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The Gut Microbiota Response to Electroconvulsive Therapy for Schizophrenia: A Prospective Cohort Study

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Although electroconvulsive therapy（ECT）is an effective treatment for schizophrenia, the treatment response rate is only approximately 50%. In addition, it is not clear what the optimal conditions are for maximizing ECT responsiveness. Meanwhile, an association between gut microbiota and the pathophysiology of schizophrenia has recently been reported. Therefore, we explored whether gut microbiota might predict the therapeutic efficacy of ECT. We examined the bacterial percentage of the gut microbiota of 11 patients with schizophrenia who received ECT treatment. Linear regression analyses showed that high *Bifidobacterium* and low *Lactobacillus* levels in stools before ECT were associated with a decrease in symptom severity, as measured by the Brief Psychiatric Rating Scale, after ECT. No bacteria showed significant changes in proportion before and after ECT. Our results suggest that *Bifidobacterium* and *Lactobacillus* levels could predict the responsiveness to ECT but not changes in the severity of schizophrenia.

Keywords: ECT, gut microbiota, schizophrenia, *Bifidobacterium*, *Lactobacillus*

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INTRODUCTION

Schizophrenia is a common psychiatric disorder that presents with hallucinations, delusions, and decreased motivation. The treatment of schizophrenia is mainly pharmacotherapy with antipsychotic drugs. However, not all patients achieve remission with pharmacotherapy. In addition, pharmacotherapy has disadvantages such as a long onset time, side effects, and contraindications.［1］

With electroconvulsive therapy（ECT）, the aim is to achieve remission by delivering electric currents to the brain. ECT is considered to be effective mainly in the treatment of catatonic schizophrenia. ECT is invasive but fast-acting. For this reason, ECT is primarily used in schizophrenia refractory to pharmacotherapy or in catatonic schizophrenia.［2］

In the treatment of schizophrenia, ECT is generally administered to people whose disease is poorly controlled by pharmacotherapy. Therefore, we believe it is important to predict the outcomes of refractory ECT patients.

The treatment response rate to ECT of patients with schizophrenia is only approximately 50%［3］. Previous studies have shown that ECT is particularly effective in patients with catatonic schizophrenia. However, the optimal conditions and clinical features for ECT treatment responsiveness are not yet clear［4-6］.

Studies about gut microbiota have revealed links with several diseases［7-11］. For example, in psychiatric disorders such as autism and depression, the response to treatment may differ depending on the type of bacteria in the gut. It has been hypothesized

that a deficiency in specific bacteria causes symptoms to worsen [8,9]. Deficiency in certain bacteria may lead to the development of disease. It has also been proposed that there is an association between the gut microbiota composition and the pathophysiology of schizophrenia [10,11].

However, the association between the gut microbiota and the response to ECT in schizophrenia has not yet been investigated. Furthermore, findings regarding differences in the gut microbiota between patients with schizophrenia and healthy controls have been inconsistent [12-17]. Table 1 provides a summary of previous case–control studies of patients with schizophrenia and healthy individuals, showing that the results have been inconsistent. These inconsistencies may be a result of differences in race, sex, and symptom severity among studies. In addition, only one study has compared changes in microbiota before and after pharmacological treatment [13]. Table 2 shows that *Bifidobacterium* and *Escherichia* levels increase, whereas *Lactobacillus* and *Escherichia* levels decrease, in response to treatment. Although it may be possible to elucidate the reason for autism onset in some cases, no studies have examined the association between responsiveness to ECT and the gut microbiota.

Given that the pathophysiology of schizophrenia has been reported to be related to the gut microbiota, the gut microbiota might in turn influence the response to ECT in patients with schizophrenia. Therefore, we investigated whether the relative proportions of various bacteria in the gut microbiota predict the response to ECT in patients with schizophrenia and assessed differences in the gut microbiota before and after ECT.

