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Evolution of symptoms and quality of life during Zika virus infection: A 1-year prospective cohort study

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ABSTRACT

Background: Although the complications of Zika virus infection have been well described, the clinical pattern has not been reported in enough detail to differentiate this infection from those with other arboviruses, and no longitudinal study has yet been published on the persistence of symptoms and quality of life.

Objectives: were to describe bio-clinical pattern and quality of life during ZIKV infection, and their evolution.

Study design: We present a 1-year clinical follow-up of 49 people infected with Zika virus in French Guiana, for whom the diagnosis was confirmed by RT-PCR in serum or urine.

Results: Fever was inconsistent (95% confidence interval (CI), 39–67). Exanthema (CI, 84–100) was maculo-papular, with pruritus and conjunctivitis, variable over time and disappeared 12 days after the onset of symptoms (CI, 10–14). Joint pain (CI, 39–67) occurred mainly in the hands, wrists, knees and ankles and lasted for 10 days (CI, 7–13). Asthenia (CI, 61–85) scored low (3/10) but lasted for 19 days (CI, 16–22). The last two symptoms strongly limited patients’ activities in the acute stage of the disease (RAPID-3 score, CI, 5–8). None of the patients had neurological complications, but 41% (CI, 27–55) had areflexia during the first month.

Conclusions: We found no real chronic evolution or decreased quality of life, function or ability to work from the first month after symptom onset.

Summary

We present a 1-year follow-up of clinic, biology and quality of life from 49 ZIKV infected volunteers in French Guiana (diagnosis confirmed by RT-PCR in serum or urine).

1. Background

Zika virus (ZIKV) is a flavivirus (Flaviviridae family) transmitted to humans by mosquito bites (genus Aedes), sexual transmission, blood transfusion and from mother to fetus in utero [1]. The virus was first identified in 1947 in East African wildlife. Although several cases of human infection were notified subsequently, it really emerged in Micronesia in 2007 [2] and then spread through French Polynesia (2013) to South America and the Caribbean islands (2015) [3].

Investigations on Yap Island in Micronesia showed that ZIKV infection is often asymptomatic (81%, 95% CI 77–85); when symptoms are observed, it manifests as a dengue-like syndrome [2,4]. The clinical
description is, however, still imprecise with regard to the development of cutaneous rash, the number of joints involved and the duration of symptoms. Complications of ZIKV infection were well described as the epidemic progressed, and it is now established that it is responsible for neurological complications (Guillain-Barré syndrome, myelitis, encephalitis) [5–7] and Zika congenital syndrome in infants (microcephaly, visual deficiency) infected in utero [8,9].

ZIKV infection is difficult to differentiate from dengue (DENV) and chikungunya (CHIKV) virus infections [10], which circulate in similar regions [11]. Molecular confirmation, when available, may give a negative result because of the short viraemia, and the results of serological tests are difficult to interpret because of cross-reactions among flaviviruses [12], complicating diagnosis of ZIKV infection [13,14].

When CHIKV (Togaviridae family) emerged and spread in an outbreak in Réunion in 2006, the clinical pattern was not described [15], and scientists were surprised to learn that this new infection could be responsible for chronic arthritis and a significant, prolonged decrease in the quality of life [16]. Although CHIKV and ZIKV do not belong to the same viral family, the infections have a similar pattern. We therefore investigated whether ZIKV infection was likely to have a prolonged clinical effect and decrease the quality of life, as there has been no longitudinal clinical follow-up of ZIKV-infected patients that would provide answers to these questions [17].

2. Objectives

The objective of this prospective study was to observe the clinical symptoms during ZIKV infection, compare them with the symptoms caused by other arboviruses and observe the evolution of the symptoms and quality of life.

3. Study design

3.1. Study population

The local health authorities in French Guiana, a French overseas territory located in north-east South America, officially announced a ZIKV epidemic between January and October 2016 [3]. During the epidemic, a longitudinal cohort survey of ZIKV-infected patients was established to observe clinical symptoms and their evolution. Military personnel and their families and civilians who consulted for a cutaneous rash in the French armed forces medical facilities in Cayenne or Kourou were invited to participate. If ZIKV infection was confirmed by reverse transcriptase polymerase chain reaction (RT-PCR, see supplementary material) in serum or urine, and DENV and CHIKV infections were ruled out, patients were enrolled in a longitudinal study comprising 12 medical consultations over 1 year after onset of symptoms. After an initial consultation, they were examined on days (D) 3, 5, 7, 15, 21 and 28 (date of censorship for the acute stage) and then at months (M) 2, 3, 6, 9 and 12 (follow-up).

Previous DENV infection was identified by IgG indirect enzyme-linked immunosorbent assay (ELISA). Analyses were performed for malaria, haematological and biochemical parameters and coagulation factors. If any of these biological parameters was abnormal, repeated samples were analysed until normal values were obtained.

