scan was available for CHIKV-associated encephalitic cases, although DWI is increasingly recognized as the most sensitive technique for timely diagnosis of acute brain parenchymal inflammation. Subsequently, no radiologic image evocative of acute stage of CHIKV-associated encephalitis was observed among the 22 other patients submitted to brain CT scans, late MRI scans, or both.

**Cumulative incidence rates of CHIKV-associated encephalitis.** The overall CIR estimate of CHIKV-associated encephalitis was 8.6 per 100,000 persons (95% confidence interval 6.9–10.4). Importantly, the age distribution pattern of CHIKV-associated CNS disease (figure 2A) or CHIKV-associated encephalitis incidence (figure 2B) exhibited a U-shaped parabolic pattern with a clear trend to the highest incidence towards the youngest age than the oldest.

**Prospective cohort study.** Six adult patients died (mean age 67.5 years; SD 15.7 years; range 41–83 years) during hospitalization (case-fatality rate [CFR] 10.5%). Detailed cause-specific mortality were cardiac failure (n = 2), septic shock (n = 2), respiratory failure (n = 1), and sudden death (n = 1). Death certificates mentioned Chikungunya as the primary cause for degradation in each case. As a consequence, 51 patients were eligible for the follow-up study.

Eight adults were discharged with neurologic sequelae (table e-3). One died 3 months after discharge (case 6). He was a 72-year-old man free from medical history presenting with altered mental status, classified as NECACD. He deteriorated gradually towards dementia and died in a clinical picture of metabolic encephalopathy due to dehydration and hypernatremia. EEG revealed a global slowdown without spike. Subacute stage CT scans showed extensive demyelination and cerebral subcortical atrophy. Four adult survivors were lost to follow-up and the 10 others were assessed clinically at 3 years. Of these, we diagnosed 3 patients with neurologic indicators of CSF inflammation, leukocyte count and protein level, were higher in patients with encephalitis than encephalopathy, but viral loads or IgM titers in serum or in CSF were not significantly different between these groups of patients (table 2). Importantly, encephalitic cases required more intensive care support than did NECACD cases (table 3).

The cohort contained 21 adults (mean age, 63.9 years; SD, 15.6 years; range, 33–88 years) and 36 infants (mean age, 1.6 months; SD, 1.15 months; range, 4 days–5.4 months).

Five infants were in the early neonatal period (<7 days) and 4 in the late neonatal period (7–28 days), corresponding to cases of mother-to-child and postnatal mosquito-borne transmission, respectively.

Infants were more likely to experience a recent onset of fever prior to hospitalization, behavioral changes, skin rash, or survival and adults were more likely to experience decreased consciousness, coma,
A study was conducted to investigate the neurologic outcomes of children with CHIKV-associated encephalitis in La Réunion Island. The study found that there was a high burden of neurologic sequelae, with 17% of children developing seizures, 36% developing cognitive disorders, and 9% developing blindness. The study also found that 16.6% of children died as a result of the encephalitis.

The study involved 52 patients, with 37 encephalitic cases and 15 cases of NECACD (nonencephalitic Chikungunya virus-associated CNS disease). Of these patients, 19 were lost to follow-up, and 17 were evaluated at an average of 38 months of age.

The study found that the CFR of sequelae resulting from CHIKV-associated CNS disease could not be calculated precisely and was estimated to be in the range of 17.6% to 43.1%. Nevertheless, lost-to-follow-up children corresponded to the milder forms of CNS disease, so that our estimates are likely conservative owing to the fact that the incidence of sequelae often correlates with the intensity of the acute stage of infection in a previously healthy population.

The study also found that for CHIKV-associated encephalitis, the CFR was 16.6% (4/24) and the 3-year burden of neurologic sequelae in the range of 30% (6/20) to 45% (9/20). Importantly, we observed an age difference in 3-year outcome of CHIKV-associated encephalitis, poor prognosis (i.e., death or sequelae) being predominant in adults (52.6% vs 18.2%, p = 0.020).