MATERIALS AND METHODS

Participants

We recruited patients who had been diagnosed with schizophrenia and referred for ECT treatment at Shimane University Hospital. Schizophrenia diagnoses were made by a trained psychiatrist (MK) using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, followed by discussions with other psychiatrists. We collected as much data as possible between August 2016 and January 2019. This was a preliminary study to explore the relationship between the gut microbiota and the ECT response. The Shimane University Ethics Committee

Table 1. Differences in the gut microbiota between patients with schizophrenia and healthy controls in previous studies (bacteria for which there were fewer than three reports were excluded from the table)

Author, year of publication (reference number)	*Lactobacillus*	*Bifidobacterium*	*Clostridium*	*Bacteroides*	Notes
Schwarz, 2017 (11)	↑	→		→	First onset. Severity: BPRS score = 12.8 ± 7.3
Yuan, 2018 (12)	↓	↓	↑		First onset. Severity: PANSS score = 82.3 ± 12.7
He, 2018 (13)	↑		↑	↑	Asians
Nguyen, 2018 (14)			↓		Male: female ratio = 11:14
Shen, 2018 (15)	→	→	↑	→	Asians
Zheng, 2019 (16)	↑	→	→	↑	Asians

The upward, downward, and horizontal arrows denote greater, lesser, and equal abundance of bacteria, respectively, in patients with schizophrenia compared with healthy controls.
BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale.

Table 2. Differences in the gut microbiota in schizophrenia patients before and after treatment in a previous study

Author, year of publication (reference number)	*Lactobacillus*	*Bifidobacterium*	*Clostridium*	*Escherichia*
Yuan, 2018 (12)	↓	↑	↓	↑

The upward and downward arrows denote greater and lesser abundance of bacteria, respectively, after treatment.

approved this study (approval number: 20160727-1). Written informed consent for participation in this study and the publication of its results was obtained from each participant or their caregiver. We did not obtain consent to share the data of the patients, because data sharing was not a common practice at the time of recruitment.

ECT treatments

ECT was administered using a constant-current, brief-pulse device (Thymatron System IV; Somatics, Venice, FL, USA). ECT was administered two or three times per week according to the revised edition of the Electrical Convulsive Therapy Recommendation of the Japanese Society of Psychiatry and Neurology, which was created using the American Psychiatric Association treatment guidelines as a reference. The seizure threshold was determined according to these guidelines. All participants were treated with bitemporal ECT. Anesthesia was induced by an anesthesiologist, mainly with propofol 1.5 mg/kg and succinylcholine 1.0 mg/kg; if seizure was not induced by propofol, thiopental 4 mg/kg or ketamine 2 mg/kg was used instead in subsequent sessions to ensure that seizures could be induced easily. Moreover, to ensure an adequate seizure duration and quality, spasm was monitored by clinical observations and electroencephalography. Participants were required to fast for 8 hours prior to the treatment. The number of ECT sessions required was reevaluated at the 10^{th} session. ECT continued until it was judged that no further clinical improvement could be expected, which was determined on the basis of discussions among the psychiatrists.

MEASURES

Clinical characteristics

Nutrition, exercise, and defecation habits before and after ECT were determined in all patients on the basis of medical charts provided by clinical nurses. A clinical interview was conducted at baseline to collect information on demographics and potential covariates, including the severity of the current schizophrenic episode (indexed by the baseline scores on the Brief Psychiatric Rating Scale [BPRS] and the Bush-Francis Catatonia Rating Scale [BFCRS]), the dose of antipsychotic (chlorpromazine equivalent value [mg]), and the seizure length in each ECT session. Clinical measures were assessed at baseline and at the first defecation after the end of the ECT treatment course. Table 3 details the patient characteristics and ECT treatments.

Psychiatric Symptoms of Schizophrenia

The BPRS and the BFCRS were used as clinical response variables. The BPRS is a gold-standard rating scale that assesses the psychiatric symptoms of schizophrenia [18]. The BPRS consists of 18 items, each of which is scored from 1 (*mild*) to 7 (*severe*). Shafer *et al*. demonstrated the validity of the 18-item BPRS in a meta-analysis [18].

