

Zika without symptoms in returning travellers, what are the implications

Mylène Ginier^{1,2}, Andreas Neumayr^{2,3*}, Stephan Günther^{4,5}, Jonas Schmidt-Chanasit^{4,5}, Johannes Blum^{2,3}

1. University of Lausanne, Switzerland

2. Swiss Tropical and Public Health Institute, Basel, Switzerland

3. University of Basel, Switzerland

4. WHO Collaborating Centre for Arbovirus and Haemorrhagic Fever Reference and Research, Bernhard-Nocht Institute for Tropical Medicine, Hamburg, Germany

5. German Centre for Infection Research (DZIF), partner site Hamburg-Luebeck-Borstel, Hamburg, Germany

* corresponding author: Email: andreas.neumayr@unibas.ch; Tel.: +41 61 284 8255; Fax: +41 61 284 8183

Abstract

Against the background of the emergence and rapid spread of Zika virus (ZIKV) in the Americas we report the case of an afebrile ZIKV infection in a traveller returning from Central America to exemplarily highlight relevant clinical and diagnostic aspects. ZIKV should be considered in the differential diagnosis of patients with clinical symptoms suggestive of dengue or chikungunya fever. Regarding the frequent subfebril and afebrile manifestation of ZIKV infections we propose to abstain from the term "Zika fever (ZF)" in favor of "Zika virus disease (ZVD)". Owing to its unspecific clinical presentation and cross-reactivity in serological assays, ZVD may easily be missed or misdiagnosed as dengue fever. Until conclusive data on the currently suspected link between ZIKV infection in pregnancy and foetal microcephaly become available, pregnant women and women who are trying to become pregnant should be advised against travelling to regions with ongoing ZIKV transmission. In addition, male travellers returning from regions with ongoing transmission should be informed on the potential risk of sexual transmission until conclusive data on the significance of this mode of transmission become available. Although probably low and seasonally restricted, there is a risk of ZIKV importation to *Aedes* mosquito infested regions in temperate climates (including regions of North America and Europe) with consecutive autochthonous transmission.

Background

Like DENV, yellow fever virus, West Nile virus and Japanese encephalitis virus, ZIKV is a medically important mosquito-transmitted virus belonging to the flavivirus family. Similar to other flavivirus infections, asymptomatic infections are common with only one in five infected individuals developing unspecific symptoms (mild fever, rash, conjunctivitis, and arthralgia) and the clinical presentation may easily be confused with other viral infections, especially with DENV and CHIKV [1]. Since the virus's discovery in a sentinel Rhesus monkey in the Zika forest in Uganda in 1947, human infections have only sporadically been reported in Asia and Africa. In 2007, ZIKV emerged outside its known endemic boundaries for the first time and caused an epidemic on Yap Island in the Federated States of Micronesia [1], followed by a large epidemic in French Polynesia in 2013–14 [2] and subsequent spread to several countries in Oceania, including New Caledonia and the Cook Islands [3]. While ZIKV was generally considered to only cause mild human disease, the outbreak in French Polynesia revealed the virus's potential to cause neurological complications (i.e. Guillain-Barré syndrome and meningoencephalitis)[4].

On May 7, 2015, the Pan American Health Organization issued an alert about potential ZIKV transmission in northeastern Brazil [5]. Following this first detection of ZIKV on the American continent, autochthonous ZIKV transmission has rapidly been confirmed throughout Central and South America (Figure 2). The number of cases observed in Brazil alone was estimated at 440'000–1'300'000 [6]. Closely following the emergence and rapid spread of CHIKV in the Americas since 2013 [7, 8], ZIKV is now the second arbovirus emerging on the American continent in recent years. As ZIKV shares the *Aedes* mosquito vector with DENV and CHIKV, and half of the world's population is living in *Aedes*-infested regions, the possibility of ZIKV epidemics are a major public health concern [9]. On top, data suggest that ZIKV may be sexually [10] as well as transplacental transmissible [11, 12]. Especially the latter is currently raising concerns, after in October 2015, the Brazilian ministry of health reported a twentyfold increase in the number of microcephaly cases among newborns compared with previous years [12]. Although maternal-foetal transmission of ZIKV has been documented throughout

pregnancy and the detection of ZIKV RNA in pathologic specimens of foetal losses as well as confirmed ZIKV infections in infants with microcephaly suggest a link between ZIKV infection in pregnancy and microcephaly of the foetus, the incidence of ZIKV infection in pregnant women is currently not known and the definitive proof of a causal link is still pending [13].

