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Immunopathogenesis of rabies encephalitis. Studies in murine model and its implications in human rabies

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Abstract

Rabies is a fatal encephalitis caused by a single stranded negative sense RNA virus of the genus Lyssavirus and family Rhabdoviridae. Though it is fatal , it can be prevented by effective vaccination and immunoglobulins. The vaccines mostly give protection by induction of virus neutralizing antibodies. The role of cellular immune responses is still not clear. For many years it has been observed that in experimental mice inadequate immune or inappropriate immune responses may actually enhance rabies infection and may contribute to mortality. rather than offering protection. This is also seen in humans where half hearted attempts to vaccinate enhances rabies mortality compared to un immunized persons. In this series of experiments we have addressed these issues by designing challenging and vaccination studies in Swiss albino mice using street rabies virus. In Groups of mice challenged IM with street virus (100 LD 50) and vaccinated 6 hours later on day 0,3,7, the survival rate was 100%. In groups of challenged mice where vaccination was delayed for up to 4 days, symptoms appeared at least 5 days earlier than control mice where as groups of challenged but unvaccinated mice developed symptoms by day 14 and died with in 2-3 days after development of symptoms. Further investigations on these mice revealed interesting findings. The RVNA response was significantly higher in mice which developed symptoms compared to un vaccinated mice, though they had just received 2 doses of vaccine at that timed point. The distribution of virus antigen in several areas of the brain was markedly increased as revealed by FAT in comparison to un vaccinated mice. Similarly, by Taq Man real time PCR, it was found the quantity of virus in several regions of brain of delayed vaccinated mice was at least 4 fold higher compared to mice which were challenged but not vaccinated.. Another striking observation we made was marked atrophy of spleen and thymus in both control mice which did not receive vaccination and mice which succumbed to illness much earlier than control mice. There was no atrophy in normal mice. The spleen and thymus were homogenized, cells harvested and subjected flow cytometry. In comparison to normal mice there was marked decrease in both T and B cells in spleen and Tells in thymus.

The role of inflammatory cells and cytokines in the brain of mice were investigated by doing flow cytometry and Luminex XMAP assay respectively . It was found that there was a marked increase in CD3, CD4 and CD8 cells in brain of mice which received delayed immunization and died earlier than control mice. There was a marked increase in the levels of Proinflammatory cytokine such as IL 4, TNF alpha , IL 10 and chemokine Rantes in the brains of these mice. Virus replication also occurred much faster in immunized mice though there was no significant difference in the quantities produced among the different groups. Taken together, these findings suggest that immune responses offer protection only till the virus is in periphery and once virus reached CNS, the local and systemic immune responses may actually flare up the infection and cause early development of the disease process rather than offering protection.

These findings prompts us to think whether in humans , delayed or inadequate immunization following a known rabid exposure can produce immune related pathogenesis rather than offering protection. Indeed, several cases of paralytic rabies seen over past 3 decades at NIMHANS were inadequately immunized either with Semple vaccine or cell culture vaccine and these people developed disease much earlier than those who were not vaccinated . Significant RVNA titers in serum and CSF was found only in the vaccinated groups. These findings once again confirms , that in true rabid exposures , the WHO recommendations of immediate wound washing , prompt local infiltration with rabies immunoglobulins and administration of full course of a potent rabies vaccine on specified days is extremely important to prevent rabies encephalitis.