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ORIGINAL ARTICLE

Impact of co-amoxiclav–induced gut microbiota modulation on seizure frequency in children with drug-resistant epilepsy

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ABSTRACT

Background and Objectives: Epilepsy is one of the most common neurological disorders; despite advances in antiepileptic medications, approximately 15-30% of patients continue to experience drug-resistant seizures. The ketogenic diet has emerged as an effective non-pharmacological treatment for these individuals. Recent studies suggest that changes in gut microbiota may play a role in the diet's ability to reduce seizures. Given this information, our study aimed to investigate the short-term modulation of gut microbiota through antibiotics influences seizure frequency in children with drug-resistant epilepsy.

Materials and Methods: In this open-label clinical trial, 20 children with drug-resistant epilepsy were enrolled in 2020 at a tertiary pediatric clinic in Sari, Iran. Participants received oral co-amoxiclav (amoxicillin-clavulanate) at a dose of 40 mg/kg per day for five consecutive days. Seizure frequency was monitored before and after the antibiotic intervention. Stool samples were collected at baseline and immediately following treatment, and quantitative real-time PCR was performed to assess all bacterial load as well as the relative abundance of the major gut bacterial groups, Firmicutes and Bacteroides.

Results: The short-term course of co-amoxiclav significantly altered the gut microbiota composition, with a notable reduction in Bacteroidetes and a significant increase in all bacterial gene copies, while the abundance of Firmicutes remained largely unchanged. However, there was no statistically significant change in seizure frequency during the 12-week follow-up period.

Conclusion: Although short-term co-amoxiclav treatment modified the gut microbiota, it did not lead to a meaningful reduction in seizure frequency in children with drug-resistant epilepsy. These findings underscore the complexity of the gut-brain axis and suggest that simple, short-term antibiotic interventions may not be sufficient to influence seizure outcomes. Future studies should involve larger, multicenter cohorts, longer treatment durations, and more comprehensive analyses of microbiota profiles.

Keywords: Co-amoxiclav; Gut microbiota; Drug-resistant epilepsy; Pediatric epilepsy

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INTRODUCTION

Epilepsy is among the most prevalent neurological disorders worldwide, affecting approximately 0.5-1% of the population (1, 2). Despite substantial advances in antiepileptic drug development, nearly one third of patients continue to experience seizures that are refractory to pharmacological treatment. Drug resistant epilepsy (DRE), defined by the failure of at least two appropriately chosen and tolerated antiepileptic drugs (e.g., sodium valproate, levetiracetam, carbamazepine, lamotrigine, topiramate, clobazam, primidone) to achieve sustained seizure freedom, is associated with increased morbidity, mortality, and impaired quality of life (3-8).

Managing children with drug-resistant epilepsy (DRE) can be challenging, but several treatment strategies have shown promise, including surgery, neurostimulation, and dietary approaches (4). One of the most effective non-drug treatments is the ketogenic diet (KD) a high-fat, low-carbohydrate eating plan (9-11). While researchers are still uncovering exactly how it works, there's growing evidence that changes in the gut microbiota the community of microbes living in our intestines play a major role in its ability to reduce seizures. The gut microbiota is more than just bacteria; it is a bustling ecosystem that affects metabolism, immunity, and even brain function through what is called the gut–brain axis. Studies have found that people with epilepsy often have lower microbial diversity and shifts in key bacterial groups, especially Firmicutes and Bacteroidetes, compared to healthy individuals. This imbalance may make the brain more prone to seizures. Excitingly, experiments in animals show that introducing bacteria that mimic this altered microbial pattern can actually protect against seizures. These findings suggest that targeting the gut–brain connection could open new doors for treating epilepsy (12).

Although the ketogenic diet is an established and effective treatment for pediatric DRE, its long-term implementation is often limited by poor adherence, dietary restrictions, and metabolic adverse effects (13, 14). Consequently, alternative strategies capable of safely modulating gut microbiota are of increasing interest. Antibiotics induce rapid and profound alterations in microbial composition, and observational reports have described transient seizure reduction following antibiotic exposure in some patients with refractory epilepsy. Among commonly used antibiotics, co-amoxiclav has been shown to modify gut microbial diversity in a manner that partially overlaps with ketogenic diet–associated changes. Research has shown that it significantly reduces microbial diversity in the gut while increasing the Actinobacteria / Firmicutes ratio. This shift in gut microbiota resembles the changes seen in patients who respond positively to ketogenic therapy (15, 16). Therefore, this study aimed to evaluate the effects of short-term co-amoxiclav administration on gut microbiota composition and seizure frequency in children with DRE.

