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FEATURES OF THE INTESTINAL MICROBIOTA COMPOSITION IN MULTIPLE SCLEROSIS PATIENTS RECEIVING ORAL DISEASE-MODIFYING THERAPY

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BACKGROUND: Heterogeneous dysbiosis of the intestinal microbiome is a common hallmark of multiple sclerosis. In this pilot study, we compared the level of some gut bacteria in multiple sclerosis patients receiving oral disease-modifying therapy versus untreated.

MATERIALS AND METHODS: Subjects were patients with relapsing-remitting or secondary and primary progressive multiple sclerosis. Multiple sclerosis patients were treated by Fingolimod ($n = 31$), Teriflunomide ($n = 21$) or were untreated ($n = 31$). The bacterial levels in stool samples were analyzed by cultivation method and real time PCR.

RESULTS: The levels of symbiotic and opportunistic bacterial species in the fecal samples of multiple sclerosis patients receiving disease-modifying therapy were different from those in untreated patients. Also, there was a difference in the spectrum of gastrointestinal tract disorders between these patients. Fingolimod-treated patients showed decreased levels of some bacterial species compared to untreated subjects, including *Escherichia coli* with regular enzymatic activity, *Sutterella wadsworthensis* (phylum Proteobacteria), butyrate-producing bacteria *Roseburia* spp., *Faecalibacterium prausnitzii*, and *Ruminococcus* spp. (phylum Firmicutes, class *Clostridia*). Teriflunomide-treated patients demonstrated decreased levels of *Lactobacillus* spp. and *Enterococcus* spp. (phylum Firmicutes, class *Bacilli*) and *Ruminococcus* spp. Increased levels of *Bifidobacterium* spp. were observed in treated and untreated multiple sclerosis patients with higher EDSS scores.

CONCLUSIONS: This study shows the negative effect of oral disease-modifying therapy on intestinal microbiota composition and gastrointestinal tract disorders. However, more extensive studies are needed to confirm these preliminary results and develop ways to normalize intestinal dysbiosis in multiple sclerosis patients.

Keywords: multiple sclerosis; dysbiosis; intestinal microbiota; disease-modifying therapy; fingolimod; teriflunomide.

ОСОБЕННОСТИ СОСТАВА МИКРОБИОТЫ КИШЕЧНИКА У ПАЦИЕНТОВ С РАССЕЯННЫМ СКЛЕРОЗОМ, ПОЛУЧАЮЩИХ ПЕРОРАЛЬНЫЕ ПРЕПАРАТЫ, ИЗМЕНЯЮЩИЕ ТЕЧЕНИЕ РАССЕЯННОГО СКЛЕРОЗА

Е.А. Тарасова[1], В.И. Людыно[1], А.В. Мацулевич[1], И.Г. Негореева[2], А.Г. Ильвес[2], Е.В. Ивашкова[2], Г.Г. Шкильнюк[2], И.Н. Абдурасулова[1]

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Введение. Гетерогенный дисбиоз кишечного микробиома является частым признаком рассеянного склероза. В этом пилотном исследовании мы сравнили уровень некоторых кишечных бактерий у пациентов с рассеянным склерозом, которые получали пероральные препараты, изменяющие течение рассеянного склероза, и у пациентов без терапии.

Материалы и методы. В исследование вошли пациенты с ремиттирующим или вторично прогрессирующим / первично прогрессирующим рассеянным склерозом. Пациенты с рассеянным склерозом получали лечение финголимодом ($n = 31$), терифлуномидом ($n = 21$) или не получали лечения ($n = 31$). Уровни бактерий в образцах стула определяли методом культивирования и полимеразной цепной реакцией в режиме реального времени.

Результаты. Выявлены различия в уровнях симбиотических и условно-патогенных бактерий в образцах фекалий пациентов с рассеянным склерозом, которые получали препараты, изменяющие течение рассеянного склероза, и пациентов без терапии. Кроме того, у этих пациентов существовала разница в спектре расстройств

Abbreviations

EDSS — Expanded Disability Status Scale; DMT — disease modifying therapy; UT — untreated; FG — fingolimod; TF — teriflunomide; IFNs — Interferons; GA — Glatiramer Acetate; DMF — Dimethyl Fumarate; GIT — gastrointestinal tract; DD — disease duration; CFU — colony forming units.

желудочно-кишечного тракта. У пациентов, получавших финголимод, уровень некоторых видов бактерий был снижен по сравнению с пациентами без терапии, включая *Escherichia coli* с нормальной ферментативной активностью, *Sutterella wadsworthensis* (тип Proteobacteria), бутират-продуцирующие бактерии *Roseburia* spp., *Faecalibacterium prausnitzii* и *Ruminococcus* spp. (тип Firmicutes, класс *Clostridia*). У пациентов, получавших терифлуномид, наблюдалось снижение уровня *Lactobacillus* spp. и *Enterococcus* spp. (тип Firmicutes, класс *Bacilli*) и *Ruminococcus* spp. Повышенный уровень *Bifidobacterium* spp. отмечен у пациентов всех групп с более высокими баллами по шкале EDSS.

Выводы. Исследование показало негативное влияние пероральных препаратов, изменяющих течение рассеянного склероза, на состав кишечной микробиоты и расстройства функций желудочно-кишечного тракта. Однако необходимы более масштабные исследования, чтобы подтвердить эти предварительные результаты и разработать способы нормализации дисбиоза кишечника у пациентов с рассеянным склерозом.

Ключевые слова: рассеянный склероз; дисбиоз; кишечная микробиота; препараты, изменяющие течение рассеянного склероза; финголимод; терифлуномид.

Background

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the CNS, characterized by myelin loss and damage of nerve cells [1]. The causes of MS are unknown, and the mechanisms of the disease progression are not fully understood. The potential role of gut microbiota in the pathogenesis of MS has been actively discussed in recent years [2]. Intestinal microbiota affects the development and function of the immune and nervous systems by promoting differentiation of Th [3, 4] and Treg [5, 6] cell subpopulations, blood-brain and gut barrier integrity [7–9] and myelination [10].

Several studies show that gut microbiota in MS patients are altered compared to healthy subjects and is characterized by dysbiosis [11–14]. In addition, 70–90% of patients with MS have GIT dysfunction [14, 15], resulting from intestinal microbiota dysbiosis.

With the key role of immune auto-aggression in MS pathogenesis recognized, immunomodulators/immunosuppressors were developed to modify this disease. IFN-β based drugs and glatiramer acetate (GA) are the first and best-studied substances for disease-modifying therapy (DMT) [16, 17]. These drugs have a complex, multifaceted effect on the body; however, not all of these effects are fully understood. Several small studies have shown that GA and interferon therapy may influence gut microbiota composition [18–20]. At the same time, the efficacy of GA therapy may be influenced by the presence of some microorganisms [21].

