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BLADDER DYSFUNCTION IN EXPERIMENTAL AUTOIMMUNE ENCEPHALITIS: A MOUSE MODEL FOR STUDYING BLADDER DYSFUNCTION IN DEMYELINATING DISEASE

Hypothesis / aims of study

Experimental autoimmune encephalitis (EAE) is a murine model of demyelinating disease, in which mice that are injected with myelin-specific proteins develop an autoimmune reaction to their own central nervous system myelin. The mice then develop gait and limb dysfunction in a relapsing and remitting pattern, mimicking multiple sclerosis (MS) in the human. EAE mice have been extensively studied in the field of neurology; to date, no studies have reported whether these mice develop bladder dysfunction in a manner similar to humans with MS. As EAE disease severity in mice can be measured using a 0 to 5 scale, with 5 being most severe, we also examined whether mice with more severe EAE disease develop distinct functional bladder pathology when compared to mice with moderate disease.

Study design, materials and methods

Female SJL mice were injected between 6 and 8 weeks of age with myelin-specific proteins (subcutaneous) and an immune catalyst (inactivated *B. pertussis* injected intraperitoneally), while controls were injected with vehicle and the immune catalyst. Immune catalyst injections were repeated on day 3 and 7. Mice were then followed for 3 months with disease scores recorded daily. Mice with moderate EAE symptoms during relapse (mean peak score 2.5) and mice with severe EAE symptoms (mean peak 4), as well as age-matched controls, underwent suprapubic tube implantation followed two days later with cystometric studies at a filling rate of 3ml per hour. Mean intercontraction interval (ICI), baseline bladder pressure (BBP), and contraction magnitude (CM) were measured and compared. The mice were continuously observed during the cystometric study to correlate voids with contractions seen on the CMG tracing.

Results

8 of 15 mice developed clinical signs of disease. The control mice (n=3) had a mean ICI of 6.6s (SD 2.2), BBP of 39cmH2O (SD 7.8), and CM of 4.2cmH2O (SD 1.2). The mice with moderate disease (n=2) had a mean ICI of 1.85s (SD 0.75), BBP of 82.5cmH2O (SD 3.5), and CM 9.3cmH2O (SD 4.3) ($p < 0.05$ for all three measures). All contractions correlated with voids in the control mice, whereas those in the moderate disease group did not. Contractions in the control group were peaked and of brief duration, while contractions in the disease group had a plateau-like appearance, suggestive of outlet obstruction. In the severe disease group (n=2), no contractions were observed, and the mean BBP was 12.5cmH2O (SD 3.5). (Table 2).

Interpretation of results

The EAE mouse model involves triggering a demyelinating response in the mouse by injecting the mouse with murine myelin-specific peptides. The clinical course in these mice regarding motor skills is similar to that in humans—minor impairments in motor function, such as tail limpness or poor righting occur first, followed by more severe impairments such as limb paralysis. The EAE mice also experience remissions in symptoms, often improving from a severe deficit to a normal or minimal-deficit state. Also like humans with MS, EAE mice develop differing severities of disease, with some having only minor symptoms during relapses whereas others develop more severe symptoms.

This pilot study shows that mice with “moderate” EAE disease have a higher baseline bladder pressure, higher contraction magnitudes, and shorter intercontraction intervals than control mice. Also, bladder contractions in the moderate EAE mice did not always correlate with witnessed voids. Mice with more severe EAE disease had a much lower baseline bladder pressure, and flat CMG tracings, indicative of detrusor atony. This suggests that EAE mice do indeed develop lower urinary tract dysfunction. Much like humans with MS, the pattern of voiding dysfunction in these mice is widely varied, with some developing findings of overactivity and dyssynergia while other develop hypotonicity.

Concluding message

severity of disease. These data imply that mice with EAE develop bladder dysfunction that in some cases mimics detrusor overactivity with outlet obstruction or detrusor-sphincter dyssynergia, while others develop bladder hypotonicity. The EAE mouse model should prove useful as an animal model to study bladder dysfunction in MS and its response to novel therapies.

FUNDING: National Institutes of Health
DISCLOSURES: NONE
ANIMAL SUBJECTS: This study followed the guidelines for care and use of laboratory animals and was approved by The Cleveland Clinic IACUC