

Gender differences in multiple sclerosis: induction of estrogen signaling in male and progesterone signaling in female lesions (NBB project 650).

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Research question and background

The basis of gender differences in the prevalence and clinical progression of multiple sclerosis (MS) is not understood. In this study, we analyzed gender-specific responses in steroid synthesis and signaling in the brains of MS patients as possible contributors to these differences.

Methods and tissues used

Brain material was provided by the NBB. We investigated gene expression changes in steroidogenic pathways and of inflammatory cytokines in MS lesions and normal-appearing white matter (NAWM) of male and female patients (n = 21) and control NAWM (n = 14) using quantitative polymerase chain reaction (25 MS lesions, 21 MS NAWM, and 14 control NAWM) and immunohistochemistry (3/4 sections per group).

Results and conclusion

In MS lesions in males, there was local upregulation of aromatase (an enzyme involved in estrogen biosynthesis), estrogen receptor-A (ERA), and tumor necrosis factor (TNF) mRNA; whereas in females, there was local upregulation of 3 α -hydroxysteroid-dehydrogenase, a progesterone synthetic enzyme, and of progesterone receptor. Astrocytes in the rim and center of MS lesions were found to be the primary source of steroidogenic enzyme and receptor expression. Aromatase and ERA mRNA levels were positively correlated with that of TNF in primary cultures of human microglia and astrocytes; TNF caused increased ERA, suggesting that inflammatory signals stimulate estrogen signaling in this cell type. Together, these findings suggest that there are gender differences in the CNS of MS patients that may affect lesion pathogenesis, that is, in males, estrogen synthesis and signaling are induced; whereas in females, progesterone synthesis and signaling are induced. These differences may represent contributing factors to gender differences in the prevalence and course of MS.