Studying microbiota in patients with MS has become even more relevant with the development and widespread clinical use of oral DMTs [22, 23]. Upon entering the intestine, drugs may affect the gut microbiota causing or exacerbating dysbiosis, which is implicated in GIT disorders and reduces the patient's quality of life. On the other hand, gut microbiota composition may influence treatment efficacy either by altering drug metabolism and bioavailability or by affecting the immunocytes targeted by these DMTs. A recent study has evaluated the potential effects of dimethyl fumarate on gut microbiota composition [24].

The purpose of our study was to compare gut microbiota composition in MS patients treated with two widely used DMTs – Fingolimod or Teriflunomide and in untreated patients.

Materials and methods

Ethics approval and patient consent. The study was approved by the ethics committees of both Institute of Experimental Medicine and the Institute of the human brain; written informed consent has been obtained from all participants.

Patients. 81 patients with MS were enrolled in the observational study. All patients were under observation in the Clinical Department of the Institute of Experimental Medicine and the Institute of the Human Brain from 10.01.2017 to 01.09.2019. They had relapsing-remitting MS (RR-MS), secondary

Table 1

The characteristics of enrolled multiple sclerosis patients

Characteristic	UT	DMT	
		FG	TF
Age, years	42.9 ± 2.3	42.9 ± 2.0	36.0 ± 2.0
Duration of disease, years	10.5 ±1.7	12.3 ± 1.1	7.8 ± 1.6
EDSS score	3.2 ± 0.4	3.7 ± 0.4	3.2 ± 0.3
Age of MS onset, years	32.2 ± 1.9	30.9 ± 1.5	28.3 ± 1.6
Duration of therapy, years	–	5.0 ± 0.4	2.1 ± 0.1
Total patients (male/female)	31 (9/22)	31 (11/20)	21 (10/11)

Notes: UT — untreated group; DMT — disease-modifying therapy group; FG — Fingolimod; TF — Teriflunomide; EDSS — Expanded Disability Status Scale; MS — multiple sclerosis.

Table 2

Incidence of various gastrointestinal tract symptoms and metabolic disorders in a cohort of study subjects with multiple sclerosis

Symptom		Percentage of patients with symptom, %					
		Untreated (UT) (n = 31)		FG (n = 31)		TF (n = 21)	
Defecation disorders, total: Diarrhea/constipation, %		45.2 19.4/25.8		74.2* 29.0/45.2		66.6 33.3/33.3	
Bloating, %		22.6		35.5		23.8	
Rumbling, %		16.1		29.0		52.6#	
Stomach heaviness, %		22.6		29.0		21.1	
Abdominal pain, %		22.6		54.8*		52.4*	
Nausea/Vomiting, %		35.5		29.0		36.8	
Heartburn, %		22.6		45.2		52.6*	
Change in appetite, %		22.6		29.0		31.6	
Body mass change (total %)	↑ (%)	45.2	35.5#	29.0#	12.9	42.1	0
	↓ (%)		9.7		16.1		42.1#

Notes: *differences from UT group, $p < 0.05$; #differences from other groups $p < 0.05$ (Fisher test). UT — untreated group; FG — Fingolimod; TF — Teriflunomide.

progressive MS (SP-RS), or primary progressive MS (PP-MS). Patients received oral DMT, Fingolimod (FG, $n = 31$) or Teriflunomide (TF, $n = 19$), or were untreated (UT, $n = 31$). All patients were in the remission stage during an assessment. The characteristics of the studied cohort are shown in Table 1.

Methods. A modified Neurogenic Bowel Dysfunction Score [25] questionnaire was used to assess GIT functions.

Two methods were used for the analysis of microorganism's levels in fecal samples: the culture method according to the algorithm described earlier [19] and real-time polymerase chain reaction (RT-PCR) with the "Colonoflor" Kit (Alphalab, St.-Petersburg, Russia). Fecal samples were delivered to the laboratory; the same sample was used for two methods. The sample were analyzed without a storage period; freezing of samples was not allowed.

Statistical analysis. Analysis of variance with post-hoc HSD test for unequal groups was performed in Statistica-8 for compare effects of DMTs. Fisher exact test was used to compare proportions. Differences at $p < 0.05$ were considered statistically significant.

Results

Assessment of gastrointestinal tract function. The questionnaire-based survey revealed that 64.5% of subjects not receiving DMT had GIT dysfunction. The percentage of subjects with GIT disorders was higher in groups receiving treatment: 81% for subjects treated with Teriflunomide (TF) and 100% for those treated with Fingolimod (FG). The most frequent complaints among patients are listed in Table 2. Subjects with GIT dysfunction had 2 to 6 symptoms in varying combinations. The distribution of patients depending on the number of complaints presented is shown in Figure 1.

The functional defecation disorders (fecal incontinence or constipation) were 1.2 and 1.8 times less prevalent in the untreated patients than those receiving TF and FG, respectively. Half of the TF-treated patients experienced rumbling and heartburn, which is more common than patients from the other groups. Half of the patients in both groups receiving DMT experienced abdominal pain, twice the share in the untreated group.

In addition to GIT disorders, some patients in all groups reported changes in appetite and body mass. Thus, most untreated patients (35.5%) with a change in body mass reported an increase in body mass, whereas all patients receiving TF with a change in body mass reported a decrease in body mass. In addition, the patients receiving FG reported both an increase in body mass (13%) and a reduction in body mass (16%).

Generally, oral DMT exacerbated GIT disorders in MS patients, with specific changes depending on the drug used.

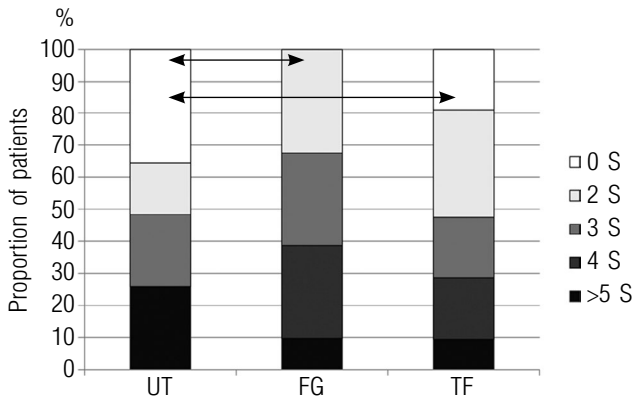

Fig. 1. Proportion of multiple sclerosis patients according to number of symptoms. UT — untreated; FG — Fingolomod-treated; TF — Teriflunomide-treated; 0 S — without symptoms; 2 S, 3 S, 4 S, >5 S — two, three, fore, and five and more symptoms GIT disorders from table 2

