学 位 論 文 の 要 旨

氏名　　金山三紗子

学 位 論 文 名　　The Gut Microbiota Response to Electroconvulsive Therapy for Schizophrenia: A Prospective Cohort Study

発 表 雑 誌 名（巻，初頁～終頁，年）　　Shimane Journal of Medical Science (In Press)

著 者 名　　Misako Kanayama, Michiharu Nagahama, Koji Otsuki, Tsuyoshi Miyaoka, Jun Horiguchi, Masatoshi Inagaki

論 文 内 容 の 要 旨

INTRODUCTION

Electroconvulsive therapy (ECT) is an effective treatment for schizophrenia, but it is a somewhat invasive treatment, involving general anesthesia and energizing the brain. The treatment response rate is only about 50%. In addition, at present, the definitive conditions that determine whether or not a patient responds to ECT treatment have not been clarified. On the other hand, while the relationship between gut microbiota and psychiatric disorders and their treatment responsiveness has been increasingly pointed out in recent years, its relationship with the pathophysiology of schizophrenia is also being reported. In other psychiatric disorders, there have been scattered reports that the response to certain treatments differs depending on the intestinal microbiota. Therefore, we investigated whether the gut microbiota could predict the therapeutic efficacy of ECT for schizophrenia.

MATERIALS AND METHODS

The percentage of bacteria in the stool before and after ECT was examined in 11 patients with schizophrenia who were scheduled to receive ECT treatment at Shimane University Hospital from 2016 to 2019.The effect of ECT treatment was investigated using the Brief Psychiatric Rating Scale (BPRS), a commonly used symptom rating scale for schizophrenia, and other measures. 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. 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). The study protocol was approved by the Research Ethics Committee of Shimane University.

RESULTS AND 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. 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. 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. In addition, animal studies have demonstrated a relationship between inflammatory cytokines and ECT. In recent years, it has been posited that hematogenous mechanisms or neuroinflammatory responses may be involved in the therapeutic effect of ECT. Diseases that respond to ECT have been shown to be characterized by elevated inflammatory cytokine levels. Our colleagues have reported that, in animal studies, some of these cytokines are released from intracerebral immune-related glial cells. 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.

Gut microbiota may also be involved in inflammation. In particular, Bifidobacterium has been reported to enhance the immune system in animal models of schizophrenia. 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. Regulatory T cells promote inflammation suppression. 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. 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. 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.

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.