3.2. Clinical follow-up

At each consultation, a general practitioner performed a standardized, systematic clinic examination. In addition, patients filled in a form each day during the acute stage on the evolution of symptoms. Concordance was checked by the general practitioner at each consultation.

Quality of life was assessed at each consultation from two validated self-reporting questionnaires, the SF-12 [18] and the RAPID-3 [19], which are used for patients with inflammatory joint diseases, on the assumption that ZIKV might be responsible for chronic arthralgia and asthenia.

3.3. Statistical analysis and ethical approval

Continuous variables are expressed as mean ± SD and discrete variable as percentages, with 95% confidence intervals (CIs). We analysed also individuals features that could influence symptoms synthesized via a clinical score (see supplementary material). All statistical analyses were performed with R-3.4.3 software; the significance level was 5%.

Ethical approval was given by the Comité de Protection des Personnes Sud-Méditerranée I corresponding to the "Etude descriptive prospective de la maladie à virus Zika au sein de la communauté de défense des Forces Armées en Guyane – ZIFAG" and was registered on 29 February 2016 as RCB: 2016-A00394-47. Written consent was obtained from participants.

4. Results

Forty-nine ZIKV-infected patients were included (Fig. 1). The sex ratio was 39:10, and the mean age was 38 years (± 9). No underlying disease was observed, but 15 (37%) patients were initially positive for dengue IgG. Of the 13 patients who were reassigned to metropolitan France and therefore lost to follow-up, 8 were subsequently contacted to investigate any sequelae.

4.1. Acute stage and follow-up

The symptoms are listed in Table 1. At the first consultation, the main symptom observed was exanthema (92%, CI, 84–100), with or without fever (53%, CI, 39–67). With pruritus (63%, CI, 49–67), this was the common reason for a first visit to a general practitioner. Patients had a maculopapular cutaneous rash, which became more or less severe over an average of 3 days (CI, 2.5–3.5). It was located on the head (80%, CI, 68–92), thorax and back (all patients), abdomen, arms and legs (96%, CI, 90–100) and hands and feet (38%, CI, 24–52). The condition progressed to a macular rash and then disappeared on average 12 days (CI, 10–14) after the onset of symptoms (Fig. 2).

Arthralgia (53%, CI, 39–67) was located mainly in the hands, wrists,
In some patients, all the joints were affected. Of the 26 patients with arthralgia, 20 had mild joint swelling (77%, CI, 61–93). Puncture to remove excess fluid was not required, and joint damage disappeared progressively after an average of 9 days (CI, 5–12), although three patients reported persistence up to 1 year (Table 2).

The mean pain score in relation to arthralgia was moderate (3/10, CI, 1.9–3.5) at the beginning of symptoms and decreased from day 15 (1.2/10, CI, 0.7–1.7) (Fig. 3). Nevertheless, seven patients (14%) had initial scores ≥6. Paracetamol was taken according to the evolution of pain, by 22 patients during the acute stage of the disease (45%, CI, 31–59), by nine at M2–M3 and by five at M6–12.

With regard to neurological signs, 20 patients had reversible areflexia (41%, CI, 27–55), affecting the patellar reflex in 19 cases, the Achilles reflex in 14 and the biceps reflex in one; the areflexia was mainly bilateral (17). Ten patients had paresthesia (20%, CI, 9–31) in the hands (10), feet (1) or face (1), and 10 reported a mild decrease in arm muscle strength (20%, CI, 9–31), often expressed as difficulty in opening a jar. An electromyogram performed on the patient with the most symptoms showed normal conductivity, thus excluding Guillain–Barré syndrome.

Asthenia at the first visit was frequent (73%, CI, 61–85) but moderate (3/10, CI, 2–4). Two patients scored 8/10. The score decreased to 2/10 at M2 (CI, 1–3) and stabilized at 1/10 in M3–12, although 22% of the patients still reported being tired at M12 (Table 2).

