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Understanding the Role of Concussions as a Risk Factor for Multiple Sclerosis

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Abstract : Adolescents engaged in contact-sports can suffer from recurrent brain concussions with no loss of consciousness and no need for hospitalization, yet they face the possibility of long-term neurocognitive problems. Recent studies suggest that head concussive injuries during adolescence can also predispose individuals to multiple sclerosis (MS). The underlying mechanisms of how brain concussions predispose to MS is not understood. Here, we hypothesize that: (1) recurrent brain concussions prime microglial cells, the tissue resident myeloid cells of the brain, setting them up for exacerbated responses when exposed to additional challenges later in life; and (2) brain concussions lead to the sensitization of myelin-specific T cells in the peripheral lymphoid organs. Towards addressing these hypotheses, we implemented a mouse model of closed head injury that uses a weight-drop device. First, we calibrated the model in male 12 week-old mice and established that a weight drop from a 3 cm height induced mild neurological symptoms (mean neurological score of 1.6+0.4 at 1 hour post-injury) from which the mice fully recovered by 72 hours post-trauma. Then, we performed immunohistochemistry on the brain of concussed mice at 72 hours post-trauma. Despite mice having recovered from all neurological symptoms, immunostaining for leukocytes (CD45) and IBA-1 revealed no peripheral immune infiltration, but an increase in the intensity of IBA1+ staining compared to uninjured controls, suggesting that resident microglia had acquired a more active phenotype. This microglia activation was most apparent in the white matter tracts in the brain and in the olfactory bulb. Immunostaining for the microglia-specific homeostatic marker TMEM119, showed a reduction in TMEM119+ area in the brain of concussed mice compared to uninjured controls, confirming a loss of this homeostatic signal by microglia after injury. Future studies will test whether single or repetitive concussive injury can worsen or accelerate autoimmunity in male and female mice. Understanding these mechanisms will guide the development of timed and targeted therapies to prevent MS from getting started in people at risk.

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