Case description

A 51-year-old female Swiss traveller presented to our outpatient department six days after returning from a two-week holiday to Guatemala and El Salvador in November 2015. Four days after returning, the patient noticed a slightly pruritic maculopapular rash on the face, trunk, and extremities without accompanying symptoms (neither fever nor symptoms suggestive of a systemic infection). On the next day the rash worsened and a non-purulent conjunctivitis developed. We saw the patient another day later when additionally painful oedemas of the hands, elbows, knees and feet (Figure 1) had developed. Besides the rash, the conjunctivitis, the oedemas and a generalized lymphadenopathy the physical examination was unremarkable. The performed laboratory tests included complete blood count, hepatic transaminases, creatinine, C-reactive protein and rapid tests for dengue virus (DENV) (NS1-Ag, IgM, IgG [SD Dengue Duo; Standard Diagnostics Inc., Korea]) and chikungunya virus (CHIKV) (IgM [Nadal Chikungunya IgM Combo; Nal von Minden GmbH, Germany]). Besides an elevated C-reactive protein (8mg/l [reference <5]) and a raised creatinine (87µmol/l [reference range 35–80]) all laboratory parameters were unremarkable and the rapid tests for DENV and CHIKV indicated no acute or past infection. On follow-up six days later, the conjunctivitis and oedemas had completely resolved and the rash was fading (finally disappearing two days later) while the patient was complaining about fatigue. As the suspicion of a viral infection remained high, we repeated testing for DENV and CHIKV infection with the above mentioned rapid tests and demonstrated seroconversion for anti-DENV IgG while anti-DENV IgM remained negative. Due to the well known serological cross-reactivity among flaviviruses we considered a Zika virus (ZIKV) infection of the patient and sent both sera to the WHO Collaborating Centre for Arbovirus and Haemorrhagic Fever

Reference and Research at the Bernhard-Nocht-Institute, Hamburg, Germany were the sera were tested for DENV, CHIKV and ZIKV, respectively (Table 1). Our suspicion of a ZIKV infection was confirmed by real-time RT-PCR (RealStar® Zika Virus RT-PCR Kit 1.0, altona diagnostics, Hamburg, Germany) and serology. Two weeks after the onset of symptoms the patient had fully recovered.

Discussion

As clinical symptoms of Zika fever (ZF) may easily be confused with dengue fever (DF), it deserves to be highlighted that unlike in DF, fever is more sporadic and frequently milder in ZIKV infections [1]. In our patient ZF only manifested with skin rash and peripheral oedema while neither fever nor general symptoms were noted. Similar afebrile and subfebrile manifestations of ZF have repeatedly been reported in the past, including e.g. two cases imported from French Polynesia to Japan [14] and, more recently, the case of a Dutch traveller returning from Surinam who presented with a maculopapular rash on the trunk and extremities, skin hypersensitivity, and arthralgia only [15]. Therefore, the absence or only mild manifestation of fever and general symptoms in a patient presenting with symptoms suggestive of DF (i.e. headache, rash, conjunctivitis, musculoskeletal complaints) should raise the suspicion of a ZIKV infection and we propose to abstain from the term "Zika fever (ZF)" in favor of "Zika virus disease (ZVD)".

As ZIKV and DENV are both flaviviruses, cross-reactivity in serological assays may lead to confusion and misdiagnosis. While DENV NS1-antigen tests are mostly specific for DENV, serological assays detecting anti-DENV-IgM and anti-DENV-IgG may show cross-reactivity. The diagnostic value of RT-PCR for detection of ZIKV RNA in blood is limited as viremia is usually low and limited to the first 2–3 days after disease onset (which is often not determinable as fever and general symptoms may be mild or absent)[16]. However, ZIKV RNA detection in urine provides a feasible alternative: ZIKV is detectable with higher RNA loads and for a longer period (10–20 days after onset of symptoms) in urine samples than in serum samples [16].