MATERIALS AND METHODS

Study design and participants. This prospective, open-label clinical trial was conducted in 2020 at the Pediatric Neurology Clinic of Bou Ali Sina Hospital, Sari, Iran. The study protocol was approved by the Ethics Committee of Mazandaran University of Medical Sciences, and written informed consent was obtained from the parents or legal guardians of all participants. The trial was registered in the Iranian Registry of Clinical Trials (IRCT20090412001808N8).

Twenty pediatric patients aged 3-18 years with a confirmed diagnosis of DRE were eligible for inclusion. All participants experienced at least two seizures during the baseline observation period. DRE was defined according to the International League Against Epilepsy (ILAE) criteria as the failure of adequate trials of at least two appropriately chosen and tolerated antiepileptic drugs (either as monotherapy or in combination) to achieve sustained seizure control. All participants had experienced two or more seizures during a 7-day baseline period before enrollment.

Exclusion criteria. included antibiotic or corticosteroid use within the previous month, known hypersensitivity to penicillin derivatives, significant hepatic disease, planned changes in antiepileptic drug regimens during the study period, or eligibility for epilepsy surgery.

Primary assessment. At the initial visit, a pediatric neurologist conducted a comprehensive evaluation, including demographic data, seizure characteristics, medical and family history, and review of electroencephalography (EEG) and brain magnetic resonance imaging (MRI) findings. Patients were included only if the diagnosis of refractory epilepsy with a potential to respond to gut microbiota modulation was confirmed.

Intervention. Eligible participants received oral co-amoxiclav (amoxicillin–clavulanate) at a dose of 40 mg/kg/day, administered in two divided doses for five consecutive days. Families were instructed to avoid probiotics, prebiotics, vitamins, or dietary supplements during the study period.

Microbiota analysis: Sample collection and microbiological analysis. Stool samples were collected at baseline and on day 5 following initiation of antibiotic therapy. Genomic DNA was extracted using a commercial kit according to the manufacturer's instructions (Bioneer, Korea). Quantitative real-time polymerase chain reaction (qPCR) targeting the bacterial 16S rRNA gene was performed to quantify all bacteria, Firmicutes, and Bacteroidetes. Primer sequences, amplification conditions, and normalization procedures are described in Table 1. PCR amplification products for each bacterial group were validated with positive controls and purified using a FavorPrep Gel Purification Kit (Yektatajhiz, Iran). For quantification, these PCR products were cloned into the pTG19-T PCR cloning vector (Vivantis Technologies, Malaysia) and transformed into TOP10 *E. coli* cells. Positive clones were identified using X-gal/IPTG blue–white screening and cultured overnight in LB-ampicillin broth at 37°C. Plasmid DNA was extracted using a Plasmid DNA Mini Extraction Kit (Yektatajhiz, Iran), following the manufacturer's protocol. The concentration of each plasmid was measured, and the plasmid copy number was calculated to generate standard curves. A 10-fold serial dilution series was prepared starting from 2×10^{10} copies of each plasmid. Real-time PCR was performed in triplicate using a Real-Q Plus 2× Master Mix Green (Ampliqon, Denmark) in a final reaction volume of 20 µL, containing 250 nM of each primer, 10 µL of master mix, 2 µL of template DNA, and 7 µL of nuclease-free water. Amplification was carried out on an ABI Real-Time PCR System (Applied Biosystems, USA) under the following cycling conditions: initial activation at 95°C for 3 minutes, 35 cycles of denaturation at 95°C for 10 seconds, annealing/extension at 62°C for 30 seconds, and final extension at 72°C for 30 seconds. Cycle threshold (Ct) values from each dilution were used to generate standard curves in StepOnePlus software (v2.0), enabling quantification of the relative abundance of bacterial taxa within each sample (17). To detect Bacteroides, Firmicutes, and all bacteria, we extracted DNA and performed real-time PCR using the same Real-Q Plus 2× Master Mix Green. The PCR conditions mirrored those used for the standard curves. Each sample was amplified three times, and the bacterial load was calculated by averaging the cycle threshold values. Finally, the counts of Bacteroides and Firmicutes were normalized to the total bacterial count (17).

