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# BRAIN INFLAMMATORY INJURY IN *S. PNEUMONIAE* PNEUMONIA-INDUCED SEPSIS

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## INTRODUCTION

Sepsis occurs as a result of a systemic inflammatory response syndrome to infection. *Streptococcus pneumoniae* (*S. pneumoniae*), a gram positive bacterium, is a lethal pathogen to humans, accounting for the majority of cases of pneumonia and sepsis [1]. Sepsis survivors demonstrate long-term cognitive impairment including alterations in memory, attention, concentration and /or global loss of cognitive function [2]. The mechanisms involved in the brain dysfunction are not clear. Therefore, it is the aim of this study to characterize the brain inflammatory injury in a mouse model of *S. pneumoniae* pneumonia- induced sepsis.

## METHODS

A mouse model of *S. pneumoniae* pneumonia-induced sepsis was used in this study [3]. Wild-type mice (C57BL/6) were used in this study. Lung pneumonia was assessed by histology, myeloperoxidase and bacterial load. Brain leukocyte recruitment was assessed by intravital microscopy. Brain function was measured by behavioral tests that evaluate general activity, exploratory behavior, novelty recognition, anxiety, spatial learning and memory. Brain MRI imaging and myelin content assessments were conducted. Cytokines levels in blood and brain were assessed by Luminex.

## RESULTS

*S. pneumoniae* infection induces an increased bacterial load in the lungs of infected mice. However, blood bacterial load is very low. In the brain of infected mice, an increased neutrophil rolling flux and adhesion is observed by intravital microscopy (Figure 1). Behavioral tests show that there is long-term cognitive impairment in infection recovered mice compared to control mice. Specifically, a long-term deficit in spatial memory is found that could be attributed to an altered hippocampus function in these mice. However, anatomically, there are not evident changes in the hippocampus volume by brain MRI imaging. In addition, decreased myelin content in the brain corpus callosum is observed. With regard to brain cytokines, the levels of KC (IL-8 in humans) are significantly increased. On the other hand, in blood the levels of both KC and IL-6 are highly increased.

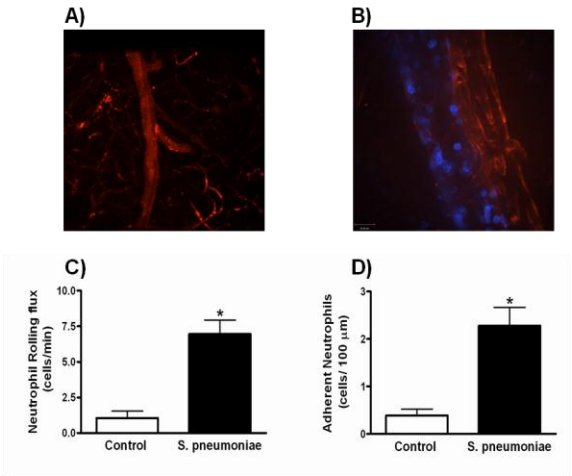


**Figure 1.** Effects of *S. pneumoniae* pneumonia-induced sepsis on brain neutrophil recruitment. Wild-type mice were treated with S. pneumoniae or PBS (control) for 24 h. Intravital microscopy image of the brain vasculature in control mice (A) and infected mice (B). Increased number of neutrophils (blue, detected by GR-1 antibody) is observed. The endothelium is red detected by PECAM antibody. Quantification of neutrophil rolling flux (C) and adherent neutrophils (D). Data are expressed as the mean ± SEM of n= 4-5 mice. * $P < 0.01$ vs. control mice.

## DISCUSSION AND CONCLUSIONS

*S. pneumoniae* pneumonia-induced sepsis causes brain dysfunction associated with long-term cognitive impairment. Our data suggest that bacterial dissemination from the lungs into the brain is not the cause of the outcome observed in the brain. From these data we hypothesize that brain inflammation triggered in the acute systemic inflammatory response is responsible for the long-term cognitive impairment. More studies are underway to characterize the role cytokines as well as neutrophils in the brain inflammatory injury.

## REFERENCES

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