728

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DIFFERENTIAL PHENOTYPES OF NEUROGENIC VOIDING DYSFUNCTION IN A VIRAL MURINE MODEL OF MULTIPLE SCLEROSIS

Hypothesis/aims of study
Neurogenic voiding dysfunction often develops in patients with neurodegenerative disorders such as multiple sclerosis (MS). Recent studies using a murine coronavirus-induced encephalomyelitis (CIE) model of MS established that a significant neurologic deficit in the central nervous system (CNS) triggers the development of neurogenic bladder dysfunction that is comparable with lower urinary tract symptoms (LUTS) observed in MS patients. The underling mechanisms included morphological changes in the CNS centres controlling micturition, glial activation in the spinal cord, and increased expression of pro-inflammatory cytokines in the lumbosacral spinal cord. The aim of this study was to determine the long-term impact of neurodegenerative changes in MS on micturition patterns and bladder physiology, as well as to uncover the mechanisms of long-lasting neurogenic voiding dysfunction.

Study design, materials and methods
Adult C57BL/6J mice received a single injection of mouse hepatitis virus (MHV, N=44) in experimental group, and PBS in the control group (N=19). Neurological symptoms and body weight were recorded daily for each animal, and voiding behaviour was monitored weekly for up to 10 weeks (wks) post-inoculation. Neurologic symptoms were assessed by the Clinical Symptoms Score (CSS) on a scale from 0 (asymptomatic) to 4 (quadriparesis/paralysis). Detrusor contractility was evaluated *in vitro* by organ bath studies. Based on the CSS, CIE mice were assigned into 2 groups: recovery (REC group), and relapse (RELAP group). Mice in the REC group experienced an improvement in CSS after the initial acute stage of disease, whereas animals in the RELAP group went through additional episodes of increase in CSS. Animals were assigned to the RELAP group if they met the following criteria: (1) presence of symptom-free period at least for 24 hrs after initial rise in CSS, (2) presence of 2 symptom-free periods (24 h duration each), and (3) CSS>2 during the relapse episodes.

Results
Long-term follow up of CIE mice (8-10 wks post-inoculation) revealed two different neurological phenotypes: 1-recovery from the initial acute neurological impairment (REC, 73.5% of all CIE mice, N=25); and 2-relapse in symptoms (RELAP, 26.5% of all CIE mice, N=9). Eight percent of mice in the REC group still had CSS≥2 at 8 wks in comparison to 22.2% in the RELAP group. Animals in both REC and RELAP groups showed the most significant body weight loss at 1wk after inoculation with the virus (22.3±0.28g at baseline vs 16.5±0.3g in REC group, and 9.2±0.86g in RELAP group, $p<0.05$). Muscarinic responses evaluated by contractility studies *in vitro* of bladder strips isolated from REC mice were similar to the control group. However, the bladders from RELAP group showed significantly decreased responses to stimulation of M3 muscarinic receptors. Micturition patterns evaluated by filter paper assay *in vivo*, also confirmed an increased micturition frequency in mice from RELAP group.

Interpretation of results
Long-term follow up of CIE mice revealed two differential phenotypes of neurologic impairment mimicking two forms of MS in humans: relapsing-remitting MS and chronic type of MS. Mice in the RELAP group expressed overactive voiding patterns, and also had decreased M3 responses suggesting that anti-muscarinic drugs may have limited effects on neurogenic bladder dysfunction in patients with relapsing-remitting type of MS.

Concluding message
Our study confirmed that initial neurological damage in murine viral model of multiple sclerosis can cause long-lasting alterations in neural pathways controlling micturition contributing to the maintenance of neurogenic voiding dysfunction.

Disclosures
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