Outcome measures. Primary laboratory outcomes included changes in the relative abundance of gut microbial taxa. The primary clinical outcome was the change in seizure frequency during the 12-week follow-up period after antibiotic administration. Patients were classified as responders if they exhibited a ≥50% reduction in seizure frequency relative to baseline, and as non-responders if the reduction was <50% during the study period.

Statistical analysis. The data was analyzed using SPSS software. Descriptive statistics were checked for all variables, and the normal distribution test was performed using the Shapiro-Wilk method. To investigate the relationship between the studied parameters, Pearson and Spearman correlation tests were used. Results are presented as Mean ± SEM, and significant results were considered as p-value < 0.05.

Ethics approval and consent to participate. This trial was conducted with the approval of the Ethics Committee of Mazandaran University of Medical

Table 1. Sequences of the oligonucleotide primers (17).

Primer	Bacteria	Primer sequence	Approximate amplicon size
Eub338F	All bacteria	ACTCCTACGGGAGGCAGCAG	200 bp
Eub518R		ATTACCGCGGCTGCTGG	
Firm934F	Firmicutes	GGAGYATGTGGTTTAATTCGAAGCA	126 bp
Firm1060R		AGCTGACGACAACCATGCAC	
AllBac296F	Bacteroides	GAGAGGAAGGTCCCCCAC	106 bp
AllBac412R		CGCTACTTGGCTGGTTCAG	

Sciences and the Institutional Review Board. Parents of the children participating in the trial provided informed written consent.

RESULTS

A total of 29 participants were included in the study, twenty children with drug-resistant epilepsy and nine age-matched healthy controls were included in the analysis. The mean age of patients was 9.15 ± 4.93 years. Most patients were receiving multiple antiepileptic drugs concurrently, including sodium valproate, levetiracetam, carbamazepine, lamotrigine, topiramate, clobazam, and primidone. No adverse events related to co-amoxiclav administration were reported (Table 2).

Table 2. Characteristics of the patient

Characteristic	Case	Control	Total
Age (year)			
Mean±SD	9.15 ± 4.93	4.33 ± 2.34	7.65 ± 4.82
Median (range)	8.5 (2-18)	4 (2-10)	6 (2-18)
Sex- no (%)			
Female	7 (35)	4 (44.4)	11 (37.9)
Male	13 (65)	5 (55.6)	18 (62.1)
Body weight (kg)			
Mean ± SD	23.92 ± 11.70	15.66 ± 5.59	21.36 ± 10.82
Onset of seizures (%)			
0-1 months	45		
1-12 months	40		
1-5 years	15		
Epilepsy classification (%)			
Structural	30		
Genetic	45		
Unknown	25		
Infectious	0		
Metabolic	0		
Immune	0		
Epilepsy risk factors (%)			
No risk factors	10		
Perinatal injury and HIE	9		
Febrile Seizure	2		
Trauma	0		
MRI finding (%)			
Normal	55		
Abnormal	45		
EEG findings (%)			
Normal	10		
Abnormal	90		
mild	20		
moderate	55		
severe	15		
Family history of seizure (%)			
Yes	30		
No	70		
Developmental delay (%)			
Yes	85		
No	15		
No. of concomitant antiepileptic drugs			
Median (range)	3 (2-4)		
2 drugs	6 (30)		
≥ 3 drugs	14 (70)		
Antiepileptic drugs — no.			
Sodium valproate	14		
Primidone	8		
Levetiracetam	7		
Clobazam	7		
Carbamazepine	7		
Lamotrigine	6		
Topiramate	5		
Clonazepam	3		
Nitrazepam	2		
Phenobarbital	1		
Ethosuximide	1		

Seizure frequency and duration were monitored on a weekly basis. Before treatment, patients experienced an average of seven seizures over a four-week period, with individual seizure durations ranging from 1 to 5 minutes. After the administration of Co-amoxiclav, no statistically significant changes were observed in either seizure frequency or duration (Fig. 1). Throughout the 12-week follow-up period, seizure frequency remained consistent with baseline levels. Further analyses showed no significant correlations between seizure frequency and patient sex or body weight.