**DISCUSSION** This study reports findings on CHIKV-associated CNS disease (encephalitis and encephalopathy) using both CSF examination findings and IEC criteria for encephalitis. Our data reveal that during the 2005–2006 CHIKV outbreak in La Réunion Island, the incidence of CHIKV-associated encephalitis contributed to a twofold increase of the regional overall incidence (14.6 vs 6.0 cases per 100,000 persons per year at baseline) of all encephalitis. Remarkably, this burden far exceeds the annual rate of encephalitis calculated from CHIKV-associated CNS disease.

### Table 2 Biological parameters of CHIKV-associated CNS disease in La Réunion Island (2005–2006)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Probable or possible encephalitis (n = 24)</th>
<th>NECACD (n = 33)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF leukocytes ≥5/mm³, n (%)</td>
<td>1 (70.8)</td>
<td>4 (12.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CSF proteins ≥40 mg/dL, n (%)</td>
<td>21 (91.3)</td>
<td>16 (50.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>CSF leukocytes/mm³, mean (SD)</td>
<td>12.8 (21.9)</td>
<td>1.7 (2.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CSF proteins, mg/dL, mean (SD)</td>
<td>75.3 (39.4)</td>
<td>47.2 (23.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CSF glucose, mmol/L, mean (SD)</td>
<td>4.2 (1.3)</td>
<td>3.7 (1.0)</td>
<td>0.086</td>
</tr>
<tr>
<td>CSF chloride, mmol/L, mean (SD)</td>
<td>123.3 (4.3)</td>
<td>121.1 (5.8)</td>
<td>0.039</td>
</tr>
<tr>
<td>CSF CHIKV load, cp/mL, mean (SD)</td>
<td>578,815 (1,787,072)</td>
<td>221,914 (796,673)</td>
<td>0.126</td>
</tr>
<tr>
<td>Serum CHIKV load, cp/mL, mean (SD)</td>
<td>1.2 x 10⁶ (2.2 x 10⁶)</td>
<td>9.0 x 10⁵ (1.7 x 10⁵)</td>
<td>0.330</td>
</tr>
<tr>
<td>CSF anti-CHIKV IgM, UI/L, mean (SD)</td>
<td>101.0 (83.0)</td>
<td>143.7 (168.7)</td>
<td>0.885</td>
</tr>
<tr>
<td>Serum anti-CHIKV IgM, UI/L, mean (SD)</td>
<td>139.3 (115.6)</td>
<td>57.3 (92.9)</td>
<td>0.219</td>
</tr>
<tr>
<td>CSF/serum CHIKV loads ratio, mean (SD)</td>
<td>0.63 (0.14)</td>
<td>0.55 (0.20)</td>
<td>0.055</td>
</tr>
<tr>
<td>CSF/serum IgM levels ratio, mean (SD)</td>
<td>0.41 (0.33)</td>
<td>0.96 (0.57)</td>
<td>0.069</td>
</tr>
</tbody>
</table>

Abbreviations: CHIKV = Chikungunya virus; IgM = immunoglobulin M; NECACD = nonencephalitic Chikungunya virus-associated CNS disease.
for mainland France in 2000–2002 concerning encephalitis of infectious or specified etiology,29 as well as the rate reported in the United States between 1998 and 2010 for all encephalitis.21 Of note, the CIR of CHIKV-associated encephalitis in La Réunion Island was also superior to those observed with West Nile virus (WNV) and other neuroinvasive arboviral infections in the United States between 1999 and 2007,24 or to the global incidence observed with Japanese encephalitis.25

Though no similar study has been reported previously to our knowledge, our findings are consistent with earlier report of CNS conditions complicating CHIKV infection, ranging from mild neurocognitive or behavioral disorders to severe neurologic syndromes including acute stage encephalopathy/encephalitis, postinfective ADEM (encephalomyelodendritis), and postinfective Guillain–Barré syndrome (polyradiculo-neuritis).14–17 They are also in agreement with earlier observational studies, even though the criteria used to define encephalitis differ from those we used.3,26–28 CHIKV-associated CNS disease prognosis seems similar to that of other viral etiologies. It was associated in our setting with much more severe neurologic consequences than previously reported in India,26,27 or even recently in Thailand.28

