EXPERIMENTAL TBI RESULTS IN PATHOPHYSIOLOGY RESEMBLING MOTOR NEURON DISEASE

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Target Audience: Researchers and clinicians with an interest in motor neuron diseases and traumatic brain injury

Purpose: Motor neuron diseases (MND) are a group of neurological disorders affecting motor neurons. Amyotrophic lateral sclerosis (ALS) is the most common of these conditions and is pathologically characterized by the progressive death of motor neurons, degeneration of the corticospinal tract (CST), and the presence of protein inclusions consisting of transactive response DNA binding protein 43 (TDP43)[1]. Traumatic brain injury (TBI) is a common progressive neurodegenerative condition, and has been linked to the onset of ALS[2,3]. However, the notion that TBI may cause ALS has been highly contested within the field, as there are many limitations and confusion associated with studying this relationship in patients. As such, here we aimed to further study the potential relationship between TBI and ALS by administration of experimental TBI to rats and, after a 3-month recovery period, assessment of whether pathological and functional abnormalities resembling those that occur in ALS were present.

Methods: 27 male Long-Evans hooded rats were included in this study. 10 control rats were used to define a template atlas for CST segmentation. The TBI model used was the lateral fluid percussion injury. Rats in the TBI group (n=8) received a fluid percussion pulse of 3 atm and the protocol was identical for sham injuries but no fluid percussion pulse was given (n=9). MRI scanning was performed using a 4.7 Tesla Bruker Avance III scanner. T_2-weighted images were acquired using a RARE sequence with: TR = 10,000 ms; RARE factor = 8, TE_{eff} = 36 ms; FOV = 28.8 × 28.8 mm^2; matrix size = 192 × 192; number of slices = 80; resolution = 150 × 150 × 150 μm^3; and NR = 2. Diffusion weighted imaging (DWI) was performed using a 2D echo planar sequence with: TR = 9000 ms, TE = 37 ms, FOV = 38.4 × 38.4 mm^2, matrix size = 128 × 128, number of slices = 36, resolution = 300 × 300 × 300 μm^3, diffusion duration (δ) = 5 ms, diffusion gradient separation (Δ) = 14 ms, 126 directions with 10 non-diffusion images (b_0). Two diffusion datasets were acquired, the first with b-value = 1200 s/mm^2 and the second with b-value = 3000 s/mm^2. After imaging and behavioural assessment with a beam task, rat brains were fixed and sections stained for NeuN, phospho-TDP43 and NeuN+phospho-TDP43. Spinal cord sections were stained with cresyl violet for motor neuron counting. The extensor digitorum longus muscles were excised and single fibre contractile properties assessed. Finally atrogin-1 and m-calpain mRNA expression was quantified. Voxel-wise two-sample t-tests between TBI and sham groups were performed on diffusion tensor, constrained spherical deconvolution-based tractography and VBM measures using randomise (FSL) with 5,000 permutations fully corrected for multiple comparisons using threshold-free cluster enhancement. Independent samples t-tests were used to compare sham versus TBI groups on all other measures (SPSS 21.0, IBM Corp, USA) with statistical significance set at $p < 0.05$.

Results/Discussion:

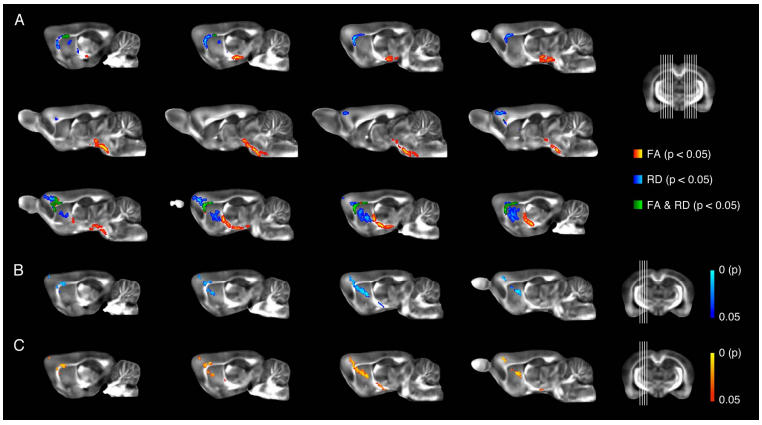

Figure 1. TBSS analysis of diffusion-weighted data revealed voxels of significantly reduced fractional anisotropy (FA, red/yellow), increased radial diffusivity (RD, blue/light-blue) and co-localized reductions in FA with increased RD (green/light-green), in the CSTs of TBI rats compared to Sham ($p < 0.05$). All results are shown overlaid on the mean FA image with sagittal slice position indicated on a coronal section at right.

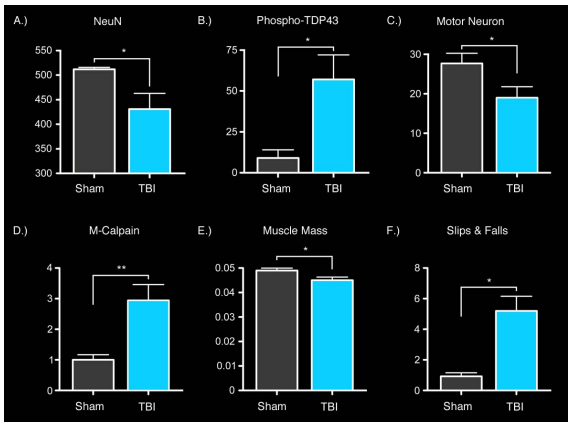

Figure 2. Rats given TBI had significantly fewer cortical neurons (A), increased numbers of neurons overexpressing phospho-TDP43 (B), greater loss of spinal cord motor neurons (C), increased expression of m-calpain (D), reduced muscle mass (E), and recorded more slips and falls (F) on a beam task (* $p < 0.05$, ** $p < 0.002$).

After a 3-month recovery period, volumetric analysis of in vivo MR images found that rats given a TBI had bilateral atrophy of the motor cortex compared to rats given a sham injury, and DWI metrics revealed that TBI also induced degeneration of the CSTs. Additionally, we found that rats given a TBI had fewer neurons and increased numbers of neurons overexpressing phospho-TDP43 in the cortex, loss of motor neurons in the spinal cord, increased expression of the muscle atrophy markers m-calpain and atrogin-1, changes in muscle fibre contractile properties and muscle atrophy. Finally, assessment of motor function on a beam task revealed severe impairments in rats given a TBI.

Conclusion: Taken together, these findings resemble the pathological and functional abnormalities common in ALS, and support the notion that TBI can induce a progressive disease process bearing similarities to those in MND. A follow-up longitudinal study is planned to further investigate the progression of MND-like symptoms after TBI.

References:

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