Impact of co-amoxiclav on the human gut microbiome. During treatment with co-amoxiclav, none of the patients reported any adverse effects. At baseline, the total copy number of bacterial genes (EUB target) in the patient group was slightly lower than that in the control group, but this difference was not statistically significant. After antibiotic therapy, the total bacterial

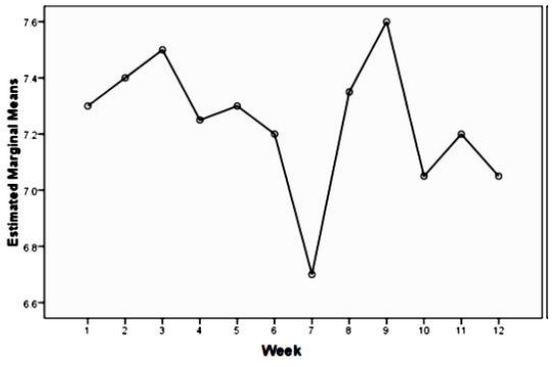

Fig. 1. Graph of the average frequency of epileptic attacks 12 weeks after antibiotic treatment in patients

gene copy number in the patient group increased significantly compared to pre-treatment levels (p = 0.05) (Fig. 2). Regarding the Firmicutes, both at baseline and after treatment, the copy number in the patient group showed no significant difference compared to the control group (p = 0.85) (Fig. 3). Fig. 4, indicates that the Bacteroidetes copy number in the patient group was slightly lower before antibiotic administration than in the control group, though this difference was not statistically significant. However, after antibiotic treatment, there was a significant decrease in the Bacteroidetes copy number in the patient group compared to pre-treatment levels (p = 0.001).

DISCUSSION

In this study, we evaluated whether short-term modulation of the gut microbiota using co-amoxiclav could influence seizure frequency in children with DRE. Our findings indicate that although co-amoxiclav administration induced measurable changes in gut microbiota composition—most notably a significant reduction in Bacteroidetes and an increase in total bacterial load—these alterations were not associated with a significant reduction in seizure frequency or duration during the 12-week follow-up period.

The gut–brain axis is increasingly recognized as a key pathway linking intestinal microbiota composition to central nervous system function. Gut microbes can influence neuronal excitability through several mechanisms, including modulation of immune responses, production of short-chain fatty acids, regulation of neurotransmitter metabolism (such as γ-aminobutyric acid and glutamate), and effects on blood–brain barrier integrity (18). Experimental

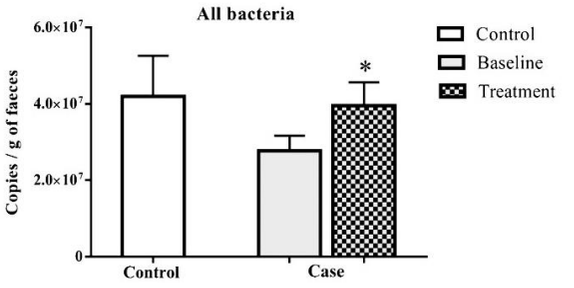

Fig. 2. Changes in all bacteria after treatment with Co-amoxiclav

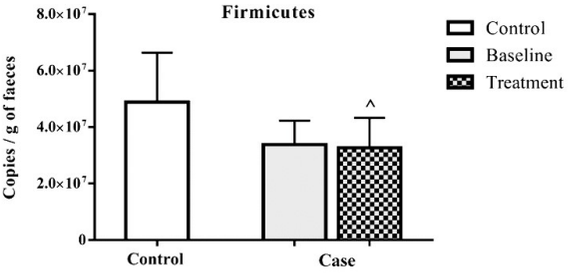

Fig. 3. Changes in Firmicutes after treatment with co-amoxiclav

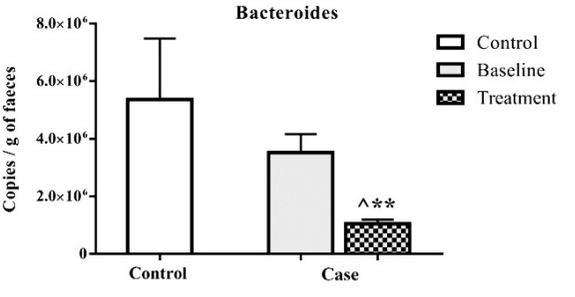

Fig. 4. Changes in Bacteroides after treatment with co-amoxiclav

and clinical evidence has highlighted the relevance of this axis, particularly in dietary interventions such as the ketogenic diet (9, 13).

