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Title: The importance of virus neutralizing antibodies (VNA) in clearing rabies virus from the CNS: can VNA be used for clinical therapy?

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Abstract: One of the major hallmarks for rabies is the almost 100% mortality. There is still no proven therapy for clinical rabies despite of the development of Milwaukee protocol. It has been known for many years that most of the rabies patients (>70%) do not develop virus neutralizing antibodies (VNA) at the time of death, which has also been observed in laboratory animals including mice, dogs and skunks after experimental infection with wt rabies virus (RABV). It has been demonstrated that wt RABV is incapable of inducing innate (inflammation, DC activation) and adaptive immunity (VNA), most likely due to the restricted expression of the glycoprotein (G). Thus evasion of the host immunity is one of the important pathogenic mechanisms for rabies. It has been further demonstrated that VNA alone in the periphery is unable to clearing an established RABV infection in the CNS unless present in the CNS. It has been demonstrated that wt RABV in the CNS can be cleared and infected animals saved by direct intracerebral administration of attenuated or recombinant RABV, which not only lead to the production of VNA in the periphery, but also enhance the Blood-brain Barrier (BBB) permeability. It has been further shown in mice that intravenous administration of VNA in combination with chemokines that enhances the BBB permeability can clear wt RABV from the CNS and prevent the development of rabies. With all these new discoveries, is it possible to try such modalities alone or in combination in large animals or even in humans?