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We report three unrelated cases of Zika virus infection in patients returning from Martinique, Brazil and Colombia respectively, to Montpellier, France. They developed symptoms compatible with a mosquito-borne disease, and serological and molecular investigations indicated a recent Zika virus infection. Considering the recent warning for the likely teratogenicity of Zika virus and the presence of competent mosquito vectors in southern France, these cases highlight the need for awareness of physicians and laboratories in Europe.

Since early 2015 there has been a rapid spread of Zika virus infections in South America with a subsequent threat for importation of that emerging disease in other regions of the world. Here we describe three cases in travellers returning to France from affected areas.

Description of cases

Case 1

On 24 December 2015, a woman in her sixties presented at the Department of Infectious and Tropical Diseases at the University Hospital of Montpellier, France. Three days earlier she had developed sudden fever associated with myalgia, maculopapular rash located on face, trunk and limbs, and conjunctivitis. Symptoms onset occurred two days after having returned from a three-week vacation on Martinique Island (French West Indies). Blood cell count, liver enzymes and renal function were normal. Fever and rash resolved on day 3, but fatigue and muscular symptoms lasted for seven days. Zika virus (ZIKV) real-time polymerase chain reaction (RT-PCR) was negative in blood on day 5 after symptom onset; urine samples were not collected for testing. ZIKV IgM antibodies were detected on 24 December (day 5 after symptom onset) with an increasing level in subsequent samples, whereas the rise of ZIKV IgG antibodies was noticed three weeks later.

Case 2

On 13 January 2016, a man in his twenties was examined in the same department. He had experienced gradual onset of fever, myalgia, diarrhoea, arthralgia and cutaneous rash on trunk and limbs, starting on 5 January, one day after his return from a one-week stay in Rio de Janeiro, Brazil. Upon examination in hospital, fever and cutaneous rash had disappeared, but arthralgia persisted, in association with asthenia, non-productive cough and conjunctivitis. On the day of admission (13 January), laboratory tests showed normal blood cell count and normal renal function, while transaminases were slightly increased. RT-PCR for ZIKV was negative in blood and urine samples. ZIKV IgG and IgM antibodies were detected in serum concomitantly with DENV antibodies; however, the specificity of these anti-ZIKV antibodies was confirmed by a neutralisation assay. Three of the patient's relatives living in Brazil were concurrently diagnosed with symptomatic ZIKV infection.

Case 3

A man in his fifties progressively developed myalgia in lower limbs, pruriginous rash and fever, two days after returning from a three-week vacation in Columbia. He was examined in the same hospital department on the third day (13 January), and showed intense fatigue, extensive maculopapular eruption on the face, trunk and both upper and lower limbs, ulcerative pharyngitis, and conjunctivitis. Results of the neurological examination were normal. Blood cell count showed mild leucopenia (3,800 cells/µL; norm: ›4,000 cells/µL),

Table

Temporal and virological data related to three imported cases of Zika virus infection, Montpellier, France, December 2015 to January 2016

Cases		Case 1	Case 2	**Case 3**
Temporal information				
Returning country		Martinique	Brazil	Colombia
Duration of stay		3 weeks	1 week	4 weeks
Date of return		18 Dec 2015	4 Jan 2016	10 Jan 2016
Symptoms onset		20 Dec 2015	5 Jan 2016	11 Jan 2016
Viral investigation				
First sample date		24 Dec 2015 (D5)	13 Jan 2016 (D9)	13 Jan 2016 (D3)
Dengue virus	RT-PCR[a] plasma	Negative	Negative	Negative
	RT-PCR urine	NS	Negative	Negative
	IgM[b] (OD[c] 1/200)	Negative (0.096)	Positive (0.241)	Positive (0.106)
	IgG[d] (OD 1/500)	Negative (0.061)	Positive (1.139)	Positive (0.209)
Chikungunya virus	RT-PCR[a] plasma	Negative	Negative	Negative
	RT-PCR urine	NS	Negative	Negative
	IgM[b] (OD 1/200)	Negative (0.077)	Negative (0.089)	Negative (0.064)
	IgG[d] (OD 1/500)	Negative (0.048)	Negative (0.047)	Negative (0.052)
Zika virus	RT-PCR[a] plasma	Negative	Negative	Positive (Ct = 37.0)
	RT-PCR urine	NS	Negative	Positive (Ct = 33.2)
	IgM[b] (OD 1/200)	Positive (0.264)	Positive (0.501)	Negative (0.104)
	IgG[d] (OD 1/500)	Negative (0.047)	Positive (0.301)	Negative (0.061)
Second sample date		4 Jan 2016 (D14)	18 Jan 2016 (D14)	18 Jan 2016 (D8)
Dengue virus	IgM (OD 1/200)	Negative (0.095)	Negative (0.191)	Positive (0.364)
	IgG (OD 1/500)	Negative (0.049)	Positive (0.899)	Positive (0.823)
Zika virus	RT-PCR plasma	ND	Negative	Negative
	RT-PCR urine	NS	Negative	Positive (Ct=33.9)
	RT-PCR saliva	NS	Negative	Positive (Ct=30.3)
	IgM (OD 1/200)	Positive (0.895)	Positive (0.446)	Positive (0.433)
	IgG (OD 1/500)	Negative (0.065)	Positive (0.406)	Positive (0.368)
	Zika virus neutralising antibodies[e]	1/320 (‹1/40)	1/640 (1/160)	1/40 (‹1/40)
Third sample date		14 Jan 2016 (D21)	NS	NS
Zika virus	IgM (OD 1/200)	Positive (0.313)	NS	NS
	IgG (OD 1/500)	Positive (0.155)	NS	NS
	Zika virus neutralising antibodies[e]	1/640 (‹1/40)	NS	NS

Ct: Cycles threshold; D: days from symptom onset; ND: not determined; NS: not sampled; OD: optical density; RT-PCR: real-time polymerase chain reaction.