Table 3. Characteristics and ECT parameters of patients with schizophrenia

	Number	Proportion (%)		
Males	4	36.4		
Females	7	63.6		
	Mean	Standard deviation	Median	Range
Age (years)	47.5	12.2	51	26–61
Duration of illness (years)	19.7	14.6	19.0	0.08–44
Number of ECT sessions	8.9	3.4	10.0	3–14
Duration of energy bursts (seconds)	7.5	0.6	7.8	6.3–8
Duration of seizures on motor (seconds)	48.8	14.6	50.4	25–68.1
Duration of seizures on EEG (seconds)	66.0	30.7	73.5	15.3–110.3
Interval between hospitalization and the first stool sampling (days)	90.0	136.2	14	2–437
Interval between the last ECT and stool sampling (days)	3.9	5.6	2.5	0–17

ECT, electroconvulsive therapy; EEG, electroencephalogram.

The BFCRS is a gold-standard measure of catatonia developed by Bush in 1996 [19-21]. The BFCRS comprises 23 items, each of which is scored from 0 (*mild*) to 3 (*severe*). According to a systematic review of rating scales for catatonia by Sienaert *et al*. [22], the BFCRS is preferred for routine use because of its high validity and reliability.

Gut microbiota samples

Stools of patients were sampled at baseline and after ECT. Stools were collected promptly after defecation and stored below -25°C until analysis. The bacterial composition of the gut microbiota was analyzed using the terminal restriction fragment length polymorphism method (Techno Suruga Labo Co. Ltd., Shizuoka, Japan).

Statistical analyses

We examined associations among bacteria using Pearson's correlation analyses. Then, a linear regression analysis was performed to predict the treatment response. The dependent variable was the change in the total BPRS score, and the independent variables were bacteria, age, sex, and the number of ECT sessions. As supplementary analyses, we constructed exploratory models that included only bacteria as an independent variable. We performed similar analyses using the change in BFCRS score as the dependent variable. To compare the composition of the gut microbiota before and after ECT, the Wilcoxon rank-sum test was applied.

There were no missing data and no patients were lost to follow-up. All statistical tests were two-tailed, and significance was set at an alpha level of 0.05. All analyses were performed using SPSS 22 software (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

Eleven people who met the criteria for this study were investigated (mean age = 47.5 years; median age = 51.0 years; range: 26–61 years). All patients were receiving antipsychotic medication (see Table 3). Medication type was not changed in any patient during ECT sessions, but the amount of antipsychotics was changed in six patients. Because psychiatric symptoms were relieved by ECT, the dose of antipsychotic medication was reduced by an average of 155 mg (chlorpromazine equivalent) in six patients. There were no changes in the antipsychotic medicine amount in the remaining five patients.

ECT treatments

We performed an average of 8.9 ECT sessions, two or three times per week.

Clinical measures

All patients' BPRS and BFCRS scores decreased after ECT. The BPRS score dropped by 40 points, and the BFCRS score decreased by 24 points (Table 4). The Wilcoxon rank-sum test revealed no significant difference in the percentage of each bacterium before and after ECT (data not shown).

Table 4. Clinical data of the patients

	Before ECT				After ECT			
	Mean	SD	Median	Range	Mean	SD	Median	Range
BPRS score	75.6	20.4	76.0	37-101	35.5	15.1	33.0	21–72
BFCRS score	31.0	13.0	33.0	11-51	6.2	8.4	2.0	0–28
Antipsychotics (CP [mg])	530.5	527.2	250.0	0-1356	375.5	389.8	300.0	0–950
Bifidobacterium	10.7	11.9	8.9	0-35.5	12.7	15.1	6.8	0–43.5
Lactobacillus	5.0	5.2	4.1	1.1-18.5	8.6	10.1	5.6	2.1–38.0
Bacteroides	29.1	19.5	28.8	3.5-60.6	29.5	15.0	31.5	6.5–50.0
Prevotella	0.4	1.4	0.0	0-4.8	0.1	0.2	0.0	0–0.7
Clostridium	38.1	20.8	37.4	12.1-76.5	30.5	11.7	29.6	14.6–50.0
Others	16.7	10.6	13.2	6.6-40.7	18.7	10.4	14.3	9.2–37.4

