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Commentary

Can Rabies Infection have an Abortive Phase? Need for Further Evidence to Understand Rabies Epidemiology

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Rabies is known to mankind for more than 4000 years; one of the oldest known zoonoses with 100% fatality. It is well known that the rabies virus (RABV) can evade innate immunity.[1] RABV has evolved diverse strategies for immune evasion as "accessory" functions of the P, N, and M proteins, although many of these studies have used in vitro approaches focusing on the molecular biology of immune evasion.[2] However many in vivo studies have shown rabies antibodies in humans[3,4] cows & buffaloes,[5] dogs,[6] and bats[7] without a rabies vaccination. Abortive vampire bat rabies in Peruvian peri-domestic livestock has been reported.[8] Another study observed an inverse relationship between the presence of lyssavirus antigens and levels of rabies antibodies in unvaccinated dogs that underscores the notion of immune evasion following lyssavirus infection.[9] In another study by Vaughn et al[10], thirteen groups totaling 117 dogs were inoculated with the rabies virus and 54 dogs developed fatal rabies (49%) pointing out abortive clinical infection after actual virus inoculation.

In India, no rabies vaccine prophylaxis (Pre-Exposure) is done for domestic bovines. In our study on domestic cows and buffaloes,[5] that are left to graze in open pastures, out of 60 animals recruited, 25 animals (41.7%;17 cows and 8 buffalos), were having natural antibody titers without vaccination above 0.5 IU/ml in the range of 0.9 IU/ml and 15IU/ml by Rapid Fluorescent Focus Inhibition Test (RFFIT). While 12 unvaccinated cows tested at the HP University farm were having neutralizing rabies antibodies below 0.5 IU/ml (0.11-0.46 IU/Ml) because these cows were kept on an isolation farm since birth at Agriculture University, Palampur, Himachal Pradesh, India and did not have any contact with outside stray dogs.[5] This clearly indicated that domestic cows and buffalos, when left for grazing in the open pastures, interact with the rabies virus carrier stray dogs[11] and get infected and have rabies antibodies in their blood without vaccination.

Findings by Gold S et al. indicate that nonlethal rabies exposure does occur. However, serology studies that do not use appropriate controls and cutoffs are unlikely to provide an accurate estimate of the true prevalence of nonlethal rabies exposure.[12] In a study among Tanzanian

dogs there was a close association between the location of rabies cases and the location of seropositive dogs when using liquid- phase blocking ELISA (LPBE) but not when using RFFIT. These results suggest that LPBE may be of value in rabies sero-epidemiological studies and could be developed as a reference technique for the detection of rabies antibodies in domestic/ stray dogs.[13] Presumptive Abortive Human Rabies[14] has been reported in Texas in 2009 and points out that rabies may not be 100% fatal and innate immune responses can alter the course of rabies infection and needs more understanding of this phenomenon using animal models.

Based on our work we can say that natural rabies antibodies without vaccination are protective as none of the rag pickers, cows, and buffaloes who had antibodies titers without vaccination have died of rabies after 2-3 years of follow-up, though their exposure risk is not known. These incidents need further validation from experts all over the world to put rabies epidemiology in perspective and to know if rabies infection has an abortive phase due to the strong innate response of the infected individuals, mammals or bovines.[15]

Scientists are baffled by the long incubation periods[16] in rabies and natural antibodies in living organisms without vaccination. Hemachudha et al.[17] in their chapter describe that during most of the incubation, RABV lies in the muscle as a so called smouldering, or low-replication-rate, infection. We presume this smouldering infection is probably due to resistance offered by the innate immune system of the living organism and may contribute to longer incubation periods in rabies till innate immune system is defeated by the rabies virus infection that helps it to multiply and infect the nerves. Houssein et al in a study titled "**Structural Elucidation of Viral Antagonism of Innate Immunity at the STAT1 Interface**"[18] identifies a complex interface comprising several distinct sites and demonstrates that targeted modifications of these can significantly attenuate pathogenic virus. Loss of viral protein-STAT1 interaction attenuates a rabies virus street strain. We presume that somehow the innate immune system attenuates the rabies virus upon inoculation, before its attachment to the nerve, and this attenuated 1 rabies virus acts as antigen to illicit higher immune response in the form of rabies antibodies that are protective. However if one's innate immune system fails to do that, rabies virus multiplies so as to attach to nearby nerve ending to cause frank rabies. These presumptions however need to be validated scientifically by more and more *in vivo* studies.

Conflict of Interest: None

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