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Short Communication

Zika Virus-Bovine Viral Diarrhea Virus Potential Interaction in the Etiopathology of Birth Defects in Brazil, a One Health Issue?

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Abstract

In 2015, Brazil has lived an unprecedented epidemic of microcephaly that has not yet been fully elucidated. Also cases of Guillain-Barré syndrome increased dramatically. Preliminary observations suggested involvement of cofactors in the etiopathology of Zika virus associated microcephaly in Brazil. Research teams identified Bovine Viral Diarrhea Virus (BVDV) in fetal samples with microcephaly, originating in the state of Paraíba, and two virus sequences, obtained from the amniotic fluid collected from mothers with babies affected by Zika and microcephaly, have been characterized as sub genotype BVDV-1b1, of cosmopolitan diffusion, and BVDV-2b, typical genotype circulating in South America, showing unreported variants in the Internal Ribosome Entry Site (IRES). Further studies established a statistical association between microcephaly and cattle breeding in the north-eastern Brazilian states of Rio Grande do Norte, Paraíba and Ceará. The expanded epidemiological analysis throughout Brazil showed that the association between cattle breeding rural areas and microcephaly was confirmed for the entire Brazil, against typical arbovirus diffusion patterns.

Keywords: Bovine viral diarrhea virus; Microcephaly; Zika virus

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The "One Health" concept, based on the evidence that human health and animal health are inter-dependent and bound to the health of the ecosystems in which they exist, was introduced at the beginning of the 2000's, envisaged and implemented by the World Organization for Animal Health (Office International des Epizooties - OIE) to strengthen the fight against transmissible diseases from living animals to humans. Taking into account that 60% of existing human infectious diseases are zoonotic, at least 75% of emerging diseases of humans have an animal origin, and 3 of 5 new human diseases which appear every year are of animal origin [1], it is therefore necessary a close collaboration between medical and veterinary sanitary professionals. Investigation of potential interaction among human and animal pathogens is also a topic of interest in the framework of a collaborative global approach to understand risks and roles in the human animal ecosystems interface.

In 2015, epidemic in South America revealed unprecedently described severe sanitary impact of Zika virus infection. About 150 countries have been notified at risk of Zika virus, and 31 countries and territories have reported cases of microcephaly and other Central Nervous System (CNS) malformations associated with Zika virus infection, particularly since 2015 in the Americas [2]. Brazil was the most affected country, where 3,071 confirmed cases of affected infants and 2,869 suspected cases, still under investigation, have been reported [3]. Most observations referred to in particular the north-eastern states of Ceará, Paraíba, Pernambuco and Rio Grande do Norte. Relation was also suspected with neurological disorders, mainly Guillain-Barré syndrome, in adults. Zika virus was rapidly declared a public health emergency of international concern by the World Health Organization (WHO), in February 2016, because of the potential association with serious fetal cerebral anomalies. In November 2016, WHO announced that the Zika virus was not anymore a worldwide emergency. The decision taken by the WHO crisis committee to withdraw the emergency status was motivated on the base of International Health Regulations, while Zika virus and its consequences remain persistent and important public health challenge that has not yet been fully explained.

Given the new epidemic-pathological traits, from a previously relatively neglected disease, Zika became a global long term important problem. At present, despite progress toward discovery of Zika virus vaccines and therapeutics [4], no preventive or curative measures are available; therefore, it is important to improve our understanding on epidemiology and etiopathogenesis of the disease. First identified in Uganda in 1947 in monkeys and subsequently in humans

in 1952, Zika virus had never been previously reported as a danger in man. Comparison of Zika virus deposited sequences with those recently detected in Brazil did not reveal relevant differences or mutations supporting hypothetical acquisition of higher virulence due to genetic changes. Therefore, other co-factors can be suspected and should be reasonably identified and evaluated.

The similarity of Zika related birth defects with Bovine Viral Diarrhea Virus (BVDV) prenatal infection, pathological outcomes in cattle and, previous reports indicating circulation of BVDV in man [5-7] and suspected correlation to Central Nervous System (CNS) fetal damage including microcephaly in man [8,9] induced some researchers to investigate in this direction.

