Biomarkers of Electroconvulsive Therapy (ECT) Response in Treatment-resistant Schizophrenia (TRS)

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ABSTRACT

Electroconvulsive therapy (ECT) is a well-established treatment option for individuals with treatment-resistant schizophrenia (TRS). However, predicting treatment response and identifying potential biomarkers to guide electroconvulsive therapy interventions in treatment-resistant schizophrenia remains a challenge. This review paper aims to explore the current literature on clinical biomarkers associated with electroconvulsive therapy in treatment-resistant schizophrenia. We discuss various potential biomarkers, including clinical, neuroimaging findings, EEG markers, and genetic markers, that have shown promise in predicting electroconvulsive therapy response and understanding the underlying mechanism of action. Additionally, we highlight the limitations and future directions for research in this field.

KEY WORDS

Biomarkers, Electroconvulsive therapy, Treatment-resistant schizophrenia

INTRODUCTION

According to the World Health Organization, schizophrenia ranks as one of the top illnesses contributing to years lost due to disability. It affects approximately 0.35-0.75% of the global population.[1,2] People with the disorder are 2 to 3 times more likely to die early than the general population due to co-morbid cardiovascular, metabolic, and infectious diseases.[3,4] Studies conducted worldwide indicate that up to 30% of patients struggling with schizophrenia develop treatment resistance.[5,6] While there are varying definitions of treatment-resistant schizophrenia, in 2017, the Treatment Response and Resistance in Psychosis (TRRIP) Working Group established consensus-based criteria for its diagnosis. According to the group, treatment resistance is defined as a failure of prior treatment with 2 antipsychotics for more than 6 weeks at a therapeutic dose, along with moderate symptom severity and functional impairment.[7] Although clozapine has been the medication of choice and has shown promising outcomes in these patients, 30-40% of them show insufficient response to clozapine.[8] Furthermore, a recent prospective randomized study demonstrated that ECT improved positive symptoms of schizophrenia in patients who were resistant to clozapine and combining ECT with clozapine resulted in better response compared to using only clozapine.[9] However, not all patients respond equally to ECT, despite it emerging as an effective treatment option for TRS. Biomarkers, which are measurable indicators, can provide valuable insights into the underlying biological processes associated with a particular condition or treatment response. In the context of TRS and ECT, biomarkers can help identify patients who are more likely to respond to ECT, allowing for targeted interventions and improved clinical outcomes.

METHODS

A comprehensive literature search was conducted using electronic databases, including PubMed, Scopus, and Psych INFO. Keywords such as “electroconvulsive therapy” “treatment-resistant schizophrenia” “biomarkers” “neuroimaging” “genetic markers” “clinical markers” “EEG

markers" and "cognitive markers" were used to identify relevant studies. Only studies published in English and focusing on clinical biomarkers associated with ECT in TRS were included.

RESULTS

Clinical Biomarkers

There have been multiple papers showing clinical predictors of ECT response in major depressive disorder (MDD). Some of the clinical predictors include - older age, psychotic features, and high severity of suicide behavior appear to be shared by ECT responders.[10] Although studies have been conducted to figure out clinical predictors of ECT response in treatment-resistant schizophrenia, different studies reported different and often contrasting results with small sample sizes and lack of reproducibility. Amongst the studies conducted, several factors have been identified as potential predictors of ECT response in this population. Patients with shorter duration of illness, fewer failed treatment and more affective symptoms may have a higher chance of responding to ECT.[11,12] Additionally, the severity of symptoms, particularly the presence of prominent positive symptoms such as hallucinations, and delusions has been associated with better outcomes.[12] It has also been reported that greater severity of negative symptoms was predictive of poorer outcomes.[12,13] The more reliable predictor is the presence of catatonia, which responds better to ECT. The contrasting feature when compared with the population of MDD is the age group. Younger age groups with treatment resistance respond better to ECT.[12] Other clinical predictors include the absence of comorbid substance use disorder and a lack of cognitive impairment to respond better to ECT.[12,14] A recent registry-based study conducted in Sweden showed that patients with treatment-resistant schizophrenia who are on long-acting injectable antipsychotics were predictive of a better response to ECT.[15]