The clinical score was < 10 for 28 patients (57%, CI, 42–71), and

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### Table 1

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Presentation, N = 49</th>
<th>Acute period D0-D28, N = 45</th>
<th>Follow-up (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>General</td>
<td>36</td>
<td>73</td>
<td>61–85</td>
</tr>
<tr>
<td>Headache</td>
<td>34</td>
<td>69</td>
<td>56–82</td>
</tr>
<tr>
<td>Fever</td>
<td>26</td>
<td>53</td>
<td>39–67</td>
</tr>
<tr>
<td>Shivering</td>
<td>26</td>
<td>53</td>
<td>39–67</td>
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<tr>
<td>Orbital pain</td>
<td>25</td>
<td>51</td>
<td>37–65</td>
</tr>
<tr>
<td>Myalgia</td>
<td>23</td>
<td>47</td>
<td>33–61</td>
</tr>
<tr>
<td>Polyadenopathy</td>
<td>21</td>
<td>43</td>
<td>29–57</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Skin and mucous membranes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exanthema</td>
<td>45</td>
<td>92</td>
<td>84–100</td>
</tr>
<tr>
<td>Pruritus</td>
<td>31</td>
<td>63</td>
<td>49–77</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>28</td>
<td>57</td>
<td>43–71</td>
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<tr>
<td>Enanthema</td>
<td>12</td>
<td>24</td>
<td>12–36</td>
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<tr>
<td>Aphthous stomatitis</td>
<td>1</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Joints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>26</td>
<td>53</td>
<td>39–67</td>
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<tr>
<td>Swelling</td>
<td>19</td>
<td>39</td>
<td>25–53</td>
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<tr>
<td>Back pain</td>
<td>19</td>
<td>39</td>
<td>25–53</td>
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<tr>
<td>Nervous system</td>
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<tr>
<td>Areflexia</td>
<td>25</td>
<td>51</td>
<td>37–65</td>
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<tr>
<td>Decreased muscle strength</td>
<td>10</td>
<td>20</td>
<td>9–31</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>10</td>
<td>20</td>
<td>9–31</td>
</tr>
<tr>
<td>Contracture, fasciculation</td>
<td>1</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>2</td>
<td>–</td>
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<tr>
<td>Digestive system</td>
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<td></td>
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<tr>
<td>Diarrhoea</td>
<td>13</td>
<td>27</td>
<td>15–39</td>
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<tr>
<td>Anorexia</td>
<td>6</td>
<td>12</td>
<td>–</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>4</td>
<td>8</td>
<td>–</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4</td>
<td>8</td>
<td>–</td>
</tr>
<tr>
<td>Respiratory tract</td>
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<td></td>
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<tr>
<td>Pharyngitis</td>
<td>3</td>
<td>6</td>
<td>–</td>
</tr>
<tr>
<td>Cough</td>
<td>2</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Haematological system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematoxia, purpura</td>
<td>2</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Haemospermia</td>
<td>1</td>
<td>2</td>
<td>–</td>
</tr>
</tbody>
</table>

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*a* D28: date of censorship for the acute stage.

*b* Difference (p < 0.05) from ZIKV RT-PCR-negative group: asthenia = 11%, conjunctivitis = 22%, pruritus = 33%.
Female gender, age > 30, positive dengue IgG, and viral load > 1000 copies/ml were associated with a score ≥10 (p < 0.05).

Biological parameters showed no specific alterations and did not allow differentiation of ZIKV infection from other arboviral infections (Table 3). Five had moderate lymphopenia and five a moderate increase in C-reactive protein (10%, CI, 2–18).

4.2. Quality of life

The scores for both physical components of the SF-12 questionnaire (D3 = 48 ± 11, D15 = 46 ± 9, D21 = 52 ± 6, D28 = 51 ± 7, M2-M12 = 54 ± 6) and the RAPID-3 questionnaire (Fig. 3) showed a real decrease in quality of life during the 2 weeks after onset of symptoms and then tended to normalize. When we asked patients whether their quality of life was lower than before infection, 16 agreed on D3 (33%, CI, 20–46), 12 on D15 (36%, CI, 20–52) and five on D28 (11%, CI, 2–20). Subsequently, only one or two patients agreed.

These findings correspond to an inability to work: 10 patients stopped work during the acute stage of the disease (36%, CI, 22–50), decreasing to two at M2, one at M3 and none at M6.

5. Discussion

This clinical longitudinal follow-up of ZIKV-infected patients describes the pattern of ZIKV infection from the point of view of the general practitioner. It was not our purpose to describe complications that are too rare to be observed in a cohort of 49 patients. Our series provides new data on the frequency of symptoms, with detailed descriptions.

We benefited from a highly compliant population, but, because of the characteristics of the cohort (no comorbidity, preponderantly white, male and young), the results are more representative of European travellers than of the population of French Guiana [20].

The frequencies of 13 symptoms differed significantly from those reported in previous clinical reviews [21]: cutaneous rash (92% vs 86% in the literature), headache (69% vs 52%), prostration (0% vs 46%), asthenia (73% vs 43%), retro-orbital pain (51% vs 36%), photophobia (0% vs 26%), adenopathy (43% vs 25%), joint swelling (39% vs 33%), pharyngitis (6% vs 24%), enanthema (24% vs 20%), diarrhoea (27% vs 17%), paresthesia (20% vs 9%) and areflexia (41% vs 0%). These differences highlight the problem of studies that lack a non-ZIKV-infected control group; however, it would have been difficult to guarantee the absence of ZIKV infection for 1 year, because the condition may be asymptomatic or with a mild clinical presentation.

