

Zika virus: issues of concern

Giovanni Di Guardo

University of Teramo, Faculty of Veterinary Medicine, Località Piano d'Accio, 64100 - Teramo, Italy

Dear Editor,

The suspected involvement of Zika virus (ZIKV), an arthropod-borne flaviviral agent newly emerged in the Western Hemisphere, in the “epidemics” of microcephaly and Guillain-Barré syndrome (GBS) among patients from Brazil and French Polynesia is a matter of concern (Fauci and Morens, 2016).

As a consequence, characterizing the viral neurotropism and neuropathogenicity, along with the host-pathogen interaction dynamics at central nervous system (CNS) level, represent key issues in the neuropathogenic study of ZIKV infection. This would also be relevant in relation to the occurrence of anti-ZIKV antibodies in the cerebrospinal fluid (CSF) of infected patients, as in the case of other infections caused by neurotropic viruses, where the “intrathecal” production of such antibodies unequivocally proves viral replication and persistence inside the host’s CNS (Bonnan *et al.*, 2015). An “*ad hoc*” search for these anti-ZIKV antibodies could have been carried out, for instance, in the CSF from the microcephaly-affected foetus in whose brain clear-cut biomolecular and ultrastructural evidence of ZIKV has been recently reported (Mlakar *et al.*, 2016), with a strong cause-effect relationship having been made between viral colonization of foetal brain, on the one hand, and microcephaly development on the other. The same appears to be true when making reference to another recent article reporting the existence of a cause-effect relationship between ZIKV infection and GBS development (Cao-Lormeau *et al.*, 2016). Albeit quite solid and convincing, the results obtained by the aforementioned investigators could have gained additional weight based upon the occurrence, if any, of anti-ZIKV antibodies in the CSF from the GBS-affected patients under study. Indeed, anti-ZIKV antibodies have already been detected in the CSF of microcephaly-affected fetuses and babies in Brazil (Check Hayden, 2016).

Of additional concern is the time frame within which transplacental ZIKV infection occurs. Crucial morphogenetic processes are known to take place during the first 4 weeks of embryonic development inside the human uterus, with alteration(s) of these processes - which are known to be induced by a long list of “exogenous” factors, including biological noxae - leading to several structural (and functional) abnormalities (Barnes, 2010). Alongside the “embryonic/foetal developmental stage” at which human ZIKV infection occurs, it would also be important to

investigate whether the virus may infect the embryonic/foetal thymus, a pathogenetic feature which could provide it with an “extra-capability” of escaping the host’s immune defence mechanisms by means of a process/phenomenon known as “immune tolerance” (Klein, 2015). A similar infectious “strategy” could provide ZIKV with a further “pathogenic potential”, which could be made even stronger by the reduction in immune response efficiency that is “physiologically” observed during pregnancy (Sykes *et al.*, 2012).

Valuable support to the several unsolved issues about ZIKV infection’s pathogenesis is likely to come from the development of suitable animal models (Check Hayden, 2016; Fauci and Morens, 2016).

Furthermore, the possibility that - alongside its “conventional” vector, represented by *Aedes aegypti* - other mosquitoes such as *A. albopictus* could become efficient ZIKV vectors should be also taken into serious account. Indeed, this would likely “make things worse”, since *A. albopictus* is far more common than *A. aegypti* in the northern and western hemispheres (Fauci and Morens, 2016).

In conclusion, major research efforts and adequate funding are needed to gain valuable insights into ZIKV infection’s biology, ecology, epidemiology and pathogenesis.

Conflict of interest statement

The author declares that no competing financial interests nor conflicts of interest of any kind exist in relation to the publication of this manuscript.

References

- Barnes E.G. (2010). Teratogenic causes of malformations. *Ann. Clin. Lab. Sci.* **40**, 99-114.
- Bonnan M., Barroso B., Demasles S., Krim E., Marasescu R., Miquel M. (2015). Compartmentalized intrathecal immunoglobulin synthesis during HIV infection - a model of chronic CNS inflammation? *J. Neuroimmunol.* **285**, 41-52.
- Cao-Lormeau V.-M., Blake A., Mons S., Lastère S., Roche C., Vanhomwegen J., *et al.* (2016). Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. *Lancet*, doi: [http://dx.doi.org/10.1016/S0140-6736\(16\)00562-6](http://dx.doi.org/10.1016/S0140-6736(16)00562-6) (Published online February 29, 2016).
- Check Hayden E. (2016). Proving Zika link to birth defects poses huge challenge. *Nature.* **530**, 142-143.
- Fauci A.S., Morens D.M. (2016). Zika virus in the Americas - Yet another arbovirus threat. *N. Engl. J. Med.* **374**, 601-604.
- Klein L. (2015). Aire gets company for immune tolerance. *Cell.* **163**, 794-795.
- Mlakar J., Korva M., Tul N., Popović M., Poljšak-Prijatelj M., Mraz J., *et al.* (2016). Zika virus associated with microcephaly. *N. Engl. J. Med.* **374**, 951-958.
- Sykes L., Macintyre D.A., Yap X.J., Teoh T.G., Bennett P.R. (2012). The Th1:Th2 dichotomy of pregnancy and preterm labour. *Mediators Inflamm.* 967629; doi: 10.1155/2012/967629.

Corresponding author:
Giovanni Di Guardo
E-mail: gdiuardo@unite.it