Several studies have demonstrated that patients with epilepsy exhibit gut microbiota profiles distinct from those of healthy individuals, characterized by reduced microbial diversity and altered relative abundance of key bacterial taxa (10, 13). Importantly, responders to the ketogenic diet display a characteristic microbial signature, including an increase in Bacteroides and a reduction in potentially pro-inflammatory taxa. Olson et al. showed that transplantation of ketogenic diet–associated microbiota alone was sufficient to confer seizure protection in animal

models, supporting a causal role of gut microbiota in seizure modulation (9). Similarly, Zhang et al. and Xie et al. reported increased Bacteroidetes abundance following ketogenic diet therapy in children with refractory epilepsy, and this increase correlated with clinical improvement (10, 19).

In contrast to these findings, our study demonstrated a significant reduction in Bacteroidetes following co-amoxiclav treatment, while Firmicutes levels remained largely unchanged. This divergent microbial shift may partly explain the absence of clinical improvement in seizure outcomes. Bacteroidetes play a crucial role in carbohydrate metabolism, short-chain fatty acid production, immune regulation, and maintenance of gut barrier integrity (20). A reduction in this phylum may disrupt neuroprotective metabolic pathways associated with seizure control and potentially counteract any beneficial effects of microbiota modulation.

An unexpected observation in our study was the increase in total bacterial copy number following antibiotic treatment. This finding may reflect compensatory overgrowth of antibiotic-resistant or opportunistic taxa, ecological niche replacement, or rapid microbial rebound after suppression of susceptible populations (21-25). In addition, methodological considerations related to qPCR-based quantification which measures gene copy number rather than microbial diversity or functional activity may have contributed to this observation (17). These findings underscore the complexity of antibiotic microbiota interactions and suggest that broad-spectrum antibiotics may not be suitable as precise tools for therapeutic microbiota modulation.

Our results differ from those reported by Braakman et al., who described a transient reduction in seizure frequency in patients with refractory epilepsy receiving antibiotics for undercurrent infections (15). However, the anti-seizure effect observed in that study was short-lived and disappeared within two weeks after antibiotic discontinuation, indicating that temporary microbiota perturbations alone are unlikely to induce sustained clinical benefits (15, 21). Differences in antibiotic class, treatment duration, patient characteristics, epilepsy syndromes, and dietary background may further explain discrepancies among studies (14, 25).

Several limitations of this study should be considered. First, the small sample size substantially limits statistical power and increases the risk of Type II error. Second, the open-label design and lack of a placebo-controlled group may introduce reporting bias. Third, the five-day course of antibiotic therapy may have been insufficient to induce durable microbiota changes capable of influencing long-term seizure control. Fourth, microbiota analysis was restricted to phylum-level assessment using qPCR, which does not capture finer taxonomic or functional alterations. Finally, age-stratified and syndrome-specific analyses were not feasible due to the limited cohort size. Despite these limitations, this study provides valuable preliminary insights into the effects of antibiotic-induced gut microbiota modulation in pediatric DRE. Our findings suggest that non-specific disruption of gut microbiota using broad-spectrum antibiotics such as co-amoxiclav is unlikely to yield meaningful clinical benefits and may even induce microbial changes that are unfavorable for seizure control. These results emphasize that not all microbiota alterations are therapeutically beneficial, and that the direction, specificity, and functional consequences of microbial shifts are critical determinants of clinical outcomes. Future studies should focus on larger, randomized, placebo-controlled trials incorporating longitudinal microbiota sampling and high-resolution techniques such as 16S rRNA gene sequencing or metagenomics. Correlating specific microbial taxa and functional pathways with seizure outcomes may help identify targeted microbiota-based interventions. In this context, precision approaches such as bacteriotherapy, targeted microbial modulation, or microbiota-guided dietary strategies may offer greater promise than broad-spectrum antibiotics for the management of drug-resistant epilepsy.

Although short-term co-amoxiclav treatment modified the gut microbiota, it did not lead to a meaningful reduction in seizure frequency in children with drug-resistant epilepsy. These findings underscore the complexity of the gut-brain axis and suggest that simple, short-term antibiotic interventions may not be sufficient to influence seizure outcomes. Future studies should involve larger, multicenter cohorts, longer treatment durations, and more comprehensive analyses of microbiota profiles.

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