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Adaptation of WHO Definitions of Clinical Forms of Chikungunya Virus Infection for the Elderly

Lidvine Godaert,[1]* Cécilia Cofais,[2] Fanny Hequet,[1] Emeline Proye,[1] Lukshe Kanagaratnam,[3] Raymond Césaire,[4] Fatiha Najioullah,[4] and Moustapha Dramé[5]

[1]*Department of Geriatrics, Valenciennes General Hospital, Valenciennes, France;* [2]*Department of Geriatrics, University Hospitals of Rennes, Rennes, France;* [3]*Department of Research and Public Health, University Hospitals of Reims, Reims, France;* [4]*Department of Virology, University Hospitals of Martinique, Fort-de-France, Martinique;* [5]*Department of Clinical Research and Innovation, University Hospitals of Martinique, Fort-de-France, Martinique*

Abstract. The WHO defined three clinical forms for chikungunya virus infection (CHIKV, namely, acute, atypical, and severe cases) and a chronic form. These definitions seemed inappropriate for the elderly. So, we propose an adapted definition for elderly people. A cross-sectional analysis was performed including patients aged ≥ 65 years, who attended the emergency department with a positive biological diagnosis of CHIKV in 2014. A total of 267 elderly patients (80 ± 8 years) were included. When using the 2015 WHO definitions, 114 patients could not be classified (42.7%) in any of the category, of whom 43 (37.7%) reported absence of fever, 85 (74.6%) reported absence of joint pain, and 14 (12.3%) reported absence of both fever and joint pain. After adaptation of the WHO definitions, the 114 unclassifiable patients were reclassified as follows: eight as typical cases, 50 as atypical cases, 42 as severe cases, and 14 remained unclassifiable. The atypical clinical form was the most common form. The 2015 WHO definitions of the clinical forms at the acute phase of CHIKV are ill suited to the elderly. The adapted definition we propose here appears to be more appropriate and could help improved management of older patients with CHIKV.

INTRODUCTION

Chikungunya virus is an arbovirus transmitted through the bites of infected *Aedes aegypti* or *Aedes albopictus* mosquitoes.[1] Chikungunya virus infection (CHIKV) has spread in an endemic–epidemic pattern and is considered as an emerging public health problem not only in Asia and Africa but also in the Americas, and soon, in Southern Europe.[2,3] Chikungunya virus infection is usually symptomatic, with fever and acute incapacitating joint pain. Other common symptoms of viral infections may also be observed (e.g., vomiting, exanthema, headaches, or myalgia).[4,5] In 2015, experts from the WHO defined three clinical forms at the acute phase of CHIKV,[6] namely, acute clinical cases, atypical cases, and severe acute cases, and a chronic form. The clinical case definitions of chikungunya proposed by the WHO are detailed in Table 1.

There is a consensus regarding the typical form in the acute phase of CHIKV.[1] In the literature, populations with CHIKV were described as having fever and joint pain in 90% of cases or more.[7–11] Sissoko et al.[12] suggested that the pair comprising fever plus incapacitating polyarthralgia would identify suspected CHIKV during outbreaks. Thiberville et al.[8] developed clinical and clinical–biological scores for the diagnosis of CHIKV based on patients who reported fever and arthralgia. The populations studied by Sissoko et al.[12] and Thiberville et al.[8] were young adults. We studied CHIKV in a population of patients aged 65 years or older during the outbreak in Martinique in 2014. First, we studied the performance of the scores proposed by Sissoko et al.[12] and Thiberville et al.[8] in the older population.[13] Performances were very poor for both scores, and we suggested that screening scores developed in young populations were not accurate in identifying CHIKV in older people. Second, Godaert et al.[14] compared clinical presentations at the acute phase of CHIKV in older people versus their younger counterparts. Only 8.2% of those aged 65 years or older presented acute clinical cases according to the WHO definition (versus 59.6% in younger people), whereas 42.7% of older people at the acute phase of CHIKV presented an unclassifiable clinical form according to the WHO definition. These results suggest that clinical forms at the acute phase of CHIKV differ between older and younger people.

The main objective of this study was therefore to propose an adapted definition of the 2015 WHO clinical forms at the acute phase of CHIKV in populations aged 65 years or over. The secondary objective was to describe the most common clinical form of CHIKV in patients aged 65 years or older during the outbreak in Martinique in 2014.

