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**Main characteristics of Zika virus exanthema: a prospective study of 60 cases in Guadeloupe (French West Indies).**

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**To the Editor:** Zika virus (ZIKV) has recently started to spread in the Americas leading to successive outbreaks from Brazil to the French West Indies (1-3). It was declared a public health emergency by the World Health Organization due to its unpredictable associated morbidity, e.g.: fetal outcomes and severe neurologic complications (1). However the clinical characteristics of this emerging arbovirosis are not completely known and exanthema, the major symptom of ZIKV infection, has not been fully described.

**Method:** This prospective study was conducted between 02/01/2016 and 04/29/2016, a time of active ZIKV circulation preceding the outbreak on Guadeloupe Island, the largest French overseas territory in the West Indies. The aims of our study were to assess clinical characteristics of ZIKV exanthema at the time of ZIKV emergence and to familiarize physicians with cutaneous features prior to the epidemic. All private practice dermatologists, pediatricians, general practitioners and hospital doctors were asked to record each case of exanthema that was possibly due to a ZIKV infection according to the WHO definition i.e. erythematous eruption with or without fever and at least one of the following symptoms: arthralgia, arthritis, non-purulent conjunctivitis (1). Suspected cases confirmed by RT-PCR without concomitant Dengue virus infection were included. Clinical patterns of ZIKV exanthema were described and compared between adults and children using appropriate statistical tests. The study was approved by the IRB of Rouen University Hospital, Rouen, France.

**Results:** Ten out of 25 physicians collected 87 consecutive medical records of ZIKV exanthema of which 60 were laboratory-confirmed by RT-PCR (Table 1).

Among the 60 confirmed cases, 31 were adults (mean age:  $39 \pm 12$  years) and 29 children (mean age:  $7 \pm 5$  years) with a male/female sex ratio of 25/35: 0.71. Ethnic distribution was the following: Afro-Caribbean (n=30), Caucasian (n=27), Asian (n=3). The exanthema median body surface area was 45 %. The most frequent sites were :face (56/59:94.9%), upper

limbs (57/60:95%), trunk (55/59 : 93.2%), abdomen (52/58: 89.7%) , lower limbs (50/58:86.2%) but rarely the palms or soles (i.e.18/60:30% and 8/60 : 13.3%, respectively). The exanthema was primarily micropapular (51/59:86.4%), descending (38/54:70.4%) and pruritic (49/60:81.7%) in adults and in children (Figure 1). Itching was the most frequent reason for consultation due to severity (21/49 : 42.9%) with insomnia in 10/49: 20.4% of cases. A low-grade fever was present in 33/59 (55.9%) of patients. Associated mucous lesions mostly consisted of conjunctival hyperemia (i.e. 32/57:56.1%). The acral edema classically reported in the literature was rarely observed in children (4/28:14.3%) in contrast to adults, i.e.:16/31:51.6% (p=0.002).

Interestingly, most patients (31/60:51.7%, 19 adults and 12 children) complained of dysesthesia which was possibly associated with autonomic symptoms: dry mouth (21/57:36.8%), lack of tolerance to heat (15/60:25%), sweating disorder (11/59:18.6%), dry eyes (8/57:14%), bladder incontinence (6/60:10%).

**Discussion:** Although not comparative in design, this study focused on ZIKV dermatological signs rises several original patterns in comparison with other endemic arboviroses in the Americas e.g. itchy micropapular exanthema rarely located on the palms and soles with frequent conjunctival hyperemia, high prevalence of dysesthesia and possible associated autonomic symptoms. These discriminating clinical features might be useful in cases of concurrent outbreaks of arbovirose since systemic complications are not similar between Zika and Dengue or Chikungunya viral infections (3). Moreover, association of pruritus with dysesthesia and autonomic symptoms strongly suggests a small fiber neuropathy due to ZIKV whose neurological tropism has now been clearly demonstrated (4,5). Similar to West Nile virus, another neurotropic RNA flavivirus, ZIKV axonal transport from cutaneous small fibers to peripheral nerves might mediate Guillain-Barré syndrome of which high prevalence in the course of ZIKV infection remains unclear (6).

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*Study concept and design:* Cordel

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*Drafting the manuscript:* Cordel, Chosidow

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Figure legends :

Figure 1 : Zika virus exanthema in an adult woman : this case shows typical converging tiny red papules of the cheek associated with a conjunctival hyperemia.

Table 1. Clinical Characteristics of Zika virus exanthema in adults and in children

	Adults: n=31 (%)	Children: n=29 (%)	p
Type of exanthema *			
Micropapular (small tiny papules)	23 (76.7)	28 (96.6%)	0.064
Dengue “like”(confluent macules)	7 (23.3)	1 (3.4%)	
Dynamism of the exanthema **			
descending	19 (73.1)	19 (76.0%)	0.811
ascending	7 (26.9)	6 (24.0%)	
% Body surface area with exanthema median (interquartile range Q1-Q3)	50 (30-80)	40 (30-90)	0.473
Location of the exanthema***			
Face	28 (90.3)	28 (100.0)	0.273
Upper limbs	28 (90.3)	29 (100.0)	0.260
Trunk	30 (96.8)	25 (89.3)	0.533
Abdomen	27 (90.0)	25 (89.3)	1.000
Lower limbs	25 (83.3)	25 (89.3)	0.783
Palms	8 (25.8)	10 (34.5)	0.464
Soles	6 (19.4)	2 (6.9)	0.299
Pruritus			
moderate	12 (38.7)	13 (44.8)	0.631
intense	12 (38.7)	9 (31.0)	0.533
with insomnia	8 (25.8)	2 (6.9)	0.106
Acral edema	16 (51.6)	4 (14.3)	0.002
Conjunctival hyperemia****	14 (48.3)	18 (64.3)	0.223
Dysesthesia	19 (61.3)	12 (41.4)	0.123
Autonomic symptoms*****			
dry mouth	12 (38.7)	9 (34.6)	0.750
lack of tolerance to heat	10 (32.3)	5 (17.2)	0.179
sweating troubles	7 (23.3)	4 (13.8)	0.347
dry eyes	5 (16.1)	3 (11.5)	0.909
bladder incontinence	2 (6.5)	4 (13.8)	0.605
Associated low-grade fever***	16 (53.3)	17 (58.6)	0.683

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Clinical characteristics of Dengue and Chikungunya virus exanthema\*\*\*\*\*

-Dengue: non pruritic macular exanthema located on trunk and limbs including palms and or soles with frequent hemorrhagic signs (petechiae, purpura) associated with high grade fever and flu-like symptoms.

-Chikungunya : non pruritic generalized maculopapular exanthema associated with high grade fever and acute incapacitating arthralgia.

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\*missing data for one adult

\*\* missing data for 3 adults and 3 children, patients (adults n=2; children n=1) with ascending and descending exanthema not taken into account

\*\*\* missing data for one child

\*\*\*\* missing data for 4 patients( 2 adults, 1 child)

\*\*\*\*\* missing data for 4 patients( 1 adults, 3 children)

\*\*\*\*\*WHO Weekly Epidemiological Record 2016; 91: 349-64 and 2015; 90: 410-420