

Age- and sex-dependent differences in white matter pathology in the chronic phase of diffuse traumatic brain injury in the mouse

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Background

Traumatic brain injury (TBI) is commonly associated with white matter injury, leading to persistent symptoms and long-term disability. While advanced age is linked to worse outcome post-TBI, the influence of sex remains highly controversial. The present study aimed to identify age- and sex-dependent differences in white matter pathology in the chronic phase (30 days post-injury - dpi) of TBI using the central (midline) fluid percussion injury (cFPI) model in the mouse.

Methods

Young (8-12 weeks) and aged (55-78 weeks) male and female mice were used. By employing histological and immunohistochemical techniques, we aimed to investigate white matter pathology and inflammation in white matter tracts. In addition, we employed Western Blotting for the relative quantification of myelin- and axonal-related proteins post-TBI. Furthermore, we administered EdU intraperitoneally early following cFPI and quantified the number of newly generated oligodendroglia in the chronic phase of TBI.

Results

Following TBI, male mice sustained higher ventricular expansion and external capsule atrophy compared to females. While no TBI-related changes in cortical thickness were observed at 30 dpi, female mice exhibited greater cortical thickness compared to their male counterparts. Independent of age, male mice exhibited a more pronounced inflammatory response compared to females. While a TBI-induced reduction in MBP immunoreactivity was observed in young mice of both sexes, this down-regulation was not evident in aged mice. When compared to young male mice, young female mice exhibited a distinct NF-H phosphorylation pattern, a difference absent in aged mice. While a TBI-related increase in oligodendrogenesis was observed in male mice, such an effect was not seen in female mice. Independent of sex, an age-related decline in oligodendrogenesis was evident in aged mice compared to their younger counterparts.

Conclusion

This study highlights sex- and age-related differences in white matter pathophysiology that may explain sex differences in outcomes following TBI.