METHODS

Study design and population. From a historical cohort study performed in the University Hospital of Martinique (French West Indies), and previously described elsewhere,[14] patients aged 65 years or older with a positive biological diagnosis of CHIKV were selected. Patients included in the analyses were all admitted via the emergency department. Only patients presenting within 3 days of the onset of symptoms were included. The biological diagnosis of CHIKV was performed by reverse transcription PCR (RT-PCR) on a plasma sample, with the RealStar© Chikungunya RT-PCR Kit (Altona Diagnostics GmbH, Hamburg, Germany).

Ethical issues. This study was performed in accordance with the Declaration of Helsinki and French legislation relating to research involving human subjects. The study received the approval of the local ethics committee.

Data collection. Baseline characteristics were retrospectively collected, including age, gender, time since onset of CHIKV signs and symptoms, and presence or absence of the following features: fever; arthralgia; myalgia; digestive, infectious, cardiac, dermatologic, or neurological symptoms; signs of hepatic failure; history of falls; decompensated diabetes; and comorbidity burden assessed using the Charlson Comorbidity Index.[15] Biological testing included complete

* Address correspondence to Lidvine Godaert, Department of Geriatrics, General Hospital of Valenciennes, Avenue Desandrouin CS 50479, Valenciennes CEDEX F-59322, France. E-mail: lidvinegodaert@me.com

TABLE 1
Chikungunya case definitions proposed during the 2015 consultation of WHO experts in Nicaragua[6]

Clinical form	Clinical and epidemiological criteria
Acute clinical case	Fever > 38.5°C and joint pain* (usually incapacitating†) with acute onset and resident or visitor in areas with local transmission of chikungunya on the last 15 days (*suspect case* for epidemiological surveillance) or confirmation by laboratory (PCR, serology or viral culture [*confirmed case* for epidemiological surveillance])
Atypical case	Clinical case of laboratory-confirmed chikungunya accompanied by other manifestations (neurological, cardiovascular, dermatological, ophthalmological, hepatic, renal, respiratory, or hematological, among others)
Severe acute case	Clinical case of laboratory-confirmed chikungunya presenting dysfunction of at least one organ or system that threatens life and requires hospitalization

* Usually accompanied by exanthema, myalgia, back pain, headache, and, occasionally, vomiting and diarrhea (pediatric age-group).
† In children aged < 3 years, joint pain is expressed as inconsolable crying, irritability, and rejection to mobilization and/or walking.

blood count, blood biochemistry, creatinine, blood creatinine phosphokinase, and inflammatory biomarkers.

Patients were classified in two different ways according to CHIKV clinical forms as defined by the WHO (i.e., acute clinical cases, atypical cases, and severe acute cases). First, patients were classified according to the 2015 WHO expert panel definitions.[6] In this classification, patients were considered as acute clinical cases if they were present in Martinique during the epidemic period, had fever ≥ 38.5°C, and had acute onset joint pain and RT-PCR–positive identification of CHIKV. Exanthema, myalgia, back pain, headache, vomiting, and diarrhea without an impact on the overall general health status were considered as signs and symptoms usually accompanying the typical acute-phase course of CHIKV, in line with the WHO definition. Patients were considered as atypical cases if they were present in Martinique during the epidemic period, had fever ≥ 38.5°C, and had acute onset joint pain, with RT-PCR confirmation of CHIKV, and also had other manifestations, such as neurological, cardiovascular, dermatological, ophthalmological, hepatic, renal, respiratory, or hematological signs; decompensated diabetes; balance or walking disturbances; or concomitant infections. Patients were considered as severe acute cases if they were present in Martinique during the epidemic period, had fever ≥ 38.5°C, and had acute onset joint pain, with RT-PCR confirmation of CHIKV, and presented at least one organ or system failure that was life-threatening and required hospitalization. Patients without fever or without acute onset joint pain were considered as unclassifiable cases.

The second classification is an adaptation of the 2015 WHO classification, in which "fever *and* arthralgia" was replaced by "fever *and/or* arthralgia." Patients with no fever and no acute onset joint pain were considered as unclassifiable cases. Only acute clinical or biological manifestations were considered. Medical history without acute decompensation was not considered as "other signs."

