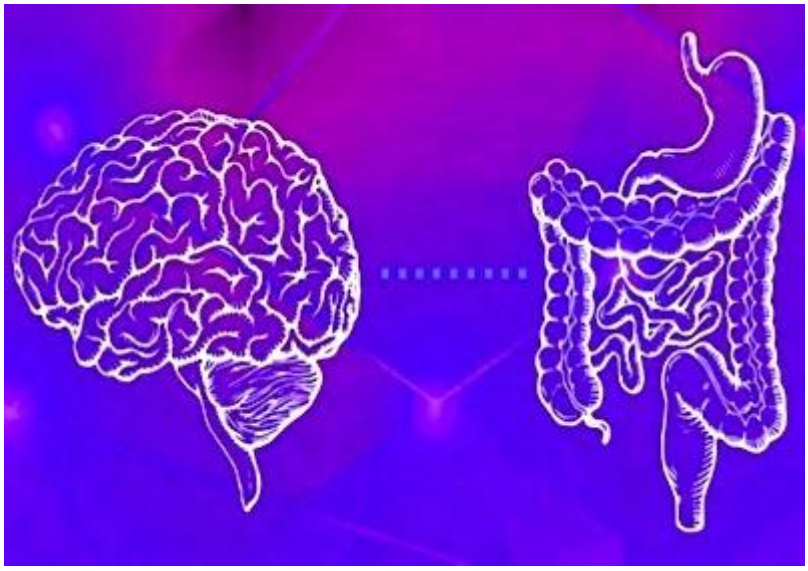
Alterations in the taxonomic and functional composition of the gut microbiome have been implicated as significant contributors to autoimmune diseases, such as multiple sclerosis (MS). The gut microbiome dysbiosis and microbial composition changes are recognized in MS, but the interactions between the gut microbiome and the host's immune response, particularly the interaction between host immunoglobulin A (IgA) and commensal organisms, are poorly understood. This study investigated the interactions between host IgA and gut microbiota in patients with newly diagnosed multiple sclerosis who had not undergone any disease-modifying, immunomodulatory treatments. The authors also explored how anti-CD20 B-cell-depleting therapies affected these interactions over time.

Mechanistic studies have shown that fecal microbial transfer from patients with MS induces a higher incidence of brain autoimmune disease in a transgenic mouse model. Studies in humans have reported different gut microbiome profiles in patients with MS compared with healthy individuals, but the functional significance of these differences remains unclear. According to the authors of this study, this gap in knowledge may be due to previous research that focused primarily on the taxonomy of the gut microbiome, ignoring the complex, dynamic relationship between the host and the microbiome.

Secreted IgA plays a critical role in regulating microbial composition along the gastrointestinal tract by opsonizing mucosal and luminal organisms, limiting their motility, and targeting them for phagocytosis or sequestration. IgA binding can also modulate bacterial gene expression in ways that benefit the host. Immune coating indices show the likelihood of bacterial taxa being found more frequently in the IgA+ fraction than in the IgA- fraction. Most pathobionts exhibit high IgA coating, which likely reflects immune targeting. The shifts in IgA binding of gut bacteria have been described in some patients with MS.



About the study

This observational cohort study had both cross-sectional and longitudinal components. The study included patients with newly diagnosed MS who had not undergone any disease-modifying, immunomodulatory treatments. Participants were excluded if they had any prior long-term exposure to immunomodulatory medications, antibiotic use within 3 months of sample collection, and preexisting diagnoses of irritable bowel syndrome or small intestinal bacterial overgrowth. Age- and sex-matched healthy individuals were recruited as controls.

All participants completed questionnaires regarding current and past diet, medications, and exposures, along with the Automated Self-Administered 24-hour Dietary Assessment Tool (ASA24), which covered the 24 hours before stool sample collection.

All participants donated blood and stool samples at the beginning of the study, on average 1.6 months after diagnosis and before starting disease-modifying therapy. 19 MS patients provided additional samples at follow-up, 6 months after starting B-cell-depleting immunotherapy (anti-CD20 monoclonal antibodies). B-cell-depleting immunotherapies rapidly induce the lysis of mature B cells and are highly effective in controlling inflammatory disease activity. In clinical practice, anti-CD20 medications are dosed every 6 months to maintain the complete depletion of circulating B cells.

The fecal microbiome and the proportions of immunoglobulin-bound and unbound

organisms were determined using flow cytometry. The full-length (long-read) 16S rRNA gene amplicon sequencing technology was used to characterize gut bacteria taxonomies' amplicon sequence variants at the strain level. Amplicon sequence variants in all samples were evaluated separately for total bacteria, IgA-coated (IgA+), and IgA-uncoated (IgA-) bacterial fractions. The Immune Coating Score measured taxon prevalence in the IgA+ fraction relative to its prevalence in the IgA- fraction.

Results

Stool samples were collected from 85 patients, 43 newly diagnosed untreated MS patients, and 42 age- and sex-matched healthy individuals as controls.

