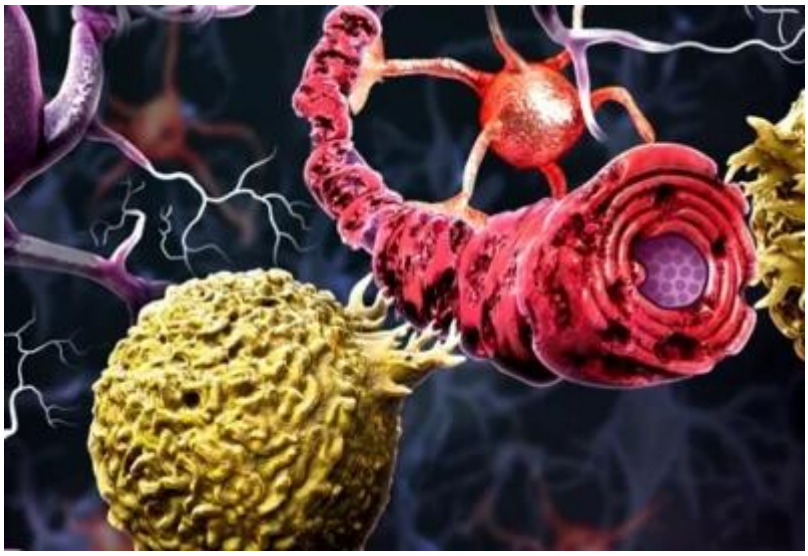
Multiple sclerosis (MS) is one of the most important neurological diseases, characterized by multiple areas of inflammation and demyelination in the white matter of the central nervous system (CNS). Demyelinating lesions of the CNS, MS plaques, are characterized by infiltration of mononuclear cells, the proliferation of macrophages, and loss of oligodendrocytes, myelin-producing cells. Neuroinflammation and CNS tissue damage result in the release of various secretory products, cytokines, immunoglobulins, and damage-associated molecules in the cerebrospinal fluid (CSF). The authors from the United States compared the intrathecal synthesis of 46 inflammatory mediators and 14 markers of glial activation or CNS injury between MS spectrum patients and patients with non-inflammatory neurological diseases. Also, they utilized a series of techniques to analyze the correlation between intrathecal inflammation, CNS injury, glial activation, and disease activity.

There are currently four recognized courses of MS: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). The most common MS phenotype is RRMS, which affects approximately 85% of patients. In RRMS, infiltrating immune cells are considered to be primed in the periphery and reactivated in the CNS by local antigen-presenting cells. Upon entry into the CNS, autoreactive T cells induce a cascade of cytokines and chemokines, which recruit hematogenic myeloid cells, neutrophils, and monocytes.

Chemokines are small proteins that attract different cytokines, cells, and substances to specific sites. They regulate cell positioning and are involved in numerous biological processes, such as homeostasis, angiogenesis, immune response, inflammation, chemotaxis, and metastases. Depending on the number of amino acids between the first two cysteine residues, the chemokines are classified into four subfamilies, CXC, CC, CX3C, and XC.

A recent study has shown that autoreactive T cells in treatment-naive MS patients migrate into the bone marrow via the CXCL12- CXCR4 axis and augment myelopoiesis (but not lymphopoiesis) of hematopoietic stem and progenitor cells. The increased number of bone marrow myeloid cells can invade the CNS and accelerate inflammation and demyelination. https://discovermednews.com/bone-marrow-unrecognized-role-in-multiple-sclerosis/

Chemokine CXCL10, also known as IFNγ-induced protein 10 (IP-10), has a role in chemotaxis, apoptosis, cell growth, and angiogenesis. However, its primary function is immune cell trafficking to inflamed sites, especially antibody-secreting cells and T cells. Proinflammatory conditions lead to the secretion of CXCL10 in various cells, such as monocytes, neutrophils, dendritic cells, microglia, and astrocytes.



About the study

The authors investigated the intrathecal synthesis of 46 inflammatory mediators and 14 markers of CNS injury or glial activation in CSF samples of MS spectrum patients. They examined how these intrathecal proteins relate to short-term disease activity (less than 12 months) in a relapsing-remitting form of MS.

After lumbar puncture (LP), patients with MS underwent clinical assessment at regular intervals, and brain and spine magnetic resonance imaging (MRI). They were followed for at least 12 months. Patients who developed clinical and/or radiologic disease activity were classified as “active”, whereas patients without disease activity were classified as “nonactive”. Disease activity in patients with clinically isolated syndrome corresponded to conversion to relapsing-remitting MS, so, they were subclassified as CIS “converters” or CIS “non-converters” based on their conversion status at the end of a 12-month follow-up.