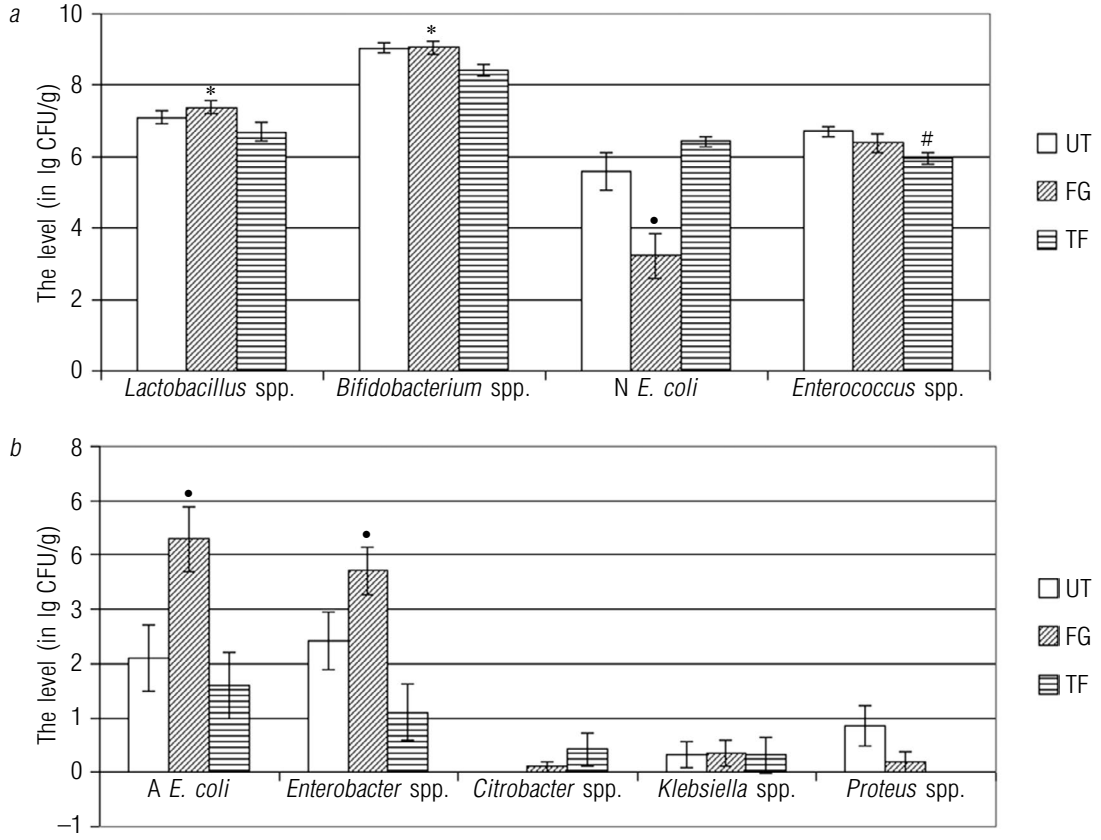

Fig. 2. The level of symbiotic (*a*) and opportunistic (*b*) bacterial species in intestinal microbiota of multiple sclerosis patients with Fingolimod or Teriflunomide therapy (culture method). Data represented as mean ± standard error. In Y axis – the bacterial level in lg colony forming units (CFU) on fecal g; in X axis – bacterial species found; UT – untreated, FG – Fingolimod-treated, TF – Teriflunomide-treated. ANOVA with post-hoc HSD for unequal N, *difference between FG and TF groups, • differences from UT and TF groups, #differences from UT group, $p < 0.05$. N — normal, A — atypical

Analysis of the intestinal microbiota by the culture method. The symbiotic bacteria species (*Lactobacillus* spp., *Bifidobacterium* spp., *Escherichia coli* (N *E. coli*), *Enterococcus* spp.) and atypical (with reduced fermenting activity, hemolytic, lactose-negative) opportunistic bacteria species (*E. coli* (A *E. coli*)), *Enterobacter* spp., *Citrobacter* spp., *Proteus* spp., *Klebsiella* spp. *Staphylococcus aureus*, *Clostridium* spp.) and yeast of genus *Candida* spp. were detected by the cultural method in fecal samples. The levels of some microorganisms differed in treated and untreated patients. There were also differences in patients receiving different drugs (Fig. 2).

Figure 2 shows that mean levels of *Lactobacillus* spp., *Bifidobacterium* spp., and *Enterococcus* spp. for every group were within the reference range, with the lowest levels of these bacteria found in patients receiving TF. However, the analysis of individual values showed that not all patients had normal bacteria levels, with levels being both lower and higher than normal. Thus, reduced levels (<6.0 lg CFU/g) of *Lactobacillus* spp. were found in 68% of patients in the TF group vs 42% in UT and 32% in FG. Reduced levels (<5.0 lg CFU/g) of *Enterococcus* spp. were found in 26% of patients receiving FG or TF vs 6.5% in the untreated group. At the same time, 13% of patients in UT group and 19% in FG group had a high (8.0 lg CFU/g) level of enterococci. No patients with high levels of enterococci were observed in TF group.

Subjects in TF treated group had lower levels of *Bifidobacterium* spp. (Fig. 2). This, however was not due to a reduction in the absolute quantity of bacteria, but because the percentage of patients with a high level (9.0–10.0 lg CFU/g) of *Bifidobacterium* spp. in this group was lower than in other groups (37% vs 74% and 68%, in UT and FG, respectively). It is noteworthy that high levels of *Bifidobacterium* spp. were found mainly in patients with higher EDSS scores (4.0–8.0) in all groups.

Normal levels (7.0–8.0 lg CFU/g) of *Escherichia coli* were found in 68% of untreated patients, in 47% of TF treated patients, and only in 29% FG treated patients ($\varphi = 3.13$; $p < 0.01$; vs UT). That is, symbiotic *E. coli* were decreased in MS patients, with a further reduction when DMTs are used, especially FG.