BPRS, Brief Psychiatric Rating Scale; BFCRS, Bush-Francis Catatonia Rating Scale; CP, chlorpromazine equivalent value; ECT, electroconvulsive therapy; SD, standard deviation.

Association between basal microbiota composition and change in symptom severity after ECT

In the analyses examining associations among bacteria, only the *Bacteroides* and *Clostridium* abundances were significantly correlated (r = -0.755, p = 0.007; data for other bacteria not shown). Therefore, we constructed two different linear regression models. In model 1, we excluded *Clostridium* to avoid collinearity problems; all other bacteria and variables were included. In model 2, we excluded *Bacteroides* but included *Clostridium*.

In model 1, a greater change in the BPRS score was associated with greater *Bifidobacterium* abundance and lesser *Lactobacillus* abundance (Table 5); the results were similar for model 2 (data not shown). In supplementary models including baseline psychiatric symptoms, these bacteria showed trends toward associations with the degree of change in the BPRS score (data not shown). In supplementary models including only bacteria, *Lactobacillus* abundance showed a significant association (Model 2), and a trend toward an association (Model 1), with the change in BPRS score (data not shown).

In model 1, change in BFCRS score was not significantly associated with bacterial composition, although there was a trend toward an association between the BFCRS score and *Bifidobacterium* abundance (Table 6). There were no significant associations in model 2 (data not shown). Moreover, there were trends toward associations of changes in BFCRS scores with *Bifidobacterium*, *Lactobacillus*, and *Bacteroides* or *Clostridium* abundances in models including baseline psychiatric symptoms (data not shown). In models including only bacteria, the *Bifidobacterium* level was significantly associated with the change in BFCRS score.

DISCUSSION

The present exploratory study showed that high *Bifidobacterium* and low *Lactobacillus* levels in stools before ECT were associated with a decrease in symptom severity in patients with schizophrenia. However, *Bacteroides*, *Prevotella*, and *Clostridium* abundances were not associated with changes in symptom severity. Moreover, no bacteria showed significant changes in abundance before and after ECT. Our results suggest that *Bifidobacterium* and *Lactobacillus* levels could be predictor of the responsiveness to ECT but not with the change in severity of schizophrenia.

In recent years, successive new discoveries have been made regarding the relationships among schizophrenia, systemic immunity, and neural inflammation in the brain [23]. The results of the present study may further elucidate the pathophysiology of schizophrenia, and additional research is expected in the future.

Although the mechanisms underlying ECT's effects have not yet been elucidated, changes in inflammatory cytokines are reportedly involved in psychiatric disorders [24, 25]. In addition, animal studies have demonstrated a relationship between inflammatory cytokines and ECT [26-28]. In recent years, it has been posited that hematogenous mechanisms or neuroinflammatory responses may

Table 5. Predictors of change in BPRS score in linear regression analysis (N = 11)

	β	p-value
Sex	2.805	0.021
Age	-0.707	0.074
Number of ECT sessions	0.584	0.081
Bifidobacterium	2.383	0.023
Lactobacillus	-1.903	0.020
Bacteroides	-0.048	0.771
Prevotella	-0.435	0.119
Others	2.481	0.026

BPRS, Brief Psychiatric Rating Scale;
ECT, electroconvulsive therapy.