Neuroinflammatory mediators and biomarkers were classified into three categories: intrathecally synthesized inflammatory mediators, CNS injury biomarkers, and glial

activation biomarkers.

The category of intrathecally synthesized inflammatory mediators included interferon-gamma (IFN-γ), interleukin 1 beta (IL-1β), IL-2, IL-4, IL-6, IL-10, IL-16, tumor necrosis factor-alpha (TNF-α), CXC motif chemokine ligand 1 (CXCL)1, CXCL2, CXCL5, CXCL6, CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, CXCL16, CX3CL1 (fractalkine), CC motif chemokine ligand 1 (CCL)1, CCL2, CCL3, CCL7, CCL8, CCL11, CCL13, CCL15, CCL17, CCL19, CCL20, CCL21, CCL22, CCL23, CCL24, CCL25, CCL26, CCL27, MIF, granulocyte macrophage colony-stimulating factor (GM-CSF), and immunoglobulins (Ig)A, IgM, IgG1, IgG2, IgG3, and IgG4.

The category of CNS injury biomarkers included fibroblast growth factor 21 (FGF-21), myelin basic protein (MBP), neurofilament light chain (NfL), Tau[pT231], Tau(total), amyloid-beta peptide 1-40 (Aβ1-40), amyloid-beta peptide 1–42 (Aβ1-42), and neurogranin (NRGN).

The category of glial (astrocytes and microglia) activation biomarkers included glial fibrillary acidic protein (GFAP), soluble receptor for advanced glycation end products (sRAGE), S100 calcium-binding protein B (S100B), soluble triggering receptor expressed on myeloid cells 2 (sTREM2), chitinase 3 like 1 (Chi3L1), kallikrein-related peptidase 6 (KLK6), and neural cell adhesion molecule 1 (NCAM1).

Results

The study included 47 patients with MS and 27 controls diagnosed with noninflammatory neurologic diseases (25 patients with headache syndromes, one with cognitive dysfunction, and one with noninflammatory epilepsy). Patients diagnosed within the MS spectrum underwent LP during their first acute demyelinating event.

Out of 47 patients with MS, 23 had relapsing-remitting MS and 24 had clinically isolated syndrome. Over the following 12 months, 18 patients (38%) developed clinical and/or radiologic disease activity and were classified as “active”. The remaining 29 patients (62%), including 13 patients with relapsing-remitting MS and 16 with clinically isolated syndrome had no disease activity in the first year after LP and were classified as “nonactive”.

The age was significantly lower among patients with active MS, effectively distinguishing those with active disease from those with non-active disease. Other parameters, including gender, immunoglobulin index, and time from activity to LP could not predict disease

activity.

The analysis of neuroinflammatory mediators and biomarkers

MS patients differentially expressed 16 proteins from the category of intrathecally synthesized inflammatory mediators compared to controls, including CXCL9, CXCL10, CXCL13, CCL11, CCL13, CCL22, CCL26, IL-1β, IL-4, IL-10, IgG1, IgM, IFNγ, TNFα, and NfL. Except for NfL, all were classified as "inflammatory".

Importantly, no single or combined intrathecally synthesized protein had a significant predictive value for short-term (less than 12 months) disease activity.

Patients with active MS shared several connections with nonactive MS patients, such as CCL26/IL-10, CCL11/IL-1β, CXCL13/CCL22, and IFNγ/CXCL9, and two connections with controls, CCL26/IL6 and IL6/CCL22. Patients with nonactive MS shared only one connection with controls, IL-6/TNFα.

In the CSF of patients with active MS and CIS converters, but not in the CSF of CIS non-converters, the IgG1 levels positively correlated with CXCL10 levels. According to the authors, this finding indicates that the interaction between intrathecally synthesized IgG1 and CXCL10 may play a crucial role in disease activity, particularly in the initial stage of MS.

Conclusion

This study has shown that a specific, intrathecally synthesized IgG1/CXCL10 signaling axis is a potential predictor of MS activity and/or conversion from clinically isolated syndrome to relapsing-remitting MS.

The authors concluded that elevated basal CXCL1 levels in the CSF, secreted by glial cells in patients with active MS, including CIS converters, may increase the recruitment and differentiation of antibody-producing plasma cells in the CNS, and contribute to increased intrathecal production of IgG.

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Welsh N, Disano K, Linzey M, et al. CXCL10/IgG1 Axis in Multiple Sclerosis as a Potential Predictive Biomarker of Disease Activity. Neurol Neuroimmunol Neuroinflamm 2024;11:e200200. (Open Access). https://doi.org/10.1212/NXI.0000000000200200