At the same time, in this group, not only the level of *E. coli* decreased, but also their properties changed. The "normal" *E. coli* were replaced by its atypical forms or other *Enterobacteriaceae*, particularly *Enterobacter* spp. The proportion of such patients in FG group was 2.7 times more com-

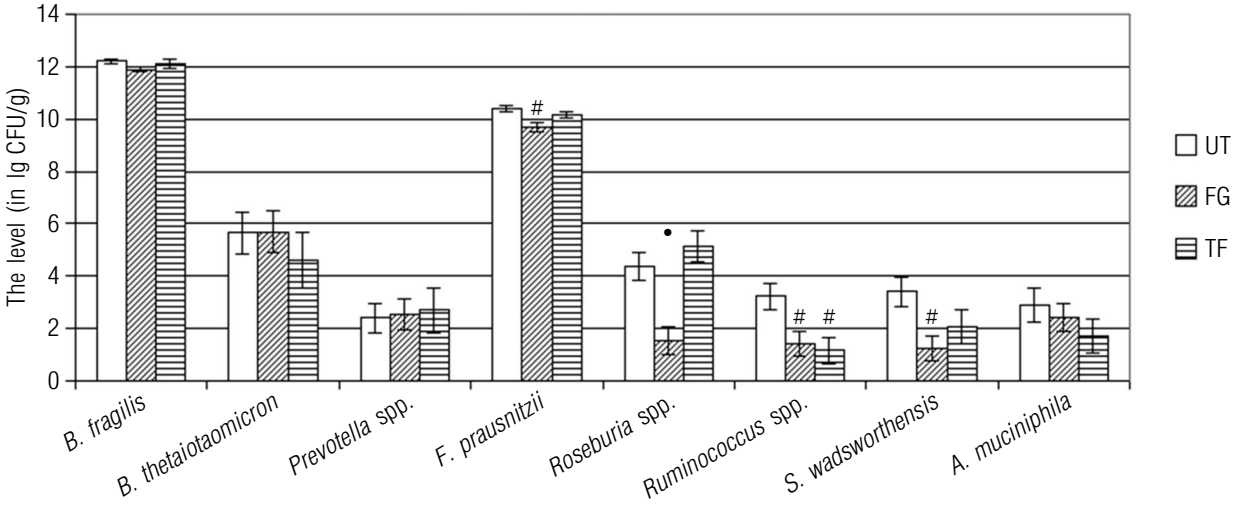

Fig. 3. Changes in bacterial levels in Fingolimod- and Teriflunomide-treated patients with multiple sclerosis (PCR method). Data represented as mean ± standard error. In Y axis — the bacterial level in lg colony forming units (CFU) on fecal g; in X axis — bacterial species; UT — untreated, FG — Fingolimod-treated, TF — Teriflunomide-treated. ANOVA with post-hoc HSD for unequal N, *differences between FG and TF groups, • differences from UT and TF groups, #differences from UT group, $p < 0.05$

pared UT group (52% vs 19%; $\varphi = 2.72$, $p < 0.01$). Interestingly, TF-treated patients showed only a decrease (to 4.0–6.0 lg CFU/g) in the level of *E. coli*.

This data has shown that Fingolimod had the most substantial adverse effect on *E. coli* compared to the two other groups (Fig. 2).

Analysis of intestinal microbiota by Real-Time PCR. We also compared the quantity of anaerobic MS marker bacteria of two dominant phyla, Bacteroidetes (*Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Prevotella* spp.), Firmicutes (*Faecalibacterium prausnitzii*, *Roseburia* spp., *Ruminococcus* spp.) and minor phyla Proteobacteria (*Sutterella wadsworthensis*) and Verrucomicrobia (*Akkermansia muciniphila*) by RT-PCR method.

We found no significant differences in the levels of *B. fragilis*, *B. thetaiotaomicron* or *Prevotella* spp. (Fig. 3), but the proportion of patients with high (>12.5 lg CFU/g) *B. fragilis* level was significantly lower in the FG group compared to the UT group ($\varphi = 2.31$; $p < 0.01$).

In addition, FG-treated patients had lower levels of butyrate-producing bacteria, *F. prausnitzii*, *Roseburia* spp., the proportion of patients with high (>10.5 lg CFU/g) level of *F. prausnitzii* was 5 times lower than in the untreated group.

Ruminococcus spp. was found in 59.1% UT patients and only in 23% of patients receiving DMT ($\varphi = 2.30$, $p < 0.05$ and $\varphi = 2.15$, $p < 0.05$ for FG and TF, respectively).

S. wadsworthensis was also found in 59.1% UT patients, but TF had less effect on the presence of these bacteria in patients (38.5%) than FG (17.6%; $\varphi = 2.75$, $p < 0.01$).

In contrast, *A. muciniphila* was found in a comparable number in UT- and FG-treated patients (44% and 41%, respectively), and only in 23% of patients receiving TF, although the differences did not reach statistical significance.

Thus, treatment with FG and TF affected the qualitative and quantitative composition of the gut microbiota, having an inhibiting effect on different groups of studied microorganisms.

Discussion

Published data demonstrate that MS patients have altered composition of intestinal microbiome compared to healthy subjects. Several studies have found an increased abundance of *Bifidobacterium* spp. (phylum Actinobacteria) [11, 20, 26], *A. muciniphila* (phylum Verrucomicrobia) [12, 27–31], methane-producing Euriarchaeota [12, 32] and decreased abundance of *Bacteroides* (phylum Bacteroidetes) and *Clostridia* (phylum Firmicutes) – producers of butyrate [12].

There are also limited data on the influence of DMTs on microbiota composition [18, 20, 24, 27, 28]. These studies show alterations in intestinal microbiome composition during GA, IFNs, or DMF treatment. The authors interpret these results as a positive effect of DMT on the intestinal microbiome.

Our study noted quantitative alterations in the same bacterial species described by other authors using sequencing methods [11–13]. At the same time, we note the negative impact of DMT on symbiotic bacterial species, which leads to an increased proportion of related opportunistic species.

Different drugs likely affect specific target bacteria. In particular, the antimicrobial effect of GA on the gram-negative bacteria *E. coli* and *Pseudomonas aeruginosa* has been shown *in vitro* [33]. Therefore it

is not surprising that some GA-treated patients have reduced *E. coli*, as shown earlier [19].

FG, TF, and DMF inhibited *in vitro* growth of *Clostridium perfringens* [34]. Since these bacteria are present in a small number of patients (about 11%) [35, 36], we could not assess the anti-clostridial effects in our cohort of FG or TF treated patients. The drugs may be expected to have the same effect on other *Clostridia*. However, FG and TF had a different impact on *F. prausnitzii* and *Roseburia* spp. levels, with the first drug decreasing their quantity and the second not affecting their number compared to UT patients.

Interestingly, other authors observed an increase in the abundance of *Faecalibacterium* after 12 weeks of DMF treatment [24]. Such differences may be related to the different influences on the *Clostridia* class of used drugs or durations of drugs treatment. Therefore, it is possible that at the beginning of treatment (12 weeks with DF) there is an increase, but as the duration of treatment increases (2 years with TF) there is a decrease, first to the level of UT patients and then lower (5 years with FG).

The decrease in *Lactobacillus* spp. and *Enterococcus* spp. levels in TF-treated patients, observed in this study, suggests that the drug is active against gram-positive *Bacilli* class species (phylum Firmicutes), while FG has a more pronounced effect on *Clostridia* class, which belongs to the same phylum.

