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Smallpox post-vaccinal encephalitis: vaccinia virus interaction with the blood brain barrier

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Smallpox vaccine is the only currently effective means to contain a smallpox epidemic, which may emerge after a bioterrorist threat. The traditional smallpox vaccine is a live vaccinia virus (VACV) responsible for rare, but serious post-vaccinal encephalitis (PVE). The physiopathology of the PVE complication is not understood and no study was performed.

To understand how VACV could enter the CNS and interact with blood brain barrier (BBB), what is supposed crucial for central nervous system (CNS) invasion, we studied interaction between VACV and the BBB. A trans-endothelial transport test performed on an *in vitro* BBB model highlighted a BBB permeability increase after 24 hours endothelial cells infection by VACV, which was correlated with a tight-junction alteration observed by immunostaining. To test the neuro-invasion from the blood compartment *in vivo*, we developed a murine model infected by intravenous injection. To study the prior BBB alteration impact, mice were pre-treated with *E. coli* LPS before being infected. Animals were observed for signs of PVE (convulsions, seizures), a grip test was performed, and morbidity and mortality were studied. Moreover, VACV was titrated in blood, spleen and brain after intra-cardiac perfusion to detect viral replication and brain invasion. Results showed that after a viremia, neuro-invasion occurred and titers were higher for LPS pre-treated mice compared to only infected ones. Immuno-staining on LPS pre-treated brain coronal sections indicated that VACV infected meninx and some endothelial cells of brain capillaries. All these results highlight the BBB integrity role in PVE.