Most MS patients exhibited mild to moderate neurologic disability at enrollment (EDSS of ≤3 for 81% of participants). About half of the participants had experienced a relapse within 3 months of enrollment, and a similar proportion had received steroids as treatment for a relapse. There were no significant differences in baseline dietary intake between patients and control subjects.

In 19 patients with MS who received B-cell-depleting immunotherapy (anti-CD20 monoclonal antibodies), clinical follow-up continued for a mean of 30.7 months. All patients had an excellent clinical response to treatment, no patients experienced clinical relapses. At the last clinical follow-up, their median Estimated Disability Status Score improved by one point.

Host response to the gut microbiome

α-diversity (i.e., microbial diversity within a sample) and β-diversity (i.e., microbial diversity between groups) of total gut bacteria differed significantly between patients with new-onset untreated MS and control subjects.

Among the total bacteria, patients with MS had a lower relative abundance of the anti-inflammatory bacterium *Faecalibacterium prausnitzii,* and a higher relative abundance of the organism *Monoglobus pectinyliticus*. *Faecalibacterium prausnitzii* is a major producer of butyrate, an immunomodulatory short-chain fatty acid that has been shown to ameliorate symptoms in a mouse model of MS.

Bacterial flow cytometry showed that proportions of IgA-coated bacteria were decreased in patients with untreated MS compared to controls. Although this reduction could be due to

reduced abundance or absence of specific bacterial strains typically coated with IgA, the results showed no difference in the cumulative sum of the relative abundances of these strains between the two groups, nor the number of these strains in each sample. This implies that IgA-binding affinity could be fundamentally compromised in MS through different factors like B-cell dysfunction, posttranslational modifications that reduce antibody polyreactivity, deglycosylation of secretory immunoglobulin A by *Akkermansia muciniphila*, or other factors that inhibit polyreactive antibody binding.

When analyzing IgA+ and IgA- bacterial fractions separately, there were no differences in α- or β-diversity between patients with new-onset untreated MS and controls, suggesting that microbial diversity remains stable despite changes in IgA coating of gut bacteria.

Within the IgA+ fraction, several short-chain fatty acid producers, including *Coprococcus comes* ATCC 27758, *Dorea formicigenerans* ATCC 27755, and 2 *Ruminococcus* variants, were more abundant in patients with untreated MS than controls.

Within the IgA- fraction, several variants, like *Emergencia timonensis, Oscillibacter*, and *Bifidobacterium longum,* were more abundant in patients with untreated MS. There was no significant difference in the relative abundance of *Akkermansia muciniphila* variant between patients with untreated MS and healthy controls, although previous studies reported its higher relative abundance in patients with MS.

Gut microbial abundance and prevalence after B-cell depletion therapy

In stool samples collected 6 months after B-cell-depleting therapy, a subset of organisms showed different abundance and prevalence in the total, IgA+ and IgA- bacterial subsets.

After 6 months of B-cell depletion therapy, *Adlercreutzia equolifaciens* DSM 19450, *Mogibacterium diversum*, *Odoribactersplanchnicus*, *Pseudoflavonifractor*, and *Desulfovibrio* showed higher relative abundance among total bacteria compared with baseline. In contrast, *Bacteroides ovatus* V975 was more abundant at baseline. Certain organisms, such as *Akkermansia muciniphila, Bifidobacterium bifidum, Blautia obeum, and Gemella,* displayed IgA coating patterns more similar to controls than patients with untreated MS.

Within the IgA+ fraction, a *Christensenella massiliensis* variant and several *Streptococcus* variants were significantly more abundant following B-cell-depleting therapy. In contrast, a *Lachnoclostridium* variant was more abundant at baseline. Within the IgA- fraction, the highest increase in relative abundance following B-cell-depleting therapy

showed a *Clostridium innocuum* variant.

The Immune Coating Score, which determines whether bacterial strains are more likely to be IgA-coated than uncoated, was significant in 10 variants in patients with untreated MS and 21 variants in controls. Among controls, *Collinsella aerofaciens*, *Escherichia coli*, and *Streptococcus mitis* had the highest scores.

Conclusion

This study demonstrated that, both before and after six months of B-cell depletion therapy, healthy people and MS patients had different host immunologic responses, particularly IgA-binding patterns to the gut microbiome. In early-stage MS, it demonstrated a notable disturbance in the host-microbe interface, namely in the engagement between IgA and microbial antigens. New-onset, untreated patients with MS show significant reductions in IgA-bound fecal microbiota, as well as changes in the abundance and prevalence of specific gut bacterial strains within both the total and IgA-bound bacterial fractions following B-cell-depleting therapy. Immune Coating Scores identified specific organisms whose IgA-coating patterns shifted to align more closely with controls.

Even while animal models indicate that modulating the gut microbiota directly may be beneficial, it is still unclear if treatments like probiotics, prebiotics, or fecal microbial transplants will work in more complicated clinical context of multiple sclerosis.

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In patients with newly diagnosed multiple sclerosis, an altered IgA-bound fecal microbiota and an altered abundance and prevalence of specific gut bacterial strains were found before and after B-cell depletion therapy | 6