[a] RT-PCRs were performed with the RealStar dengue RT-PCR kit 2.0, the RealStar chikungunya RT-PCR kit 1.0 and the RealStar Zika virus RT-PCR kit 1.0 (Altona Diagnostic, Germany).

[b] Flaviriruses IgM and chikungunya virus IgM detections were performed with in house IgM antibody-capture ELISA (MAC-ELISA) assays.

[c] At 1/200 or 1/500 working dilutions.

[d] Flaviriruses IgG and chikungunya virus IgG detections were performed with in house indirect ELISA assays.

[e] Zika virus neutralising antibodies (result of West Nile virus neutralisation antibodies assay performed as control) with the titre of serum neutralising 90%.

with normal liver enzymes and renal function. RT-PCR for ZIKV was positive in blood, urine and saliva samples. ZIKV seroconversion was detected in the second sample (day 8 after symptom onset) with observation of cross-reactivity with flaviviruses including dengue. Interestingly, two relatives who travelled with him were subsequently tested, and the results were negative for ZIKV.

Symptoms disappeared completely within one week in all patients. Temporal and viral investigation data are summarised in the Table.

Background

Zika virus is a mosquito-borne flavivirus related to dengue virus (DENV), yellow fever virus (YFV) and West Nile virus (WNV). A large outbreak of ZIKV infections involving the ZIKV Asian lineage is ongoing in Brazil since April 2015 [1] with up to 18 countries affected as

at 23 December 2015 [2]. By the first week of December 2015, nine additional South American countries and Cape Verde islands had reported locally acquired cases [3]. Furthermore, a link between ZIKV infection and neurological disorders or congenital malformations has been suspected in Brazil, and an epidemiological alert from the Pan American Health Organization (PAHO) has been issued [4]. ZIKV which is transmitted by *Aedes aegypti* has been isolated from several *Aedes* mosquito species [5] and transmission by *Ae. albopictus* has been documented in Gabon [6], leading to the threat of a worldwide spread. In the last week of December, the French Ministry of Health issued a warning about the detection of autochthonous cases of ZIKV infections in French Departments of America, French Guyana and Martinique Island, confirming the spread of ZIKV in the Caribbean [7]. Given that South American and Caribbean countries are highly touristic regions and that European overseas districts in that area have close connections with their related European mainland countries, there is a risk for imported cases to occur in Europe.

Discussion and conclusions

No autochthonous case of ZIKV infection and a limited number of cases related to the South American outbreak have been reported so far in Europe. The first one was observed in Italy, at the beginning of the Brazilian outbreak, in a traveller returning from Brazil [8] and, more recently, in November 2015, in a traveller returning to the Netherlands from Surinam [3]. Interestingly, similarly to Case 1 returning from Martinique, these imported cases were concomitantly detected close to the first reported locally-acquired cases. Since most ZIKV infections are asymptomatic or mild, this suggests that, at the time of the first autochthonous cases, the overall burden of ZIKV infection has been underestimated.

Since its first introduction in 2004, the mosquito vector *Ae. albopictus* has been well established in southern France. Autochthonous transmissions of chikungunya virus (CHIKV) or DENV previously occurred in Europe [9,10], such as in Montpellier, with an outbreak of 12 locally acquired CHIKV infections in October 2014 [11] or in Nimes, a nearby town, with an outbreak of six autochthonous DENV infection cases in 2015 [12]. Thus, prerequisites for ZIKV autochthonous transmission are likely met in southern France. However, despite the fact that *Ae. albopictus* is an in vitro competent vector for the ZIKV African lineage [13] and was identified as an efficient vector for this lineage in Gabon [6], its vectorial capacity for the ZIKV Asian lineage remains to be clarified. Furthermore, in the cases reported here, the risk of local transmission can be ruled out, considering the vector inactivity during winter time.

However, this description of imported cases, including one case from a French Overseas Department, should reinforce the preparedness plan for arboviral outbreaks which is implemented each year since 2006, during the *Ae. albopictus* activity period (May to November), in all *Ae. albopictus*-colonised areas in France [11]. This means that the network of laboratories that currently propose CHIKV and DENV diagnosis should add ZIKV diagnosis to their panel, with regular reports to regional surveillance boards, and that practitioners' awareness of clinically-suspected cases must be raised; moreover, they should be required to report to regional health authorities. However, as illustrated here, the laboratory diagnosis of ZIKV infection might be challenging due to the transient viraemia, the antibody rise that might be delayed, and the IgG flavivirus cross-reactivity that may interfere in serological testing. This will be a concern for the surveillance of pregnant women [14] as well as for blood safety policy [15].

Conflict of interest

None declared.

Authors' contributions

Managed the patients: ATM, AM, VLM; performed laboratory investigations: MM, OF, ILG, VF; wrote the manuscript: ATM, MS, VLM, VF.

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