Statistical analysis. Quantitative variables are described as mean ± SD and categorical variables as number and percentage. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Between January 10, 2014 and December 31, 2014, a total of 267 patients aged ≥ 65 years with laboratory-confirmed CHIKV were included. The average age was 80.4 ± 7.9 years. Baseline characteristics of the study population at inclusion are detailed in Table 2.

The classification of patients according to the WHO definitions and after adaptation of the definitions is presented in Table 3. According to the WHO definitions, 114 patients could not be classified (42.7%) in any of the category, of whom 43 (37.7%) reported absence of fever, 85 (74.6%) reported absence of joint pain, and 14 (12.3%) reported absence of both fever and joint pain. After adaptation of the WHO definitions, the 114 unclassifiable patients were reclassified as follows: eight were reclassified as typical cases, 50 as atypical cases, 42 as severe cases, and 14 remained unclassifiable cases. The atypical clinical form was the most common form in the study population.

DISCUSSION

In our study, according to the 2015 WHO definitions of acute-phase CHIKV, 8.2% of patients presented typical cases, 29.6% atypical cases, and 19.5% severe cases, but 42.7% could not be classified. After adapting the definition of the clinical forms at the acute phase (by replacing "fever *and*

TABLE 2
Baseline characteristics of the study population (*N* = 267)

Characteristic	*N*	%
Aged 75 years or older	197	73.8
Female gender	142	53.2
Presence of fever	224	83.9
Presence of arthralgia	182	68.2
Presence of any other symptom*	236	88.4
Charlson Comorbidity Index components		
Myocardial infarction	10	3.8
Congestive heart failure	42	15.7
Peripheral arterial disease	17	6.4
Cerebrovascular disease	22	8.2
Dementia	34	12.7
Chronic pulmonary disease	9	3.4
Connective tissue disease	1	0.4
Peptic ulcer disease	4	1.5
Mild liver disease	1	0.4
Diabetes without end-organ damage	75	28.1
Hemiplegia	15	5.6
Moderate or severe renal disease	8	3.0
Diabetes with end-organ damage	26	9.7
Tumor without metastasis	25	9.4
Leukemia	1	0.4
Lymphoma	2	0.8
Moderate or severe liver disease	1	0.4
Metastatic solid tumor	1	0.4
Aids	2	0.8
Hospital stay after emergency department admission	138	51.7

* Including other infectious signs, neurological signs, cardiac signs, hepatic signs, history of falls, decompensated diabetes, thrombocytopenia, thrombocytosis, leukocytosis, renal failure, rhabdomyolysis, hypernatremia, hyponatremia, hyperkalemia, and hypokalemia.

TABLE 3
Distribution of clinical forms according to the WHO definitions and after adaptation

	Clinical forms, *N* (%)				
	Acute	Atypical	Severe	Unclassifiable	Total
As defined by the WHO	22 (8.2)	79 (29.6)	52 (19.5)	114 (42.7)	267
After adaptation*	30 (11.2)	129 (48.3)	94 (35.2)	14 (5.2)	267

* "Fever *and* arthralgia" replaced by "fever *and/or* arthralgia."

arthralgia" by "fever *and/or* arthralgia"), 11.2% of patients presented typical cases, 48.3% atypical cases of CHIKV, and 35.2% severe acute cases of CHIKV. During the same outbreak in the French West Indies, a total of 59.6% of younger people presented typical cases.[14] In that study, older people (aged 65 years or greater) had statistically less frequent fever and arthralgia than younger subjects during the same outbreak (presence of fever: 83.9% versus 91.7%, $P = 0.04$; presence of arthralgia: 68.2% versus 87.0%, $P = 0.0001$).[14]

These results suggest that the presentation of CHIKV in older people might be different compared with younger subjects. This finding has already been reported in other illnesses[16,17]; notably, the absence of fever in elderly subjects during infectious disease has previously been described.[17–19] There are several possible explanations for this phenomenon. Older subjects may have a weaker capacity to develop fever notably because of physiological changes linked to aging, termed immune senescence.[20] Alternatively, the technique used to measure body temperature may be inappropriate,[21] or the patient may less frequently report fever. Accordingly, in 2009, Chen et al.[22] reported that very old patients (85 years and older) with pneumonia less often reported having fever than younger subjects (aged 18–64 years). Fever was observed with the same frequency across age-groups. However, it is more difficult to obtain the medical history in older subjects, and they often have symptoms that make the initial examination complicated (notably complications that compromise communication, e.g., confusion or behavioral disorders).[18,19,23] Evaluating the presence (or not) of other clinical signs more typical of the suspected disease can thus be challenging. This could explain the lower frequency of arthralgia in the older subjects in our study.