This substantial toll is compatible with that of other virus-associated encephalitis.29–31

The age distribution of encephalitis incidence was U-shaped, with 2 peaks observed in young infants and older adults, consistent with the distribution of encephalitis in general populations,31,29,30 or with overall neuroinvasive disease of viral origin reported in the United States.21 The CIR of CHIKV-associated encephalitis in these extreme age groups is 25-fold higher for children under 1 year and 6-fold higher for people over 65 years than those found for encephalitis of specified etiology in the United States.21 This also contrasts the bimodal age distribution of herpes simplex virus encephalitis, which peaks between 60 and 64 years32; that of WNV, which has a greater effect on the elderly24,33; or that of La Crosse virus, which targets young children.24,34 Higher susceptibility of children to CHIKV-associated encephalitis is also supported by the cerebral edema features observed in a neonate infected by mother-to-child transmission. Accordingly, young mice are more susceptible to CHIKV than adult mice.35 CHIKV targets the choroid plexuses and meningeal and ependymal envelopes, but does not invade brain parenchyma of adult mice deficient for type 1 interferon and adult monkeys,35,36 despite the presence of viral RNA or infectious virus in the CSF of animals during the acute phase of infection, whereas CHIKV infects neurons of neonatal/suckling mice.37 A defective host response may contribute to the higher susceptibility of neonates to CHIKV, as suggested by studies showing that the neonatal immune response is quantitatively and qualitatively distinct from that of adults.38 Thus, in contrast to New World alphaviruses that cause encephalitis in humans and in animal models as a consequence of viral invasion of the brain parenchyma,39 CHIKV is not a neurotropic virus in experimentally infected adult animals, although it disseminates and replicates in the meningeal and ependymal envelopes.39

### Table 3: Outcomes of CHIKV-associated CNS disease in La Réunion Island (2005–2009)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Probable or possible encephalitis (n = 24), n (%)</th>
<th>NECACD* (n = 33), n (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive care support</td>
<td>10 (41.7)</td>
<td>3 (9.1)</td>
<td>0.009</td>
</tr>
<tr>
<td>Length of stay &gt; 4 d</td>
<td>14 (58.3)</td>
<td>13 (39.4)</td>
<td>0.187</td>
</tr>
<tr>
<td>Extended Glasgow Outcome Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>3 (12.5)</td>
<td>4 (12.1)</td>
<td></td>
</tr>
<tr>
<td>Vegetative state</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Lower severe disability</td>
<td>1 (6.3)</td>
<td>2 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Upper severe disability</td>
<td>0 (0)</td>
<td>2 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Lower moderate disability</td>
<td>1 (6.3)</td>
<td>1 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Upper moderate disability</td>
<td>3 (12.5)</td>
<td>2 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Lower good recovery</td>
<td>1 (6.3)</td>
<td>1 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Upper good recovery</td>
<td>7 (29.2)</td>
<td>7 (21.2)</td>
<td></td>
</tr>
<tr>
<td>Not assessed</td>
<td>8</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CHIKV = Chikungunya virus; GOSE = Extended Glasgow Outcome Scale; IgM = immunoglobulin M; NECACD = nonencephalitic Chikungunya virus-associated CNS disease.

*Unless stated, the data were available for 24 encephalitic cases and 33 NECACD cases. The GOSE was assessed at discharge for nonsurvivors and at 3 years postinfection for the survivors. We used both adult and pediatric versions of the GOSE. Percentages are calculated on a total of 35 patients.

b Fisher exact overall p value testing 7 of the 8 outcome categories.