Table 6. Predictors of change in BFCRS score in linear regression analysis (N = 11)

	β	p-value
Sex	2.558	0.097
Age	-0.442	0.407
Number of ECT sessions	0.158	0.708
Bifidobacterium	2.314	0.093
Lactobacillus	-1.416	0.132
Bacteroides	-0.078	0.821
Prevotella	-0.295	0.479
Others	2.210	0.122

BFCRS, Bush-Francis Catatonia Rating Scale;
ECT, electroconvulsive therapy.

be involved in the therapeutic effect of ECT [29]. Diseases that respond to ECT have been shown to be characterized by elevated inflammatory cytokine levels [30-35]. Our colleagues have reported that, in animal studies, some of these cytokines are released from intracerebral immune-related glial cells [27]. Moreover, we also reported that microglia and astrocyte amounts, which may indicate the presence of intracerebral inflammation, decrease in the hippocampus in response to ECT [28].

Gut microbiota may also be involved in inflammation. In particular, *Bifidobacterium* has been reported to enhance the immune system in animal models of schizophrenia [36-38]. In particular, *Bifidobacterium* is known to produce short-chain fatty acids and to induce regulatory T cells via its effects on G-protein-coupled receptor 43 on the cell surface [36]. Regulatory T cells promote inflammation suppression [37]. Therefore, in patients with a high abundance of *Bifidobacterium*, the suppression of inflammation after ECT may be enhanced. Taken together, the findings suggest that the effect of ECT might be enhanced by the modulatory effect of *Bifidobacterium* on the immune system.

We found no significant changes in the gut microbiota before and after ECT, which suggests that the gut microbiota is not a marker of symptom severity in schizophrenia. In contrast, a previous study reported changes in the abundances of bacteria, such as *Bifidobacterium* and *Escherichia* (increased levels) and *Lactobacillus* and *Clostridium* (decreased levels), following risperidone treatment [13]. These different results could be explained by the possibility that oral administration of antipsychotic drugs directly influences microbiota via chemical and/or biological mechanisms rather than its relationship with the treatment response.

The mechanisms of both ECT and the pathophysiology of schizophrenia remain to be fully revealed. Various biological markers, as endophenotypes, have been investigated, including genes, protein expression and intracellular signaling, neurotransmitters, immune system activity, blood cytokines, brain microglia, brain/neural networks (elucidated by functional magnetic resonance imaging or optical topography), and disease symptoms and course [39-41]. The present study of gut microbiota and the therapeutic response to ECT covers only one part of this complex picture. Therefore, it will be necessary to examine the present results in more detail in the future to place them within the wider context of various biological markers.

The present study has some limitations. First, the number of samples was small. In line with the small sample size and limitations of the statistical model, this study can be considered exploratory and preliminary. A further study with a larger sample size should therefore be conducted to confirm the association between microbiota and the response to ECT of patients with schizophrenia. Second, we did not control for diet. All patients were admitted to the same hospital and consumed a hospital diet during their stay, including the period in which they received ECT. Third, the influence of exercise, which may affect gut microbiota, was not considered, although previous studies have reported inconsistent results regarding the effect of exercise on gut microbiota [42,43]. Fourth, the present study analyzed the composition, but not the absolute quantity, of bacteria in the gut. Finally, we did not control for the effects of drug type, body mass index, smoking, or substance use, which may also influence the gut microbiota.

CONCLUSION

Our findings suggest that some bacteria in the gut might predict the response to ECT of patients with schizophrenia. Understanding the relationship between gut bacteria and the symptoms of schizophrenia might shed light on the pathology of the disease. We hope that these findings will help to optimize the application of ECT for schizophrenia.

Author contribution

MK, JH, and TM participated in the design of the study. MK, KO and MI played a primary role in designing the statistical analysis. MK and MI drafted the manuscript. All authors revised the manuscript and approved the final version.

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Conflict of interest

MI has received lecture fees from EA Pharma, Meiji Seika, MSD, Viatris, Eisai, Otsuka, Sumitomo Pharma, Takeda, Eli Lilly, Nippon Shinyaku, Pfizer, Mochida, Janssen, and Yoshitomiyakuhin.

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All other authors declare that they have no conflicts of interest.

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