

## **Intrathecal Injections of Primary Progressive Multiple Sclerosis Derived Antibodies Result in Motor Deficits and CNS Pathology in Mice Suggesting Leading Role of Antibodies in CSF Effects**

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**Objective:** To investigate the effects of intrathecal administration of recombinant IgG<sub>1</sub> antibodies (rAbs) derived from multiple sclerosis (MS) patients' cerebrospinal fluid (CSF) on motor behavior and CNS pathology in mice.

**Background:** The presence of CSF IgG oligoclonal bands as a diagnostic marker and the effectiveness of B-cell targeted therapies suggest an essential role of B-cells in MS. Previous studies in our laboratory showed that intrathecal delivery of primary progressive MS (PPMS) CSF in mice resulted in significant motor deficiencies, astrocyte activation, and axonal damage compared to control mice.

**Design/Methods:** Following isolation of B-cells MS patient CSF samples, immunoglobulin variable regions were analyzed and rAbs were produced. In total, 53 mice received intrathecal injections under the dura mater at cervical levels 4 and 5. Control mice received injections with saline or rAbs from healthy, HTLV-1, or ALS patients. 6 PPMS and 1 RRMS antibodies were injected. Motor deficits were evaluated and spinal cords were stained with luxol fast blue, GFAP, Iba1, SMI-32, and anti-human IgG antibody.

**Results:** 20 of 27 mice injected with PPMS antibodies exhibited motor deficits while only 1 of 12 RRMS and saline injected mice developed motor deficits. 4 of 6 injected PPMS rAbs displayed higher intensity GFAP and Iba1 immunostaining, providing evidence of both reactive astrogliosis and microglial activation. Similar SMI-32 immunostaining between groups reveals that axonal damage may not cause these observed motor deficits. Anti-human IgG immunostaining was only detected following PPMS rAb injections, suggesting possible rAb binding sites in the cervical spinal cord. Luxol fast blue staining revealed areas of demyelination in the cervical spinal cord following PPMS rAb injections, while no lesions were found in RRMS injected mice.

### **Conclusions:**

Antibodies derived from PPMS patients likely contribute to motor deficits and spinal cord pathology in mice. Future investigations will seek to elucidate the pathogenic role of these CSF antibodies.