Storm-Larsen et al. have shown that after two weeks on DMF, Actinobacteria abundance was decreased mainly driven by a reduction of *Bifidobacteria* [24]. We registered a lower level of *Bifidobacteria* spp. in TF-treated patients. The level of these bacteria in FG-treated patients was comparable to the untreated group. Interestingly, regardless of receiving DMT, the level of *Bifidobacteria* was higher in patients with high EDSS scores. Considering that the level of Actinobacteria phylum, especially *Bifidobacteria* spp., significantly increased in MS patients, reducing the level of these bacteria associated with TF treatment can be seen as a positive effect of treatment.

In this study, we confirmed an earlier finding in a larger group of patients that the quantity of symbiotic *E. coli* decreases, and it is substituted with related opportunistic species in FG-treated patients [19]. Also, it is worthy of note that TF did not have this anti-coliform effect.

This study is the first to compare the effects of two oral DMTs (FG and TF) on the composition of the intestinal microbiota and the spectrum of GIT disorders. The impact of FG and TF on the levels of different classes of bacteria can cause differences in the GIT disorders' range observed in patients.

The substitution of symbiotic species of Proteobacteria phylum (*E. coli, S. wadsvorthensis*) by opportunistic bacteria in FG-treated patients is consistent with the presence of diarrhea/constipation and pain characteristic of inflammatory bowel diseases.

Since *Escherichia coli* can synthesize antibiotic-like substances – colicins and compete for adhesion and metabolite sites, they actively participate in the development of colonization resistance, suppressing the growth and multiplication of related pathogenic and opportunistic microorganisms in the intestine [37]. Therefore, it is logical that as the levels of symbiotic *E. coli* decrease, the gastrointestinal tract of FG-treated MS patients is colonized by opportunistic species. These can be atypical forms of *E. coli*, *Enterobacter* spp., *Citrobacter* spp., *Klebsiella* spp., which persist in the gastrointestinal tract of MS patients, causing intestinal disorders and possibly affecting the MS course. It is noteworthy that clearance of these bacteria is considerably slower in mice infected with *Citrobacter rodentium* when FG is administered [38], which is associated with a decrease in the number of Th17 cells that control pathogens in the intestines. The weakening of the control function of Th17 cells in the intestine, especially in combination with reduced levels of symbiotic species, may lead to excessive growth of pathogenic species and their translocation to other niches, including CNS [39]. This is likely the cause of *Listeria monocytogenes* rhombencephalitiss and other infections described in FG treated MS patients [40–42].

Bacteroides fragilis, B. thetaiotaomicron, Prevotella spp. (Bacteroidetes phylum), were found to be more resistant to FG- or TF-treatment, as their levels did not experience significant reductions compared to the untreated group. Other studies have described an increase in the abundance of *Bacteroides* with DMF treatment [43], or *Prevotella* spp. with IFN-β or GA treatment [12].

Interestingly, only patients receiving TF experienced a decrease in body mass without any patients undergoing an increase. Thus, TF likely affects metabolic processes or the bacteria involved in them.

Thus, we have demonstrated in this study that DMTs alter the composition of the gut microbiota. Furthermore, according to our preliminary data (data not shown), these changes can increase with increasing duration of treatment, and as a result, dysbiosis becomes more pronounced in patients receiving DMTs for a long time.

However, to consider the effect of the therapy duration and other factors, for example, the severity of the disease, further studies involving larger cohorts of patients are needed. In addition, expanding the list of determined microorganisms may also be advisable since it will allow to more fully characterize the changes in the microbial composition caused by the DMTs.

Conclusion

A great deal of attention is given to the study of intestinal microbiota in various CNS diseases. Alterations in the intestinal microbiota composition can contribute to GIT dysfunction and modulate the immune functions of the macroorganism, contri-

buting to the pathological process and aggravating the clinical course of the disease. We suggest that an increase in pro-inflammatory opportunistic species in patients receiving DMTs is an adverse side-effect of the drugs, negatively affecting the MS course. Moreover, the alterations in gut microbiota composition may reduce treatment efficacy. With this in mind, regular monitoring of the microbiota and its correction can be helpful in the management of patients with MS.

