The experimental diabetic brain and spinal cord: insights into the pathophysiology of white matter abnormalities, cerebral atrophy, and spinal cord atrophy with MR Imaging

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Introduction:

The central nervous system is subject to complications of diabetes mellitus, although our understanding of relevant pathophysiology remains incomplete. In humans, white matter abnormalities and brain atrophy occurring in association with diabetes have been associated with paediatric cognitive dysfunction, adult cognitive decline, and risk of stroke. The human diabetic spinal cord is also subject to atrophy as well. We used MR imaging to examine the characteristics and morphology of the diabetic brain and spinal cord compared to control brain and spinal cord in a long-term mouse model of streptozotocin-induced diabetes mellitus.

Materials and Methods:

Twelve Swiss Webster mice (6 diabetic, 6 control) had induction of diabetes through streptozotocin (STZ) injection or injection of vehicle at one month of age and were maintained under regular living conditions for an additional 9 months. Diabetes was confirmed monthly throughout life, and glycated hemoglobin was elevated significantly at the time of sacrifice in the diabetic littermates. Just prior to euthanasia, magnetic resonance (MR) imaging of the brain was performed by acquiring T1 weighted images using a spin echo sequence (TR/TE=500/8 ms), apparent diffusion coefficient of water (ADC) maps by acquiring diffusion weighted (DW) images (TR/TE=1200/40 ms at b values of 46 and 767 s/mm^2) and T2 maps by acquiring multiple echo spin-echo images (TR/TE=1200/12.5 ms, 12 echos). A total of 24 0.75 mm thick slices through the cerebrum and spinal cord were acquired with a field of view of 2cm^2 and a matrix of 256x256. MR images of brain and spinal cord were visually inspected by an observer blinded to the treatment group and analyzed to determine ADC and T2 values along with volumes and areas of regions of interest using local software. Following euthanasia, all brains were processed and examined for changes in morphology and myelin using hematoxylin and eosin (H and E) and Luxol Fast Blue (LFB) or myelin basic protein (MBP) immunohistochemistry, respectively

Results:

MRI analysis detected abnormalities in T2 images within the diabetic cerebrum over regions including the thalamus, hippocampus, caudate nuclei, and primary visual cortex (Fig. 1) when compared to control littermates. Both T1 and ADC analysis failed to detect abnormalities within the diabetic brain within selected regions of interest. The experimental diabetic brain was identified to have greater than 10% cerebral volume loss decreasing from 360 ± 52 mm^3 to 286 ± 22 mm^3 in controls and diabetic mice, respectively. There were no significant differences in brain morphology using H and E staining. However, abnormalities of myelination were identified in diabetic brains using LFB staining and MBP immunostaining, analogous to white matter abnormalities in the human diabetic brain (Fig. 2). Analysis of T2 MR images of the spinal cord in long term diabetics compared to controls demonstrated elevated T2 values in the entire grey matter, ventral horns, and anterior funiculi within the cervical spinal cord. However, significantly lower T2 values were found overall for each region within the thoracic and lumbar spinal cords of diabetic mice (Fig. 3). Spinal cord areas particularly in cervical and lumbar areas were significantly decreased in long-term diabetics compared with controls. Moreover, spinal cord volumes were significantly attenuated in cervical, thoracic and lumbar regions of the spinal cord. Examining the cervical anterior horn region more specifically showed a significant decrease in volume with long-term diabetes (Fig. 4).

Conclusions:

Long-term experimental diabetes in mice is associated with the development of MR imaging abnormalities detected with T2 imaging over regions of cerebrum including white matter and spinal cord. The distribution of MR imaging identified changes closely paralleled the regions of abnormal LFB staining and MBP immunostaining in the experimental diabetic brain. Furthermore, cervical, thoracic and lumbar ventral spinal cord area and volumes significantly decreased in long-term diabetes, suggesting a long-term diabetes-induced atrophy of the spinal cord.

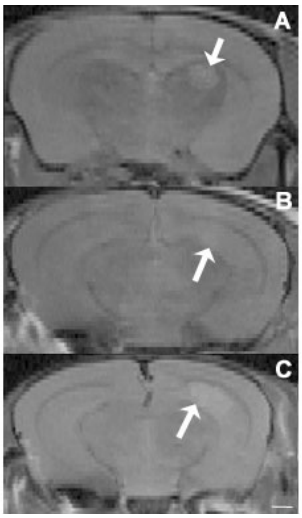

Figure 1 - Magnetic resonance images (T2 maps) from three different diabetic mice demonstrating relative regions of hyperintensity within the right thalamus (**A**) and within regions of the right hippocampus (**B, C**). (Bar, 1mm)

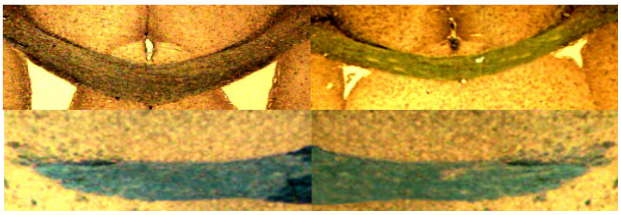

Figure 2 - Luxol-fast blue (LFB) stained sections of control (**A,C**) and diabetic (**B,D**) mouse brains demonstrating patchy myelination with less LFB staining density over regions of corpus callosum (**B**, 4X) and internal capsule (**D**, 40X) relative to control corpus callosum (**A**, 4X) and internal capsule (**C**, 40X).

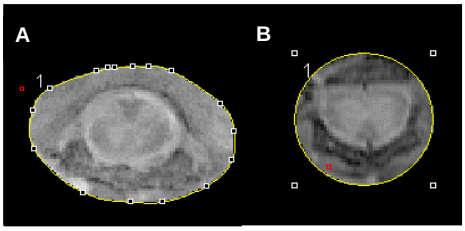

Figure 3 - Magnetic resonance images (T2 maps) from cervical (**A)** and thoracic (**B)** spinal cord regions of diabetic mice.

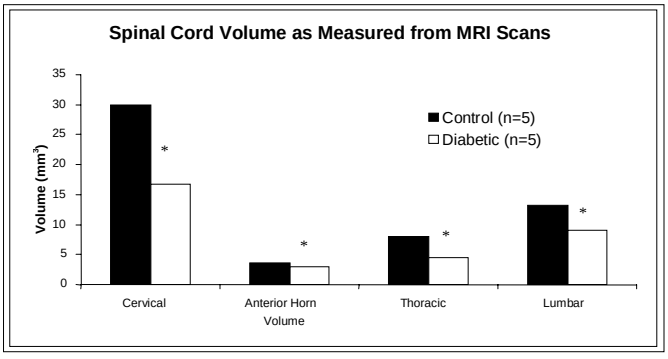

Figure 4 - Mean spinal cord areas (left) and volumes (right) as measured from MRI scans. Error bars represent SEM ± 1. (* p < 0.01).