A simple change to adapt the definition of the clinical forms of CHIKV at the acute phase in older subjects, replacing "fever *and* arthralgia" by "fever *and/or* arthralgia", made it possible to classify most of the older subjects in one of the three WHO clinical forms (i.e., acute clinical case, atypical case, or severe acute case). In our study, atypical cases were the most common form of CHIKV in people aged 65 years or older, after adaptation of the definition, followed by severe cases as the second most common clinical form in our population older than 65 years. In 2009, Economopoulou et al.[24] reported that the incidence of atypical cases and severe cases increased with age, and our results are consistent with this observation. Indeed, our findings suggest that CHIKV may be more serious in older subjects than in younger subjects.

Our study presents several strengths. The study sample is the largest sample of older subjects with CHIKV studied in the literature. The diagnosis of CHIKV was confirmed by RT-PCR using the same kits for all subjects included in the study. Clinical and biological data were recorded by geriatricians from the hospital network data-processing system, with cross-checking against the patients' medical records. The initial classification of the patients used the WHO definitions. Conversely, some limitations of this study deserve to be underlined. First, the presence of arthralgia or fever at home was self-reported. However, physicians examined the patients and noted the presence of fever or arthralgia during the clinical examination. Second, only individuals who attended the emergency department were included, thus incurring a risk of recruitment bias. Nevertheless, the proportion of atypical and severe acute cases substantially outnumbered typical acute cases (48.3% and 35.2% versus 11.2%), and possible recruitment bias is not sufficient to explain such a marked difference. Third, as explained in a previous article,[14] we included patients who were assessed within 3 days of onset of symptoms. This time limit was chosen to reduce the risk that signs or symptoms observed were a consequence of the CHIKV. However, we cannot exclude the possibility that some patients might have gone on to develop a more typical clinical profile in the days after the data recording for the study. Fourth, proposing adapted definitions of CHIKV forms in acute phase for older people may seem to complicate diagnosis of CHIKV. But having an adapted definition would above all make it possible to improve management of infected elderly people.

This study suggests that the definition of the clinical forms of CHIKV at the acute phase must be adapted in patients aged 65 years or older. We therefore propose to replace the pair "fever and arthralgia" in the WHO definitions by "fever and/or arthralgia" because many older people do not experience both signs at the beginning of CHIKV infection. It is of prime importance to adapt the definition to make it easier for physicians to diagnose CHIKV in older populations during outbreaks. We found that atypical cases were the most common clinical form of CHIKV in our population of patients aged 65 years or older, and one-third of elderly people presented severe acute phase. This older population warrants closer attention during chikungunya outbreaks, in line with previous observations in other epidemic diseases, such as influenza.

In conclusion, the WHO definitions of the clinical forms at the acute phase of CHIKV are ill suited to patients aged 65 years and older. The adapted definition we propose here appears to be more appropriate and could contribute to better classification, and thereby, improved management of older patients with CHIKV.

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Authors' addresses: Lidvine Godaert, Fanny Hequet, and Emeline Proye, Department of Geriatrics, Valenciennes General Hospital, Valenciennes, France, E-mails: lidvinegodaert@me.com, hequet-f@ch-valenciennes.fr, and proye-e@ch-valenciennes.fr. Cécilia Cofais, Department of Geriatrics, University Hospitals of Rennes, Rennes, France, E-mail: cecilia.cofais@chu-rennes.fr. Lukshe Kanagaratnam,

Department of Research and Public Health, University Hospitals of Reims, Reims, France, E-mail: lkanagaratnam@chu-reims.fr. Raymond Césaire and Fatiha Najioullah, Department of Virology, University Hospitals of Martinique, Fort-de-France, Martinique, E-mails: raymond.cesaire@chu-martinique.fr and fatiha.najioullah@chu-martinique.fr. Moustapha Dramé, Department of Clinical Research and Innovation, University Hospitals of Martinique, Fort-de-France, Martinique, E-mail: moustapha.drame@chu-martinique.fr.

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