Regarding the suspected link between ZIKV infection during pregnancy and foetal microcephaly, many questions remain to be answered, e.g. it is currently unclear whether additional factors may be involved and whether the risk of microcephaly may depend on the time point of infection during pregnancy. Since the ZIKV epidemic in the Americas is rapidly emerging and a potential link between ZIKV infection during pregnancy and microcephaly of the foetus appears plausible, the US and the European Centres for Disease Control and Prevention advise pregnant women and women who are trying to become pregnant against travelling to regions where ZIKV transmission is ongoing [13, 17]. In addition, a testing algorithm for pregnant women returning from an area with ongoing ZIKV transmission has been published [13]. An issue not yet addressed by the health authorities is the prolonged detection of ZIKV in semen and the documented transmission of ZIKV by sexual intercourse [9, 18] which may have implications in male travellers return from regions with ongoing transmission. Considering that asymptomatic infections are frequent, it should be considered to advise male travellers on the use of condoms after returning from regions with ongoing transmission until conclusive data on the significance of this mode of transmission become available.

Although the viremia in ZVD is apparently much lower and the viremic phase shorter than in DF and chikungunya fever (CF), international travellers pose a risk for the intra- and intercontinental spread of ZIKV [19]. The risk of ZIKV importation and consecutive autochthonous transmission also includes non-tropical areas like the *Aedes aegypti* and *A. albopictus* infested regions of the United States and the *A. albopictus* infested regions of Southern Europe. Reports of importation and autochthonous transmission of DENV and CHIKV in Florida and Southern Europe in recent years support this assumption [20–27]. The risk of introduction and autochthonous transmission depends on the regional prevalence and seasonal population density of suitable mosquito vectors. For example, entomological monitoring in the Mediterranean region indicates that the development period for *A. albopictus* starts in April and tapers off in October/November with activity peaks in June/July–September [28–30]. Not surprisingly, the cases of autochthonous DENV and CHIKV

transmissions in Southern Europe in recent years were all reported between August and October [20–27]. Therefore, unlike in tropical and subtropical regions, the autochthonous transmission risk in regions with temperate climate is seasonally restricted [19].

References

1. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med* 2009;360(24):2536–43.
2. Cao-Lormeau VM, Musso D. Emerging arboviruses in the Pacific. *Lancet* 2014;384(9954):1571–72.
3. Musso D, Nilles EJ, Cao-Lormeau VM. Rapid spread of emerging Zika virus in the Pacific area. *Clin Microbiol Infect* 2014;20(10):595–96.
4. Oehler E, Watrin L, Larre P, Leparc-Goffart I, Lastere S, Valour F, Baudouin L, Mallet H, Musso D, Ghawche F. Zika virus infection complicated by Guillain-Barre syndrome--case report, French Polynesia, December 2013. *Euro Surveill.* 2014;19(9):pii:20720.
5. Pan American Health Organization. Epidemiological alert. Zika virus infection. 7 May 2015.
http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&gid=30078+&Itemid=999999&lang=fr (accessed 31 December, 2015)
6. European Centre for Disease Prevention and Control. Rapid risk assessment: Zika virus epidemic in the Americas: potential association with microcephaly and Guillain-Barré syndrome – 10 December 2015. Stockholm: ECDC; 2015.
7. Weaver SC, Forrester NL. Chikungunya: Evolutionary history and recent epidemic spread. *Antiviral Res.* 2015;120:32-9.
8. Halstead SB. Reappearance of chikungunya, formerly called dengue, in the Americas. *Emerg Infect Dis.* 2015;21(4):557-61.
9. Musso D, Cao-Lormeau VM, Gubler DJ. Zika virus: following the path of dengue and chikungunya? *Lancet.* 2015;386(9990):243-4.
10. Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. *Emerg Infect Dis.* 2015;21(2):359-61.
11. Besnard M, Lastere S, Teissier A, Cao-Lormeau V, Musso D. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. *Euro Surveill.* 2014;19(13):pii:20751.
12. Pan American Health Organization. Epidemiological alert. Neurological syndrome, congenital malformations, and Zika virus infection. Implication for public health in the Americas. 1 December 2015.

http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=32405&lang=en (accessed December 31, 2015)