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Список литературы

1. Stratton C.W., Wheldon D.B. Multiple sclerosis: An infectious syndrome involving *Chlamydophila pneumoniae* // Trends Microbiol. 2006. Vol. 14, No. 11. P. 474–479. DOI: 10.1016/j.tim.2006.09.002
2. Berer K., Krishnamoorthy G. Microbial view of central nervous system autoimmunity // FEBS Lett. 2014. Vol. 588, No. 22. P. 4207–4213. DOI: 10.1016/j.febslet.2014.04.007
3. Hill D.A., Artis D. Intestinal bacteria and the regulation of immune cell homeostasis // Annu. Rev. Immunol. 2010. Vol. 28. P. 623–667. DOI: 10.1146/annurev-immunol-030409-101330
4. Atarashi K., Tanoue T., Shima T. et al. Induction of colonic regulatory T cells by indigenous *Clostridium species* // Science. 2011. Vol. 331, No. 6015. P. 337–341. DOI: 10.1126/science.1198469
5. Gaboriau-Routhiau V., Rakotobe S., Lécuyer E. et al. The key role of segmented filamentous bacteria in the coordinated maturation of gut helper T cell responses // Immunity. 2009. Vol. 31, No. 4. P. 677–689. DOI: 10.1016/j.immuni.2009.08.020
6. Ivanov I.I., Frutos R de L., Manel N. et al. Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine // Cell Host Microbe. 2008. Vol. 4, No. 4. P. 337–349. DOI: 10.1016/j.chom.2008.09.009
7. Buscarinu M.C., Cerasoli B., Annibali V. et al. Altered intestinal permeability in patients with relapsing-remitting multiple sclerosis: A pilot study // Mult. Scler. 2017. Vol. 23, No. 3. P. 442–446. DOI: 10.1177/1352458516652498
8. Camara-Lemarroy C.R., Metz L., Meddings J.B. et al. The intestinal barrier in multiple sclerosis: implications for pathophysiology and therapeutics // Brain. 2018. Vol. 141, No. 7. P. 1900–1916. DOI: 10.1093/brain/awy131
9. Braniste V., Al-Asmakh M., Kowal C. et al. The gut microbiota influences blood-brain barrier permeability in mice // Sci. Transl. Med. 2014. Vol. 6, No. 263. P. 263ra158. DOI: 10.1126/scitranslmed.3009759
10. Hoban A.E., Stilling R.M., Ryan F.J. et al. Regulation of prefrontal cortex myelination by the microbiota // Transl. Psychiatry. 2016. Vol. 6, No. 4. P. e774. DOI: 10.1038/tp.2016.42
11. Miyake S., Kim S., Suda W. et al. Dysbiosis in the gut microbiota of patients with multiple sclerosis, with a striking depletion of species belonginf to Clostridia XIVa and IV clusters // PLoS One. 2015. Vol. 10, No. 9. P. e0137429. DOI: 10.1371/journal.pone.0137429
12. Jangi S., Gandhi R., Cox L.M. et al. Alterations of the human gut microbiome in multiple sclerosis. Nat Commun. 2016;7:12015. DOI: 10.1038/ncomms12015
13. Chen J., Chia N., Kalari K.R. et al. Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls // Sci. Rep. 2016. Vol. 6. P. 28484. DOI: 10.1038/srep28484
14. Абдурасулова И.Н., Тарасова Е.А., Ермоленко Е.И. и др. При рассеянном склерозе изменяется качественный и количественный состав микробиоты кишечника // Медицинский академический журнал. 2015. Т. 15, № 3. С. 55–67.
15. Levinthal D.J., Rahman F., Nusrat S. et al. Adding to the burden: gastrointestinal symptoms and syndromes in multiple sclerosis // Mult. Scler. Int. 2013. Vol. 2013. P. 319201. DOI: 10.1155/2013/319201
16. Arnason B.G. Long-term experience with interferon beta-1b (Betaferon) in multiple sclerosis // J. Neurol. 2005. Vol. 252 Suppl 3. P. iii28–iii33. DOI: 10.1007/s00415-005-2014-2
17. Weinstock-Guttman B., Nair K.V., Glajch J.L. et al. Two decades of glatiramer acetate: From initial discovery to the current development of generics // J. Neurol. Sci. 2017. Vol. 376. P. 255–259. DOI: 10.1016/j.jns.2017.03.030
18. Cantarel B.L., Waubant E., Chehoud C. et al. Gut microbiota in multiple sclerosis: possible influence of immunomodulators // J. Investig. Med. 2015. Vol. 63, No. 5. P. 729–734. DOI: 10.1097/JIM.0000000000000192
19. Абдурасулова И.Н., Тарасова Е.А., Никифорова И.Г. и др. Особенности состава микробиоты кишечника у пациентов с рассеянным склерозом, получающих препараты, изменяющие течение рассеянного склероза // Журнал неврологии и психиатрии им. С.С. Корсакова. 2018. Т. 118, № 8–2. С. 62–69. DOI: 10.17116/jnevro201811808262
20. Castillo-Alvarez F., Perez-Matute P., Oteo J.A., Marzo-Sola M.E. The influence of interferon β-1b on gut microbiota composition in patients with multiple sclerosis // Neurologia (Engl Ed). 2021. Vol. 36, No. 7. P. 495–503. DOI: 10.1016/j.nrl.2018.04.006
21. Абдурасулова И.Н., Ермоленко Е.И., Мацулевич А.В. и др. Влияние пробиотических энтерококков и глатирамера ацетата на тяжесть экспериментального аллергического энцефаломиелита у крыс // Российский физиологический журнал им. И.М. Сеченова. 2016. Т. 102, № 4. С. 463–479.
22. Nwankwo E., Allington D.R., Rivey M.P. Emerging oral immunomodulating agents – focus on teriflunomide for the treatment of multiple sclerosis // Degener. Neurol. Neuromuscul. Dis. 2012. Vol. 2. P. 15–28. DOI: 10.2147/DNND.S29022
23. Portaccio E. Evidence-based assessment of potential use of fingolimod in treatment of relapsing multiple sclerosis // Core Evid. 2011. Vol. 6. P. 13–21. DOI: 10.2147/CE.S10101

24. Storm-Larsen C., Myhr K.-M., Farbu E. et al. Gut microbiota composition during a 12-week intervention with delayed-release dimethyl fumarate in multiple sclerosis – a pilot trial // Mult. Scler. J. Exp. Transl. Clin. 2019. Vol. 5, No. 4. P. 2055217319888767. DOI: 10.1177/2055217319888767
25. Krogh K., Christensen P., Sabroe S., Laurberg S. Neurogenic bowel dysfunction score // Spinal Cord. 2006. Vol. 44, No. 10. P. 625–631. DOI:10.1038/sj.sc.3101887
26. Takewaki D., Suda W., Sato W. et al. Alterations of the gut ecological and functional microenvironment in different stages of multiple sclerosis // Proc. Natl. Acad. Sci. USA. 2020. Vol. 117, No. 36. P. 22402–22412. DOI: 10.1073/pnas.2011703117
27. Cekanaviciute E., Yoo B.B., Runia T.F. et al. Gut bacteria from multiple sclerosis patients modulate human T cells and exacerbate symptoms in mouse models // Proc. Natl. Acad. Sci. USA. 2017. Vol. 114, No. 40. P. 10713–10718. DOI: 10.1073/pnas.1711235114
28. Cekanaviciute E., Pröbstel A.-K., Thornann A. et al. Multiple sclerosis-associated changes in the composition and immune functions of spore-forming bacteria // mSystems. 2018. Vol. 3, No. 6. P. e00083–18. DOI: 10.1128/mSystems.00083-18
29. Kozhieva M., Naumova N., Alikina T. et al. Primary progressive multiple sclerosis in a Russian cohort: relationship with gut bacterial diversity // BMC Microbiol. 2019. Vol. 19, No. 1. P. 309. DOI: 10.1186/s12866-019-1685-2
30. Ventura R.E., Iizumi T., Battaglia T. et al. Gut microbiome of treatment-naïve MS patients of different ethnicities early in disease course // Sci. Rep. 2019. Vol. 9, No. 1. P. 16396. DOI: 10.1038/s41598-019-52894-z
31. Cox L.M., Maghzi A.H., Liu S. et al. The gut microbiome in progressive multiple sclerosis // Ann. Neurol. 2021. Vol. 89, No. 6. P. 1195–1211. DOI: 10.1002/ana.26084
32. Reynders T., Devolder L., Valles-Colomer M. et al. Gut microbiome variation is associated to Multiple Sclerosis phenotypic subtypes // Ann. Clin. Transl. Neurol. 2020. Vol. 7, No. 4. P. 406–419. DOI: 10.1002/acn3.51004
33. Christiansen S.H., Murphy R.A., Juul-Madsen K. et al. The immunomodulatory drug Glatiramer Acetate is also an effective antimicrobial agent that kills gram-negative bacteria // Sci. Rep. 2017. Vol. 7, No. 1. P. 15653. DOI: 10.1038/s41598-017-15969-3
34. Rumah K.R., Vartanian T.K., Fischetti V.A. Oral multiple sclerosis drugs inhibit the *in vitro* growth of epsilon toxin producing gut bacterium, *Clostridium perfringens* // Front. Cell. Infect. Microbiol. 2017. Vol. 7. P. 11. DOI: 10.3389/fcimb.2017.00011
35. Rumah K.R., Linden J., Fischetti V.A., Vartanian T. Isolation of *Clostridium perfringens* type B in an individual at first clinical presentation of multiple sclerosis provides clues for environmental triggers of the disease // PLoS One. 2013. Vol. 8, No. 10. P. e76359. DOI: 10.1371/journal.pone.0076359
36. Абдурасулова И.Н., Тарасова Е.А., Кудрявцев И.В. и др. Состав микробиоты кишечника и популяций циркулирующих Th-клеток у пациентов с рассеянным склерозом // Инфекция и иммунитет. 2019. Т. 9, № 3–4. С. 504–522. DOI: 10.15789/2220-7619-2019-3-4-504-522
37. Ермоленко Е.И., Исаков В.А., Ждан-Пушкина С.Х., Тец В.В. Количественная оценка антагонистической активности лактобацилл // Журнал микробиологии, эпидемиологии и иммунобиологии. 2004. № 5. С. 94–98.
38. Murphy C.T., Hall L.J., Hurley G. et al. The sphingosine-1-phosphate analogue FTY720 impairs mucosal immunity and clearance of the enteric pathogen *Citrobacter rodentium* // Infect. Immun. 2012. Vol. 80, No. 8. P. 2712–2723. DOI: 10.1128/IAI.06319-11
39. Mirza A., Mao-Draayer Y. The gut microbiome and microbial translocation in multiple sclerosis // Clin. Immunol. 2017. Vol. 183. P. 213–224. DOI: 10.1016/j.clim.2017.03.001
40. Tecellioglu M., Kamisli O., Kamisli S. et al. Listeria monocytogenes rhombencephalitis in a patient with multiple sclerosis during fingolimod therapy // Mult. Scler. Relat. Disord. 2019. Vol. 27. P. 409–411. DOI: 10.1016/j.msard.2018.11.025
41. Aramideh Khouy R., Karampoor S., Keyvani H. et al. The frequency of varicella-zoster virus infection in patients with multiple sclerosis receiving fingolimod // J. Neuroimmunol. 2019. Vol. 328. P. 94–97. DOI: 10.1016/j.jneuroim.2018.12.009
42. Ma S.B., Griffin D., Boyd S.C. et al. Cryptococcus neoformans var grubii meningoencephalitis in a patient on fingolimod for relapsing-remitting multiple sclerosis: Case report and review of published cases // Mult. Scler. Relat. Disord. 2020. Vol. 39. P. 101923. DOI: 10.1016/j.msard.2019.101923
43. Sand I.K., Zhu Y., Ntranos A. et al. Disease-modifying therapies alter gut microbial composition in MS // Neurol. Neuroimmunol. Neuroinflamm. 2018. Vol. 6, No. 1. P. e517. DOI: 10.1212/NXI.0000000000000517

