

Abstract

Chronic traumatic encephalopathy (CTE) has attracted attention due to sports-related head trauma or repetitive mild traumatic brain injury (mTBI). However, the pathology of CTE remains underexplored. Reproducible and quantitative model of CTE has yet to be established. The aim of this study is to establish a highly reproducible model of CTE with behavioral and histological manifestations. First, the pathological symptoms of mTBI with no intracranial hemorrhage or contusion using the weight drop model of 52g ball from a height of 30cm was determined using hematoxylin and eosin staining. Adult rats that received single, double, or triple head impacts were compared with sham behaviorally and histologically. Results revealed that rats exposed to repetitive mTBI showed motor impairment with gradual recovery over time, which was prolonged as the number of head impact increased. Similarly, cognitive function was impaired by repetitive mTBI and the recovery depended on the number of head impact. Histologically, GFAP positive astrocytes increased with repetitive mTBI, although Iba-1 positive microglial aggregation was limited. At 4w, phosphorylated Tau significantly accumulated in the prefrontal cortex, corpus callosum, CA1, and dentate gyrus of rats that received triple mTBI, compared to sham or those exposed to single, or double mTBI. This repetitive mTBI rat model provides a highly reproducible and quantifiable brain and behavioral pathology reminiscent of CTE.

19 **Key words:** Mild traumatic brain injury, Chronic traumatic encephalopathy, Repeated head
20 trauma, Astrocyte, Microglia, Tauopathy

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22 **Highlights:**

23 - Repeated mild TBI for rats simulates chronic traumatic encephalopathy syndrome.

24 - Rats receiving repeated mild TBI showed behavioral and cognitive impairment.

25 - GFAP positive astrocytes increased with repeated mild TBI.

26 - Phosphorylated Tau protein was accumulated in rats with repeated mild TBI.

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