

STEROIDS IN HERPES SIMPLEX ENCEPHALITIS? – NO

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HSV-1 infection is very common in its human host. After a primary infection at the oral mucosa HSV-1 migrates along axons of the trigeminal nerve to the ganglionic neurons where it enters a latent state. During this latency period no infectious virus is produced. Just one transcript, the latency associated transcript, is abundantly expressed. Other immediate-early transcripts are probably expressed at very low levels. Latency is tightly controlled by local CD8 T-cell infiltrates, by neuronal host cell factors, and by the virus (e.g. by viral miRNAs). Immunosuppression including steroids can induce viral reactivation, both in humans and in the animal model of HSV-1 latency in mice.

It is still a matter of debate if herpes encephalitis is caused by a reactivation of HSV-1 from trigeminal ganglia or CNS tissue or if encephalitis is caused by a new infection with HSV-1. In any case HSV-1 encephalitis represents a devastating disease that leads to a high morbidity and mortality. Early treatment with the anti-viral drug acyclovir dramatically improved outcome. However, despite early diagnosis by MRI and CSF-PCR and early treatment the mortality is still as high as 12 % and 40-50% of patients remain moderately to severely disabled. In analogy to other infectious diseases it has been proposed to add steroids to the anti-viral therapy to ameliorate the outcome. It is hypothesized that steroids might reduce inflammation mediated brain damage but do not influence viral clearance.

So far, there is no convincing evidence that treatment with steroids is beneficial in herpes encephalitis. One way to address this issue is the use of animal experiments. Infection of mice and rabbit can cause herpes encephalitis. With these animal models it has always to be kept in mind that HSV-1 is a *human* herpesvirus that naturally does *not* infect animals. HSV-1 is highly adapted to its human host but not to mice and rabbits. The immune control in these animal models is much tighter resulting in a complete absence of reactivation under normal conditions. One reason for this firm immunological control might be that human neurons express a lower density of HSV-1 epitopes than mouse neurons due to the selective capacity of the HSV-1 immediate-early protein ICP47 to block human TAP transport of viral peptides for loading on MHC class I for presentation to CD8+ T cells. Therefore the immune response against HSV-1 in animal models might be stronger and steroids might prove useful to control this overshooting immune response. However, even in animal models it has been shown that production of cytokines like TNF α and IL1 β are essential for viral control. Also, early steroid treatment in the animal model led to a dramatically increased mortality. When acyclovir was combined with steroids this showed a trend to increased viral DNA copy numbers as compared to acyclovir treatment alone. This indicates that steroids might influence viral clearance even in the animal model that has presumably a tighter immune control of HSV-1.

Looking at clinical data there are so far only single case reports and a small retrospective non-randomized clinical trial available. This trial analyzed 22 patients that had been treated with acyclovir and steroids and 23 patients that received only acyclovir. The retrospective analysis revealed that steroid treatment is a beneficial prognostic marker. Since this was not a randomized trial it turns out that the two treatment groups were not well balanced. The steroid treated group had a younger median age (42 versus 47 years), a better median Glasgow Coma Scale score (7 versus 6), and a shorter time to treatment (median 5 versus 7 days). All these parameters were shown to be predictors of a beneficial outcome in previous studies. Due to the low patient number and these imbalances in patient groups it still remains rather speculative if steroids were responsible for the better outcome in this patient cohort. Moreover, it is still unclear which dose of steroids should be used, when steroid treatment should be started (as early as acyclovir or with a delay of days as indicated by animal experiments), and how long patients should be treated.

Taken together, due to the lack of controlled clinical data there is no scientific basis to treat every herpes encephalitis patient with steroids. Efforts to provide these data are ongoing. However, there are always exceptions to the rule. A short course of steroid therapy in severe herpes encephalitis might be reasonable when there is clinical and radiologic deterioration in spite of appropriate antiviral therapy and decreasing viral load in CSF.