References

1. Stratton CW, Wheldon DB. Multiple sclerosis: An infectious syndrome involving *Chlamydophila pneumoniae*. *Trends Microbiol*. 2006;14(11):474–479. DOI: 10.1016/j.tim.2006.09.002
2. Berer K, Krishnamoorthy G. Microbial view of central nervous system autoimmunity. *FEBS Lett*. 2014;588(22):4207–4213. DOI: 10.1016/j.febslet.2014.04.007
3. Hill DA, Artis D. Intestinal bacteria and the regulation of immune cell homeostasis. *Annu Rev Immunol*. 2010;28:623–667. DOI: 10.1146/annurev-immunol-030409-101330
4. Atarashi K, Tanoue T, Shima T, et al. Induction of colonic regulatory T cells by indigenous *Clostridium species*. *Science*. 2011;331(6015):337–341. DOI: 10.1126/science.1198469
5. Gaboriau-Routhiau V, Rakotobe S, Lécuyer E, et al. The key role of segmented filamentous bacteria in the coordinated maturation of gut helper T cell responses. *Immunity*. 2009;31(4):677–689. DOI: 10.1016/j.immuni.2009.08.020
6. Ivanov II, Frutos Rde L, Manel N, et al. Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine. *Cell Host Microbe*. 2008;4(4):337–349. DOI: 10.1016/j.chom.2008.09.009
7. Buscarinu MC, Cerasoli B, Annibali V, et al. Altered intestinal permeability in patients with relapsing-remitting multiple sclerosis: A pilot study. *Mult Scler*. 2017;23(3):442–446. DOI: 10.1177/1352458516652498
8. Camara-Lemarroy CR, Metz L, Meddings JB, et al. The intestinal barrier in multiple sclerosis: implications for pathophysiology and therapeutics. *Brain.* 2018;141(7):1900–1916. DOI: 10.1093/brain/awy131
9. Braniste V, Al-Asmakh M, Kowal C, et al. The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med*. 2014;6(263):263ra158. DOI: 10.1126/scitranslmed.3009759
10. Hoban AE, Stilling RM, Ryan FJ, et al. Regulation of prefrontal cortex myelination by the microbiota. *Transl Psychiatry*. 2016;6(4):e774. DOI: 10.1038/tp.2016.42
11. Miyake S, Kim S, Suda W, et al. Dysbiosis in the gut microbiota of patients with multiple sclerosis, with a striking depletion of species belonginf to Clostridia XIVa and IV clusters. *PLoS One*. 2015;10(9):e0137429. DOI: 10.1371/journal.pone.0137429