Research teams from the Federal University of Rio de Janeiro and Instituto de Pesquisa Professor Joaquim Amorim Neto, Campina Grande, identified Bovine Viral Diarrhea Virus (BVDV) in fetal samples with microcephaly, originating in the state of Paraíba. Using mass spectrometry proteomics to analyze protein extracts from three Zika positive brains of deceased babies with severe brain lesions and arthrogryposis, Nogueira and others detected the presence of peptides from the poly-protein of a Bovine-like viral diarrhea virus, suggesting that Zika virus may not be the only etiological agent responsible for microcephaly [10]. Melo and her team suggested that Zika infection might facilitate BVDV to cross placenta barrier and cause fetal infections; however, they haven't ruled out the possibility that their findings might be due to contamination [11]. In addition to the proteomics analysis in the brain tissue of fetuses bearing microcephaly, during the outbreak in Paraíba State, Brazil, in 2015, BVDV RNA was also found in the amniotic fluid collected from four mothers with babies affected by Zika and microcephaly. Two 5'-Untranslated Region (UTR) RNA genomic sequences, obtained by PCR and sequencing, respectively related to BVDV-1b and BVDV-2, have been provided by Professor Tanuri, Federal University of Rio de Janeiro, for further secondary structure analysis based on palindromic nucleotide substitutions method for Pestivirus genotyping [12,13]. The analysis was focused on the Internal Ribosomal Entry Site (IRES) that form specific secondary stem loop sequence structures in the 5'-UTR, recognized strategic genomic region for virus biology [14]. The BVDV-1 isolate 12p belonged to a genotype of cosmopolitan diffusion, the 1b, sub genotype 1, the only group within the heterogeneous BVDV-1 species which includes hypervirulent strains responsible of hemorrhagic syndrome in European cattle [15,16]. The highest homology (99%) was observable only with the bovine strain UEL9-BR/11 (Rodrigues et al., unpublished) collected in 2011 in the Southern Brazilian State of Paraná about 10 years later than the three other closely genetically related strains 133/02, 4092/00 and 3310/01 [17], previously identified in Spain in 2002, but showing a divergence at the stem of V2 locus in the IRES. The human strain 12p showed also homology (98% nucleotide identity) with four contaminant strains isolated in Mexico in 2012, the BVDV-1b1 NGR2, NGR3, NGR11 and NGR12 (Gomez-Romero et al., unpublished). The BVDV-2 strain 4p sequence showed high homology (96%) only with two previously deposited Brazilian bovine isolates LV Patol 0209 (Silveira et al., unpublished) and LV 56-10/13 [18], collected in 2009 and 2010, respectively. These sequences belonged to BVDV-2b, typical genotype circulating in South America, but the bovine isolates diverged from the human sequence at the level of V1 locus stem and V3 locus loop of the IRES. The fact that both detected sequences showed not previously described nucleotide base pair combinations in particularly important and strategic genomic site (e.g., IRES) and they were related with Brazilian circulating strains, corroborates that they are unlikely contaminants, and may reflects evolutionary history of the species in this geographic area and eventual involvement with human pathology. The only strain previously reported in humans belonged to genotype BVDV-1c [7], another Pestivirus cluster with cosmopolitan diffusion.

Another interesting aspect suggesting an existing link between Zika associated microcephaly and animal pathogens was the distribution of cases in the affected areas: the prevalence in large cities was low, being exponentially higher in small towns, close to farmers [19]. In addition, in Rio Grande do Norte state, the cases of microcephaly overlapped the river basins, regions surrounded by livestock, avoiding others ones where Zika vector Aedes mosquitoes infestation rates were higher. Furthermore, a significant association was found between the density of farm animals in the territory and the prevalence of microcephaly calculated by live births. Starting from an initial evaluation on three north-eastern Brazilian states of Rio Grande do Norte, Paraíba and Ceará (144 counties and 234 cases of microcephaly), an expanded analysis, considering all the 725 Brazilian counties where the totality of the confirmed cases of microcephaly have been reported under the national monitoring plan [20], showed stronger and statistically significant associations between cattle density and the prevalence of microcephaly in the entire Brazilian territory [21]. This epidemiological profile was similar even considering the different chronological stages of the disease evolution in the first affected areas as well as in the more recently affected ones. Relation with cattle density was observable in both regions affected by high and low microcephaly prevalence. Not clarified to date, the higher prevalence in the north-east of Brazil, in low-income families and in small counties might be explained by the imbrication of animals and humans so frequent in the poor rural areas of this Brazilian region [22].

Despite there is general consensus on the correlation of Zika virus with microcephaly [23], no direct experimental causal evidence confirms that the Zika virus is the sole etiological agent responsible for the development of brain malformations in human fetuses during pregnancy [10]. The zoonotic potential of BVDV, its ability to cross species barrier, to cross hemato-placental barrier, the high tropism for CNS in animal fetuses, as well as the synergistic action with other pathogens trough the virus induced transient but severe immune-depression, suggest this virus as cofactor candidate for eventual interaction with Zika virus in the etiopathogenesis of CNS lesions induced in human in epidemic areas of South America.

Subsequent to these preliminary observations, a research protocol has been elaborated under the patronage of the State Secretariat of Public Health of the Rio Grande do Norte and approved by the Brazilian National Council of Ethics in Research, with the aim to clarify existence of cofactors through serological and antigenic investigations for animal pathogens as BVDV among mothers of infants with microcephaly. Meanwhile, the Brazilian Ministry of Health made available to the Brazilian public health laboratories the serological test for the Zika virus for the confirmation of presumed diagnosis for all cases of mothers of infants with microcephaly. All these further multi-disciplinary investigations on samples associated to microcephaly and Guillain-Barré syndrome, collected since the epidemic in 2015 until current cases, will provide lights on the epidemiology of priority health risks, and they will clarify role of suspected pathogens of animal origin, in the respect of the One Health Principle.

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