Importantly, although infants appear more susceptible to CHIKV-associated encephalitis, the clinical presentation and 3-year outcome of CHIKV-associated encephalitis were more severe in adults than in infants, except for one neonate. As also observed in the CHIMERE cohort study,40 they consisted exclusively of behavioral changes and neurocognitive impairment in infants, while they affected cortical functioning and led to disabling sequelae in...
The authors thank the coinvestigators and contributors and the staff of the Microbiology Laboratory and the Center for Clinical Investigation. Alain Michault (1950–2015) dedicated his career to epidemiology of Chikungunya virus (CHIKV)-associated encephalitis, nonencephalitic CHIKV CNS disease, and CHIKV-associated CNS disease with negative CSF (i.e., CHIKV infections with neurologic manifestations compatible with aforementioned diagnoses but negative CSF for immunoglobulin M and PCR) by age categories.}

**Figure 2** CHIKV infections with neurologic signs by age categories, Réunion Island (2005–2006)

(A) Total case reports (probable + possible) of Chikungunya virus (CHIKV)-associated encephalitis, nonencephalitic CHIKV CNS disease, and CHIKV-associated CNS disease with negative CSF (i.e., CHIKV infections with neurologic manifestations compatible with aforementioned diagnoses but negative CSF for immunoglobulin M and PCR) by age categories.

(B) Age-stratified cumulative incidence rates of CHIKV-associated encephalitis (probable + possible) in La Réunion or the age-stratified cumulative incidence rates of all encephalitis in the United States.

Our study has some limitations. First, we have not searched for CHIKV RNA and IgM systematically in patients presenting neurologic manifestations. Second, LP was not repeated in the absence of clinical deterioration. We may therefore have missed pathologic changes in CSF protein level or leukocyte count, notably in neonates who are prone to prohemorrhagic conditions.14 Third, we have not performed neuroradiologic examination routinely, so that patients with mild neurologic forms were probably underestimated, while in turn, cases of major CNS disease could be unstable to undergo timely MRI scans. Thus, as our study was not population-based, we may have underestimated the real burden and slightly overestimated the CFR and incidence of neurologic sequelae. Fourth, the data collection was partially retrospective and we may have missed some minor symptoms, such as tremors or other movement disorders indicative of thalamic or basal ganglia involvement.23 We focused on the symptoms whose presence was constantly noted, so that our description of CHIKV-associated CNS disease is likely conservative and limits information bias. Fifth, our study was restricted to a fairly localized area, so we cannot rule out that the extent of CHIKV-associated CNS disease in recent years may reflect a stronger neurovirulence of the ECSA sublineage. Encephalitis has not yet been described everywhere the ECSA genotype has circulated. The occurrence of encephalitis may depend on the magnitude of the outbreak, by targeting susceptible hosts to CHIKV-associated CNS disease. The study of host and CHIKV genetic factors underlying CHIKV-associated CNS disease may help better understand the pathogenesis of CHIKV-associated CNS disease. In this regard, we have much to learn from current outbreaks throughout the world due to African and Asian lineage viruses.

CHIKV-associated CNS disease, including encephalitis as defined by the IEC, may complicate CHIKV infection. Altogether these data contribute to improve the knowledge of CHIKV-associated neuropathology and illustrate the clinical neurotropism of CHIKV and its deleterious consequences, especially in neonates.

**AUTHOR CONTRIBUTIONS**

Patrick Gérardin: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, statistical analysis. Thérèse Couderc: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Marc Bintner: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Patricia Toumezhine: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Véronique Boisson: analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Gianandrea Borgherini: analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Jérome Lémant: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, acquisition of data. Michel Renouil: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Frédéric Sraitkowsky: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, acquisition of data. Jerome Lémant: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, acquisition of data. Marc Lesuin: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Patrick Gérardin: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Thérèse Couderc: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Marc Bintner: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Michel Renouil: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Véronique Boisson: analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Gianandrea Borgherini: analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Jérome Lémant: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, acquisition of data. Michel Renouil: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Patrick Gérardin: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data.  

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communicable diseases in Réunion Island and South West Indian Ocean. Alain facilitated most of the major partnerships and publications made on the Chikungunya virus by our institution. He died on August 5, 2015, of cancer. The authors convey their sympathy to his wife, his 2 sons, and his family.

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