MICE WITH EXPERIMENTAL AUTOIMMUNE ENCEPHALITIS HAVE BLADDER DYSFUNCTION COMPARABLE TO NEUROGENIC OAB IN MULTIPLE SCLEROSIS.

Hypothesis / aims of study
Multiple sclerosis (MS) patients frequently suffer from overactive bladder (OAB) symptoms, which often become refractory to antimuscarinics. Mostly, neurogenic detrusor overactivity can be observed in urodynamical evaluation. Discovery of new targets has been hampered by the lack of good animal models. Although EAE mice have been widely used to study MS, few have investigated its usefulness in studying MS related bladder dysfunction. It is already known that EAE mice produce smaller volumes per void and that their voiding frequency is increased. It was also shown that the bladder wall undergoes morphological changes that correlate with the neurological symptoms. The aim of this work is to study whether EAE mice exhibit bladder dysfunction that is comparable to neurogenic detrusor overactivity in MS patients.

Study design, materials and methods
12-weeks-old C57/Bl-6 mice were injected with Myelin Oligodendrocyte Glycoprotein (MOG35-55) to induce EAE; controls were injected with the vehicle, Complete Freund's Adjuvant (CFA). Mice were monitored daily for clinical signs of EAE and were graded as follows: Score 1, flaccid tail; Score 2, hindlimb weakness; Score 3, hindlimb paralysis; Score 4, paralysis up to diaphragm. We used cystometry to evaluate bladder function in vivo. From each score at least 6 animals were used. A catheter was placed into the bladder dome and a continuous infusion of saline was given (20µl/min). After the experiment, bladder capacity and post void residue was measured. To measure contractility of detrusor strips ex vivo, we only used mice with score 4. The detrusor strip was exposed to carbachol (0.1µM to 10µM), to assess the muscarinic receptor function and contractile strength. Afterwards, a high-potassium (122.7mM) solution was used as a non-specific depolarizing agent, to assess contractile strength independent of receptor function.

Results
During cystometry, the intercontractile interval of the EAE mice decreased to 64%, 34%, 25% and 15% when compared to the control group, for score 1, 2, 3 and 4 respectively. A Kruskall-Wallis test confirmed that the ICI significantly decreased in the EAE mice (p<0.0001). In addition, the amount of NVC was significantly higher in score 1, 2 and 3. In score 4 we did not observe NVC, as there was dribbling or voiding after every contraction. Basal pressure on average increased 2.6 fold in all animals with score 2 or more. Maximal pressure was not altered.

Maximal contractile strength in response to high potassium reduced to 40% of normal but we did not observe a decrease in the relative contribution of muscarinic receptors to contractile function. On the contrary, at the lowest dosis of 0,1µM of carbachol, contractile strenght was significantly higher in the EAE group. Voiding efficiency, defined as the ratio of voided volume over total bladder capacity, was significantly reduced in all EAE mice with score 2 or higher.

Interpretation of results
From the in vivo experiments, it is clear that EAE mice have a bladder function which significantly differs from mice in the vehicle group. In addition, dysfunction could be closely related to the clinical symptom score. Although cystometry in mice is different from urodynamic investigations in patients, the results obtained are all consistent with what we expect to see in a model for neurogenic bladder dysfunction. Ex vivo, contractility experiments suggest that this bladder dysfunction might not only be due to direct loss of CNS control, but also to intrinsic changes in the bladder wall.

Concluding message
We showed that mice with EAE exhibit urodynamically proven bladder dysfunction that is comparable to neurogenic detrusor overactivity in MS patients. The degree of dysfunction could be predicted from clinical symptoms. In accordance with previous histological findings, we provided evidence that part of the urinary symptoms arise from local changes in the bladder wall. A detailed knowledge of its pathophysiology could greatly enhance our understanding of neurogenic OAB and the local and remote changes it induces.
Contractile strength is diminished in the EAE group. However, the relative contribution of the muscarinic receptors appeared to be higher in EAE mice. This effect was only observed at the lowest concentration of 0.1µM carbachol.

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