Selective Involvement of the Amygdala in Systemic Lupus Erythematosus.

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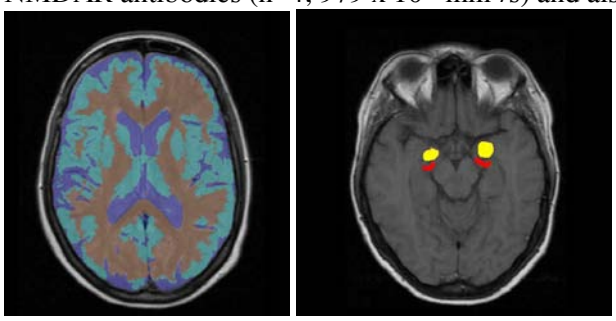
Background: Systemic lupus erythematosus (SLE) is an autoimmune disease mediated by auto-antibodies. [1] Up to to 75% of SLE patients develop neuropsychiatric symptoms. The origin of primary NP symptoms in SLE patients has long been a mystery since the scarce histological material obtained from such patients failed to provide clues for interactions between autoantibodies and the brain. Moreover, it has become clear that different pathogenic pathways can lead to neurological symptoms in SLE patients.[2] SLE patients may have autoantibodies, which interfere with blood clotting, leading to brain infarctions. SLE patients may also suffer from neurological manifestations that are presumably caused by antibodies binding to neural cells.[3,4] Previously, it was demonstrated that a subset of the anti-dsDNA antibodies in SLE patients cross-reacts with subunits of the NMDA receptor (anti-NMDAR antibodies) on neuronal cells and can cause neuronal death by excito-toxicity and apoptosis.[3] Under normal circumstances the blood-brain barrier (BBB) prevents these antibodies to cause neuronal damage. In a mouse model epinephrine, a stress hormone which is known to cause leaks in the BBB, induced brain damage only in the presence of anti-NMDAR antibodies. Vice versa brain damage by anti-NMDAR antibodies was only found after the administration of epinephrine. These animals developed a behavioral disorder characterized by a deficient response to fear-conditioning paradigms. Symptoms could be explained by the observed selective neuronal loss in the amygdala, a structure that is part of the limbic system and is involved in regulating emotions such as stress, fear, and depression.[5] The aim of our study was to investigate whether there is also specific involvement of the amygdala in human SLE.

Methods and Findings: We analyzed a group of 37 neuropsychiatric SLE (NP-SLE) patients, 21 SLE patients and a group of 12 healthy control subjects with diffusion weighted imaging (DWI). In addition, in a subset of eight patients plasma was available to determine the anti-NMDAR antibody status. From the structural MRI data the amygdala and the hippocampus were segmented as well as white and gray matter and the apparent diffusion coefficient (ADC) was retrieved. ADC values between controls SLE and NP-SLE patients were tested using ANOVA analysis with post-hoc Bonferroni correction.

No differences were found in the gray or white matter segments. The average ADC in the amygdala of NP-SLE and SLE patients (940 x 10^{-6} mm^2/s; p=0.006 and 949 x 10^{-6} mm^2/s; p=0.019 respectively) was lower than in healthy control subjects (1152 x 10^{-6} mm^2/s). Mann Whitney analysis revealed that the average ADC in the amygdala of patients with anti-NMDAR antibodies (n=4; 802 x 10^{-6} mm^2/s) was lower (p = 0.029) than the average ADC of patients without anti-NMDAR antibodies (n=4; 979 x 10^{-6} mm^2/s) and also lower (p=0.001) than in healthy control subjects.



Right figure: Axial T1 image showing segmentation of CSF (dark blue), the gray matter (turquoise) and the white matter (brown).
Left figure: Axial T1 weighted anatomical MRI scan showing segmentation of the amygdala (yellow) and the hippocampus (red).

Conclusions: This is the first study to observe specific damage in the amygdala in SLE patients. SLE patients with anti-NMDAR had more severe damage in the amygdala as compared to SLE patients without anti-NMDAR antibodies. Our observations provide an insight into the interplay of the immune system on the one hand and cognition and emotion on the other. The immune system, through generation of autoantibodies that cross-react with neuronal receptors can cause damage of specific brain structures resulting in specific types of cognitive and/or emotional changes. Vice versa emotions may be able to render specific brain structures more vulnerable through increased secretion of stress hormones that breach the BBB in specific brain areas.

References

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