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Abstracts

Papers appearing in the January 2021 issue

Clostridium bolteae is Elevated in Neuromyelitis Optica Spectrum Disorder in India and Shares Sequence Similarity With AQP4

Objective To understand the role of gut microbiome in influencing the pathogenesis of neuromyelitis optica spectrum disorders (NMOSDs) among patients of south Indian origin.

Methods In this case-control study, stool and blood samples were collected from 39 patients with NMOSD, including 17 with aquaporin 4 IgG antibodies (AQP4+) and 36 matched controls. 16S ribosomal RNA (rRNA) sequencing was used to investigate the gut microbiome. Peripheral $CD4^+$ T cells were sorted in 12 healthy controls, and in 12 patients with AQP4+ NMOSD, RNA was extracted and immune gene expression was analyzed using the NanoString nCounter human immunology kit code set.

Results Microbiota community structure (beta diversity) differed between patients with AQP4+ NMOSD and healthy controls ($p < 0.001$, pairwise PERMANOVA test). Linear discriminatory analysis effect size identified several members of the microbiota that were altered in patients with NMOSD, including an increase in *Clostridium bolteae* (effect size 4.23, p 0.00007). *C bolteae* was significantly more prevalent ($p = 0.02$) among patients with AQP4-IgG + NMOSD (n = 8/17 subjects) compared with seronegative patients (n = 3/22) and was absent among healthy stool samples. *C bolteae* has a highly conserved glycerol uptake facilitator and related aquaporin protein (p59-71) that shares sequence homology with AQP4 peptide (p92-104), positioned within an immunodominant (AQP4 specific) T-cell epitope (p91-110). Presence of *C bolteae* correlated with expression of inflammatory genes associated with both innate and adaptive immunities and particularly involved in plasma cell differentiation, B cell chemotaxis, and Th17 activation.

Conclusion Our study described elevated levels of *C bolteae* associated with AQP4+ NMOSD among Indian patients. It is possible that this organism may be causally related to the immunopathogenesis of this disease in susceptible individuals.

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Chitinase 3–like 1 and Neurofilament Light Chain in CSF and CNS Atrophy in MS

Objective To investigate cross-sectional associations of CSF levels of neurofilament light chain (NfL) and of the newly emerging marker chitinase 3–like protein 1 (CHI3L1) with brain and spinal cord atrophy, which are established MRI markers of disease activity in MS, to study CHI3L1 and NfL in relapsing (RMS) and progressive MS (PMS), and to assess the expression of CHI3L1 in different cell types.

Methods In a single-center study, 131 patients with MS (42 RMS and 89 PMS) were assessed for NfL and CHI3L1 concentrations in the CSF, MRI-based spinal cord and brain volumetry, MS subtype, age, disease duration, and disability. We included 42 matched healthy controls receiving MRI. CHI3L1 expression of human brain cell types was examined in 2 published single-cell RNA sequencing data sets.

Results CHI3L1 was associated with spinal cord volume (B = −1.07, 95% CI −2.04 to −0.11, $p = 0.029$) but not with brain volumes. NfL was associated with brain gray matter (B = −7.3, 95% CI −12.0 to −2.7, $p = 0.003$) but not with spinal cord volume. CHI3L1 was suitable to differentiate between progressive or relapsing MS ($p = 0.015$, OR 1.0103, CI for OR 1.002–1.0187), and its gene expression was found in MS-associated microglia and macrophages and in astrocytes of MS brains.

Conclusions NfL and CHI3L1 in CSF were differentially related to brain and spinal cord atrophy. CSF CHI3L1 was associated with spinal cord volume loss and was less affected than NfL by disease duration and age, whereas CSF NfL was associated with brain gray matter atrophy. CSF NfL and CHI3L1 measurement provides complementary information regarding brain and spinal cord volumes.

Classification of Evidence This study provides Class II evidence that CSF CHI3L1 is associated with spinal cord volume loss and that CSF NfL is associated with gray matter atrophy.

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