13. Petersen EE, Staples JE, Meaney-Delman D, Fischer M, Ellington SR, Callaghan WM, Jamieson DJ. Interim Guidelines for Pregnant Women During a Zika Virus Outbreak - United States, 2016. *MMWR Morb Mortal Wkly Rep.* 2016;65(2):30-3.
14. Kutsuna S, Kato Y, Takasaki T, Moi M, Kotaki A, Uemura H et al. Two cases of Zika fever imported from French Polynesia to Japan, December 2013 to January 2014. *Euro Surveill.* 2014;19(4):pii:20683.
15. Goorhuis A. ProMED-mail post: Zika virus - Netherlands ex Suriname, published 13 Dec. 2015. Archive Number: 20151213.3858300 (<http://www.promedmail.org>)
16. Gourinat AC, O'Connor O, Calvez E, Goarant C, Dupont-Rouzeyrol M. Detection of Zika virus in urine. *Emerg Infect Dis.* 2015;21(1):84-6.
17. <http://ecdc.europa.eu/en/publications/Publications/rapid-risk-assessment-zika-virus-first-update-jan-2016.pdf>
18. Patiño-Barbosa AM, Medina I, Gil-Restrepo AF, Rodriguez-Morales AJ. Zika: another sexually transmitted infection? *Sex Transm Infect.* 2015;91(5):359.
19. Bogoch II, Brady OJ, Kraemer MU, German M, Creatore MI, Kulkarni MA et al. Anticipating the international spread of Zika virus from Brazil. *Lancet.* 2016;pii: S0140-6736(16)00080-5. [Epub ahead of print]
20. Rey JR. Dengue in Florida (USA). *Insects.* 2014;5(4):991-1000.
21. Kendrick K, Stanek D, Blackmore C; Centers for Disease Control and Prevention (CDC). Notes from the field: Transmission of chikungunya virus in the continental United States--Florida, 2014. *MMWR Morb Mortal Wkly Rep.* 2014;63(48):1137.
22. La Ruche G, Souarès Y, Armengaud A, Peloux-Petiot F, Delaunay P, Desprès P et al. First two autochthonous dengue virus infections in metropolitan France, September 2010. *Euro Surveill.* 2010;15(39):19676.
23. Schmidt-Chanasit J, Haditsch M, Schoneberg I, Gunther S, Stark K, Frank C. et al., Dengue virus infection in a traveller returning from Croatia to Germany. *Euro Surveill.* 2010;15(40):pii:19677
24. Marchand E, Prat C, Jeannin C, Lafont E, Bergmann T, Flusin O et al. Autochthonous case of dengue in France, October 2013. *Euro Surveill.* 2013;18(50):20661.
25. Angelini R, Finarelli AC, Angelini P, Po C, Petropulacos K, Macini P et al. An outbreak of chikungunya fever in the province of Ravenna, Italy. *Eurosurveill.* 2007;12(36):E070906.1.
26. Gould EA, Gallian P, De Lamballerie X, Charrel RN. First cases of autochthonous dengue fever and chikungunya fever in France: from bad dream to reality! *Clin Microbiol Infect.* 2010;16(12):1702-4.

27. Delisle E, Rousseau C, Broche B, Leparç-Goffart I, L'Ambert G, Cochet A et al. Chikungunya outbreak in Montpellier, France, September to October 2014. *Euro Surveill.* 2015;20(17):pii:21108.
28. Tran A, L'Ambert G, Lacour G, Benoît R, Demarchi M, Cros Met et al. A rainfall- and temperature-driven abundance model for *Aedes albopictus* populations. *Int J Environ Res Public Health.* 2013;10(5):1698-719.
29. Zitko T, Merdić E. Seasonal and spatial oviposition activity of *Aedes albopictus* (Diptera: Culicidae) in Adriatic Croatia. *J Med Entomol.* 2014;51(4):760-8.
30. Giatropoulos A, Emmanouel N, Koliopoulos G, Michaelakis A. A study on distribution and seasonal abundance of *Aedes albopictus* (Diptera: Culicidae) population in Athens, Greece. *J Med Entomol.* 2012. 49(2):262-9.

Table 1. Virological tests performed with samples from the Zika virus infected patient.

| | First serum sample [†] | Second serum sample [‡] |
|-----------------------|---------------------------------|----------------------------------|
| Dengue IgM IIFT | negative | negative |
| Dengue IgG IIFT | 1:20 | 1:5120 |
| Dengue NS1-Ag | negative | negative |
| Zika IgM IIFT | negative | 1:640 |
| Zika IgG IIFT | 1:20 | 1:5120 |
| Zika qRT-PCR | positive | ND |
| Chikungunya IgM ELISA | negative | ND |
| Chikungunya IgM IIFT | ND | negative |
| Chikungunya IgG IIFT | ND | negative |

[†] sample obtained 6 days after onset of symptoms

[‡] sample obtained 7 days after the first serum sample

IIFT: Indirect Immunofluorescence Test; qRT-PCR: real-time reverse transcription polymerase chain reaction; ELISA: Enzyme-linked Immunosorbent Assay; ND: not done.

