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Clinical short communication

Gut microbiota composition and relapse risk in pediatric MS: A pilot study☆

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ABSTRACT

We explored the association between baseline gut microbiota (16S rRNA biomarker sequencing of stool samples) in 17 relapsing-remitting pediatric MS cases and risk of relapse over a mean 19.8 months follow-up. From the Kaplan-Meier curve, 25% relapsed within an estimated 166 days from baseline. A shorter time to relapse was associated with Fusobacteria depletion ($p = 0.001$ log-rank test), expansion of the Firmicutes ($p = 0.003$), and presence of the Archaea Euryarchaeota ($p = 0.037$). After covariate adjustments for age and immunomodulatory drug exposure, only absence (vs. presence) of Fusobacteria was associated with relapse risk (hazard ratio = 3.2 (95% CI: 1.2–9.0), $p = 0.024$). Further investigation is warranted. Findings could offer new targets to alter the MS disease course.

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1. Background

Gut microbiota perturbations have been associated with disease activity in animal models of MS [1–3] but the association with activity in MS subjects is unknown. In animal models representing relapsing-remitting MS, for instance, a germ-free environment has been associated with a milder disease course [1,2]. In addition, oral administration of members of the Bacteroidetes phyla (*Bacteroides fragilis*) have been associated with a lower 'clinical' score in relapsing models of MS [3,4]. Currently, relatively little is known as to what might trigger or facilitate the onset of a new MS relapse. Environmental exposures such as stress, season, sunlight, vitamin D and recent viral infections have been linked to risk of relapse, with the presumed pathway(s) being through immune system modulation. Interestingly, these environmental factors also influence the gut microbiota which likewise modulates the immune system which is known to be affected in MS [1–3].

☆ Statistical analyses were performed by Helen Tremlett (University of British Columbia).

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Table 1
Baseline characteristics of the pediatric multiple sclerosis (MS) cases.[a]

	MS cases, n = 17
Characteristic, n (%) unless stated otherwise	
Sex	
Girl	10 (59%)
Boy	7 (41%)
Age, years: mean (SD; range)	12.5 years (SD = 4.57; 4–17)
≤12 years old	5 (29%)
>12 years old	12 (61%)
Race	
White	8 (47%)
Non-white	9 (53%)
Ethnicity	
Hispanic	8 (47%)
Non-Hispanic	9 (53%)
Co-morbid condition [a]	
Present	7 (41%)
Absent	10 (59%)
MS-specific clinical characteristics	
Age at MS symptom onset, years: mean (SD; range)	12.1 years (SD = 4.8; 4–17)
Disease duration [b], months: mean (SD; range)	10.3 months (SD = 6.6; 2.3–23.1)
Time since last relapse or onset attack (onset attack considered): days: mean (SD; range)	183 days (SD = 140; 4 to 489 days)
Disability level - EDSS at enrolment, median (range)	2.0 (0–4.0)
0–<2.0	7
2.0–<3.0	7
3.0+	3
Immunomodulatory drug exposure status [c]	
IMD naïve	8 (47%)
IMD exposed	9 (53%)
Corticosteroids – systemic [d]	
No	11 (65%)
Yes	6 (35%)
Available prospective follow-up[b], months: mean (SD; range)	19.8 months (SD = 12.0; 1.8–41.6)

Key: SD = standard deviation; EDSS = Expanded Disability Status Scale score; IMD = immunomodulatory drug.
[a] The comorbid conditions for the 7 children were: headache, atopic dermatitis/eczema, long-term constipation, history of shingles, seizures, reactive airways disease and headache, and scoliosis.
[b] Disease duration: time from symptom onset to baseline (stool collection).
[c] 'IMD naïve' indicates never exposed pre-baseline. 'IMD exposed' indicates ever exposed pre-baseline. At baseline, all IMD exposed cases were still on an MS drug as follows: beta-interferon (n = 3); glatiramer acetate (n = 5); natalizumab (n = 1). No child had switched or stopped an IMD (although one child had previously been exposed to plasma exchange before taking glatiramer acetate).
[d] Within the previous 2 months.
[a] Data shown are in relation to baseline (i.e. date of stool sample collection) unless otherwise stated. EDSS was assessed at the clinic visit nearest to the stool sample, i.e. at enrollment into the study.
[b] All prospective follow-up was expressed regardless if (or when) a relapse occurred, with the study end being the last clinic visit or contact for each child.