12. Jangi S, Gandhi R, Cox LM, et al. Alterations of the human gut microbiome in multiple sclerosis. *Nat Commun.* 2016;7:12015. DOI: 10.1038/ncomms12015
13. Chen J, Chia N, Kalari KR, et al. Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls. *Sci Rep*. 2016;6:28484. DOI: 10.1038/srep28484
14. Abdurasulova IN, Tarasova EA, Ermolenko EI, et al. Multiple sclerosis is associated with altered quantitative and qualitative composition of intestinal microbiota. *Medical Academic Journal*. 2015;15(3):55–67. (In Russ.)
15. Levinthal DJ, Rahman F, Nusrat S, et al. Adding to the burden: gastrointestinal symptoms and syndromes in multiple sclerosis. *Mult Scler Int.* 2013;2013:319201. DOI: 10.1155/2013/319201
16. Arnason BG. Long-term experience with interferon beta-1b (Betaferon) in multiple sclerosis. *J Neurol.* 2005;252 Suppl 3: iii28–iii33. DOI: 10.1007/s00415-005-2014-2
17. Weinstock-Guttman B, Nair KV, Glajch JL, et al. Two decades of glatiramer acetate: From initial discovery to the current development of generics. *J Neurol Sci.* 2017;376:255–259. DOI: 10.1016/j.jns.2017.03.030
18. Cantarel BL, Waubant E, Chehoud C, et al. Gut microbiota in multiple sclerosis: possible influence of immunomodulators. *J Investig Med*. 2015;63(5):729–734. DOI: 10.1097/JIM.0000000000000192
19. Abdurasulova IN, Tarasova EA, Nikiforova IG, et al. The intestinal microbiota composition in patients with multiple sclerosis receiving different disease-modifying therapies DMT. *S.S. Korsakov Journal of Neurology and Psychiatry*. 2018;118(8–2): 62–69. (In Russ.). DOI: 10.17116/jnevro201811808262
20. Castillo-Alvarez F, Perez-Matute P, Oteo JA, Marzo-Sola ME. The influence of interferon β-1b on gut microbiota composition in patients with multiple sclerosis. *Neurologia (Engl Ed).* 2021;36(7):495–503. DOI: 10.1016/j.nrl.2018.04.006
21. Abdurasulova IN, Ermolenko EI, Matsulevich AV, et al. Effects of probiotic Enterococci and Glatiramer Acetate on the severity of experimental allergic encephalomyelitis in rats. *J. Neurosci Behav Physiol.* 2017;47(7):866–876. DOI: 10.1007/s11055-017-0484-1
22. Nwankwo E, Allington DR, Rivey MP. Emerging oral immunomodulating agents – focus on teriflunomide for the treatment of multiple sclerosis. *Degener Neurol Neuromuscul Dis.* 2012;2:15–28. DOI: 10.2147/DNND.S29022
23. Portaccio E. Evidence-based assessment of potential use of fingolimod in treatment of relapsing multiple sclerosis. *Core Evid.* 2011;6:13–21. DOI: 10.2147/CE.S10101
24. Storm-Larsen C, Myhr K-M, Farbu E, et al. Gut microbiota composition during a 12-week intervention with delayed-release dimethyl fumarate in multiple sclerosis – a pilot trial. *Mult Scler J Exp Transl Clin.* 2019;5(4):2055217319888767. DOI: 10.1177/2055217319888767
25. Krogh K, Christensen P, Sabroe S, Laurberg S. Neurogenic bowel dysfunction score. *Spinal Cord*. 2006;44(10): 625–631. DOI:10.1038/sj.sc.3101887
26. Takewaki D, Suda W, Sato W, et al. Alterations of the gut ecological and functional microenvironment in different stages of multiple sclerosis. *Proc Natl Acad Sci USA.* 2020;117(36):22402–22412. DOI: 10.1073/pnas.2011703117
27. Cekanaviciute E, Yoo BB, Runia TF, et al. Gut bacteria from multiple sclerosis patients modulate human T cells and exacerbate symptoms in mouse models. *Proc Natl Acad Sci USA.* 2017;114(40):10713–10718. DOI: 10.1073/pnas.1711235114
28. Cekanaviciute E, Pröbstel A-K, Thornann A, et al. Multiple sclerosis-associated changes in the composition and immune functions of spore-forming bacteria. *mSystems*. 2018;3(6):e00083–18. DOI: 10.1128/mSystems.00083-18
29. Kozhieva M, Naumova N, Alikina T, et al. Primary progressive multiple sclerosis in a Russian cohort: relationship with gut bacterial diversity. *BMC Microbiol.* 2019;19(1):309. DOI: 10.1186/s12866-019-1685-2
30. Ventura RE, Iizumi T, Battaglia T, et al. Gut microbiome of treatment-naïve MS patients of different ethnicities early in disease course. *Sci Rep.* 2019;9(1):16396. DOI: 10.1038/s41598-019-52894-z
31. Cox LM, Maghzi AH, Liu S, et al. The gut microbiome in progressive multiple sclerosis. *Ann Neurol.* 2021;89(6):1195–1211. DOI: 10.1002/ana.26084
32. Reynders T, Devolder L, Valles-Colomer M, et al. Gut microbiome variation is associated to Multiple Sclerosis phenotypic subtypes. *Ann Clin Transl Neurol.* 2020;7(4):406–419. DOI: 10.1002/acn3.51004
33. Christiansen SH, Murphy RA, Juul-Madsen K, et al. The immunomodulatory drug Glatiramer Acetate is also an effective antimicrobial agent that kills gram-negative bacteria. *Sci Rep*. 2017;7(1):15653. DOI: 10.1038/s41598-017-15969-3
34. Rumah KR, Vartanian TK, Fischetti VA. Oral multiple sclerosis drugs inhibit the *in vitro* growth of epsilon toxin producing gut bacterium, *Clostridium perfringens*. *Front Cell Infect Microbiol*. 2017;7:11. DOI: 10.3389/fcimb.2017.00011
35. Rumah KR, Linden J, Fischetti VA, Vartanian T. Isolation of *Clostridium perfringens* type B in an individual at first clinical presentation of multiple sclerosis provides clues for environmental triggers of the disease. *PLoS One.* 2013;8(10):e76359. DOI: 10.1371/journal.pone.0076359
36. Abdurasulova IN, Tarasova EA, Kudryavtsev IV, et al. Intestinal microbiota composition and populations of circulating Th cells in patients with multiple sclerosis. *Russian Journal of Infection and Immunity.* 2019;9(3–4):504–522. (In Russ.). DOI: 10.15789/2220-7619- 2019-3-4-504-522
37. Ermolenko EI, Isakov BA, Zhdan-Pushkina CKh, Tez VV. Quantitative characterization of the antagonistic activity of lactobacilli. *Zh Mikrobiol Epidemiol Immunobiol.* 2004;5:94–98. (In Russ.)
38. Murphy CT, Hall LJ, Hurley G, et al. The sphingosine-1-phosphate analogue FTY720 impairs mucosal immunity and clearance of the enteric pathogen *Citrobacter rodentium*. *Infect Immun.* 2012;80(8):2712–2723. DOI: 10.1128/IAI.06319-11
39. Mirza A, Mao-Draayer Y. The gut microbiome and microbial translocation in multiple sclerosis. *Clin Immunol.* 2017;183:213–224. DOI: 10.1016/j.clim.2017.03.001
40. Tecellioglu M, Kamisli O, Kamisli S, et al. Listeria monocytogenes rhombencephalitis in a patient with multiple sclerosis during fingolimod therapy. *Mult Scler Relat Disord.* 2019;27:409–411. DOI: 10.1016/j.msard.2018.11.025
41. Aramideh Khouy R, Karampoor S, Keyvani H, et al. The frequency of varicella-zoster virus infection in patients with multiple sclerosis receiving fingolimod. *J Neuroimmunol.* 2019;328:94–97. DOI: 10.1016/j.jneuroim.2018.12.009
42. Ma SB, Griffin D, Boyd SC, et al. Cryptococcus neoformans var grubii meningoencephalitis in a patient on fingolimod for relapsing-remitting multiple sclerosis: Case report and review of published cases. *Mult Scler Relat Disord*. 2020;39:101923. DOI: 10.1016/j.msard.2019.101923
43. Sand IK, Zhu Y, Ntranos A, et al. Disease-modifying therapies alter gut microbial composition in MS. *Neurol Neuroimmunol Neuroinflamm.* 2018;6(1):e517. DOI: 10.1212/NXI.0000000000000517

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