Exanthema was the main symptom, appearing over the entire body, sometimes including the hands and feet, which decreased within 3 days. In contrast to dengue and chikungunya [22–24], the exanthema had a maculopapular aspect and was associated with enanthema and conjunctivitis. These cutaneous signs with pruritus permitted differentiation of positive and negative ZIKV RT-PCR in the cohort.

Arthralgia is a classical sign in all viral infections, but few studies have located it precisely or described its association with swelling or functional strength [25]. We found that all the joints could be involved, including the spine, but that damage affected mainly the hands, wrists, knees and ankles, often in association with minor swelling. Our description of joint involvement is similar to that for CHIKV infection, so that it is difficult to differentiate the two infections during the acute stage. We found milder joint involvement (mean score, 3/10), however,
which regressed spontaneously within 10 days. Only arthralgia associated with moderate asthenia (found in 73% of the patients) had a real impact on patients’ activities during the acute stage of the disease. Because of the possibility of Guillain-Barré syndrome [5], we systematically recorded neurological signs to ensure rapid detection of any sensory or motor deficiency. None of our patients had serious neurological complications, but a significant proportion had mild deficiencies such as asthenia and decreased muscle strength. We did not fully explore neurological deficiency, but such symptoms are consistent with peripheral neuropathy; the electromyograms were normal, as described elsewhere [26,27]. Nascimento et al. hypothesized a mechanism related to nerve swelling in a study of three patients [28).

Diagnosis is critical for the general practitioner to monitor patients for the right infection, as dengue can lead to more severe complications than ZIKV disease, and ZIKV infection can lead to Zika congenital infection. From a public health point of view, an efficient case definition permits better reactivity when ZIKV emerges in a new territory [10,14,29]. Many epidemiological definitions have been published by international organizations and national governments [30]. By highlighting features that might allow better differentiation of ZIKV infection from other arboviruses, our aim was to improve clinical diagnosis when virological tools are not available. In comparison with dengue and chikungunya, fever was often low or absent in ZIKV infection, and conjunctivitis and pruritus accompanied exanthema. Joint involvement was present, as in chikungunya, but was milder and with no tenosynovitis. Biological alterations were rare. These findings are in accordance with those of Ho et al. [31], who concluded that rash and conjunctivitis resulted in a better likelihood ratio, while the combination of fever, lymphopenia and thrombopenia favoured DENV. According to Yan et al. [32], the presence of conjunctivitis, platelets and monocyte counts resulted in 92% diagnostic accuracy in differentiating ZIKV from DENV.

We were surprised by the duration of symptoms during the acute stage of ZIKV infection. The mean duration of cutaneous rash was 13 days and that of joint damage was 10 days after the onset of symptoms. The rash spread until D28 in two patients. The evolution of symptoms was longer than reported elsewhere [4,21], probably because of greater accuracy, as patients recorded their own symptoms every day until they disappeared, supervised by the practitioner at each consultation. During the follow-up, the only symptom that persisted continuously from M2 to M12 was asthenia, which decreased regularly to reach 22% at M12. At the same time, the mean score of < 1/10 casts doubt on this assertion.

Regarding the link between individual features and symptoms, we found that gender, age, dengue antecedent, and viral load were associated with the clinical score, but we are not able to conclude because of the small size of our cohort. We found no chronic evolution during ZIKV infection. Our patients were not severely affected, and all recovered. We also found no real decrease in quality of life, function or ability to work beyond the first month after onset of symptoms. The clinical impact of ZIKV appears to be less severe than that of DENV, which results in chronic asthenia in a quarter of patients, or of CHIKV, which can have a general or locomotor effect 6 years after acute infection [16]. We found that, when the acute stage of ZIKV infection is uncomplicated, there are no chronic sequelae.

Authors’ contributions

Franck de Laval was principal investigator, he made the clinical follow-up, analyzed data, and wrote the paper; Hubert d’Aubigny analysed data, and wrote the paper; Séverine Mathéus made the virological diagnosis; Thomas Labrousse made the clinical follow-up; Anne Laure Ensargueix made the clinical follow-up; Enguerrane Martinez Lorenzi made the clinical follow-up; François Xavier Le Flem made the clinical follow-up; Nathalie André made the clinical follow-up; Didier Belleoud made the clinical follow-up; Isabelle Leparc-Goffart made the flaviruses serologies; Dominique Rouset made the virological diagnoses; Fabrice Simon brought his clinical expertise; Sébastien Briolant was coordinator investigator, he made the virological diagnoses, and wrote the paper.

All authors have seen and approved the manuscript and contributed significantly to the work.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jcv.2018.09.015.

References