Further, differences have been observed in the gut microbiota of individuals with and without MS [3,5–8], including pediatric MS [5]. Pediatric MS offers opportunity to study disease processes in the very early stages of MS, relatively close to the actual biological onset of disease, potentially limiting confounders. We explored the association between gut microbiota profiles in early pediatric MS and subsequent relapse risk.

2. Methods

2.1. Cohort selection

Children ≤ 18 years old with a first demyelinating event and at least 2 silent brain lesions or relapsing-remitting MS (McDonald criteria) attending a University of California, San Francisco (UCSF) pediatric MS clinic provided a baseline stool sample, as described previously [5]. At baseline, all cases were within 2 years of symptom onset with no systemic antibiotic exposure in the previous 2 months.

2.2. Capture of clinical and demographic data

Baseline characteristics captured included demographic (e.g. age, sex), and clinical (e.g. disease duration, immunomodulatory drug (IMD) exposure). After stool collection, physician confirmed relapses were determined via structured forms and chart review by abstractors unaware of the child's gut microbiota profile.

2.3. DNA extraction and 16S rRNA sequencing

DNA was extracted from stool using a cetyl trimethylammonium bromide method [9] and the V4 region of the 16S rRNA gene was amplified in triplicate [5,10], combined, purified and pooled in equimolar concentrations prior to sequencing on the Illumina MiSeq platform. Reads were clustered at ≥97% similarity into operational taxonomic units and singly rarefied to 201,546 reads per sample. Taxonomy was assigned using the Greengenes database via QIIME (Quantitative Insights Into Microbial Ecology) [11].

2.4. Statistical analyses

The gut microbiota formed the exposure, expressed as phylum-level relative abundance and categorized according to the data distribution as either 'absent vs. present,' or 'low vs. high' (≤ vs. >median) when detectable in >90% of cases. Phyla with sparse data were excluded (i.e. <20% of cases had detectable reads).

The outcome was the first on-study (post-baseline) relapse. Relapse-free cases were censored at their last clinic visit. Associations between each exposure and the outcome were explored using Kaplan-Meier curves, with the log-rank test to compare groups. After applying a conservative Bonferroni correction for multiple comparisons, those phyla remaining significant were assessed though multivariable Cox regression models, adjusting for potential confounders, including age and IMD drug exposure status (see Appendix, online).

In a sensitivity analysis, any child with an attack (either the onset attack or a relapse) within 30 days pre-stool sample was excluded and the log-rank tests were repeated.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Ver. 22.0 NY: IBM Corp., 2013). UCSF's Institutional Review Board approved the study.

3. Results

Of the originally reported 18 MS cases [5], 17 had up to 41.6 months (mean = 19.8 months) post-baseline follow-up (one left the country and was excluded). Cohort characteristics are shown in Table 1, additional characteristics (e.g. diet, body mass index) are available online

Fig. 1. Association between gut microbiota (phylum-level) and relapse for: Fusobacteria [panel A, top], Firmicutes [panel B: middle] and Euryarchaeota [panel C, bottom].Key: IMD = immunomodulatory drug. Hazard ratios indicate risk of relapse from baseline and are derived from Cox regression hazards models. Age at baseline (stool collection) and IMD exposure at baseline (exposed vs. naïve) were used to adjust models as shown. Bold indicates $p < 0.05$.Binomial categories for each phylum were created based on the data distribution as either absent versus present or high versus low (≤ vs. >median relative abundance). Of the Fusobacteria phyla identified, the genera were either *Fusobacterium* or *Leptotrichia* (genus was the lowest taxonomic level available).

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