Figure 1. Clinical features of Zika virus disease: (A) conjunctivitis, (B) maculopapular rash, (C-D) peripheral oedemas.

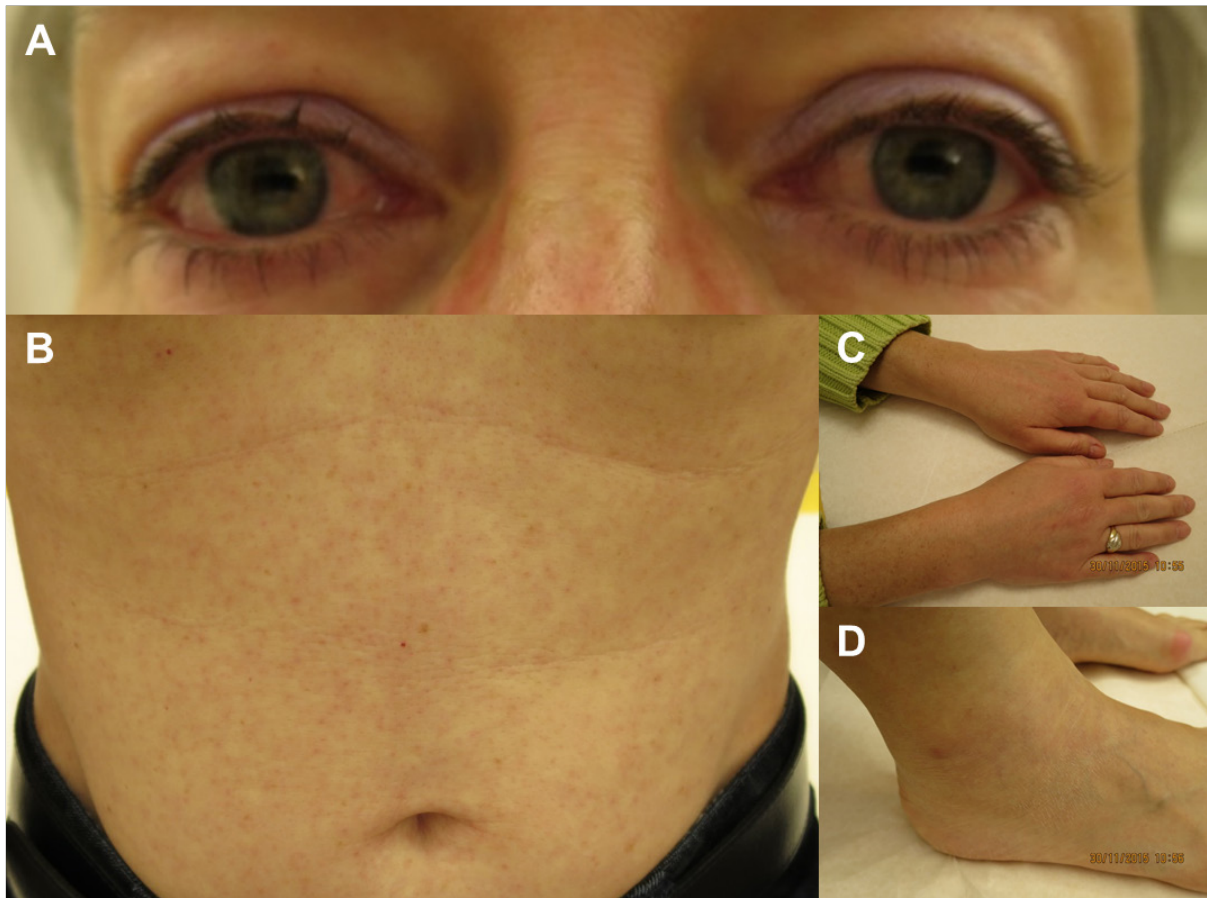


Figure 2. Reported active autochthonous Zika virus transmission in the Americas as of January 26, 2016.