Neuroimaging biomarkers

A. Gray Matter Volume and Cortical Thickness

Gray Matter Volume and Cortical Thickness are two potential structural neuroimaging measures that have been investigated as biomarkers for predicting response to electroconvulsive therapy (ECT) in treatment-resistant schizophrenia. Gray matter refers to the regions of the brain that consist of primarily neuronal cell bodies, dendrites, and synapses. Changes in gray matter volume have been observed in schizophrenia, however, multiple studies have suggested that baseline gray matter volume may be associated with ECT response in treatment-resistant schizophrenia.[16,17] It is well known that there is evidence of volume reduction compared to healthy subjects in Gray matter particularly in temporal and frontal lobes in patients with schizophrenia.[18] In patients with treatment-resistant schizophrenia, there is a more extensive widespread GM volume reduction, including areas of the temporal, parietal, frontal, and occipital lobes compared with those people with schizophrenia who are treatment responders.[17] ECT has been studied to induce brain plasticity as indexed by gray matter volume changes whose mechanism is distinct from antipsychotics.[19] Several studies have pointed out that higher baseline gray matter volume in specific brain regions, such as the prefrontal cortex, hippocampus, and anterior cingulate cortex is associated with better ECT response in treatment-resistant schizophrenia.[20] These findings suggest that the structural integrity of these brain regions may influence the efficacy of ECT in treatment-resistant schizophrenia.

B. Functional connectivity

Resting-state functional connectivity has revealed alterations in functional connectivity patterns in TRS patients have explored their association with ECT response. In treatment resistant schizophrenia altered brain function is associated with the lack of response to antipsychotic treatment. This was observed in fronto-temporal networks, subcortical networks and frontal lobe.[21] fMRI studies have reported that patients with treatment resistant schizophrenia (TRS) showed altered connectivity between ventromedial-PFC and cingulate and paracingulate regions, as well as between hippocampal formation and the posterior cingulate cortex.[22] These connectivity differences contribute to the persistence of symptoms in TRS. It has been noted that ECT led to increased functional connectivity between brain regions in various neuropsychiatric disorders. Specifically, they observed increased connectivity between the prefrontal cortex and brain regions that are part of the brain's cognitive and emotional processing networks.[23] It has been hypothesized that by increasing connectivity, ECT may help potentially improve cognitive functioning, emotional regulation, and overall symptom relief in individuals with treatment-resistant schizophrenia. The other important finding is the modulation of frontal brain regions including the dorsolateral prefrontal cortex and anterior cingulate cortex., which are known to be involved in cognitive control and emotional regulation. When we talk about the predictability of ECT outcome, it was been shown that regions such as the OFC, hippocampus, Para hippocampal gyrus, insula, amygdala, and temporal lobe had high electric field strength during ECT. The initial functional connectivity between these areas was a good predictor of ECT response.[24] Moreover, increased connectivity between the hippocampus and amygdala was linked to improved clinical outcomes.[25] This suggests that pre-treatment brain synchronization in areas with high ECT-induced electric fields could predict ECT response in treatment-resistant schizophrenia.

EEG Biomarkers

Electroencephalography (EEG) has been used to identify potential biomarkers of Electroconvulsive therapy (ECT) response in treatment-resistant schizophrenia. It has been

well documented that the greater intensity of seizure during ECT in patients with depression, is associated with better clinical outcomes.[26] However same cannot be said in patients with schizophrenia. Although a study showed that the intensity of EEG seizures during the early part of the ECT course in schizophrenia showed high predictability, the benefit was only noticed during the initial sessions of ECT27. In some studies, changes in the power of the spectrum of EEG signals, particularly in specific frequency bands such as delta, theta, alpha, and beta, have been associated with ECT response in schizophrenia.[28] Event-related potentials (ERPs) are other potential biomarkers that have been studied in patients with schizophrenia. Studies have shown that specific ERP components, such as P300 and mismatch negativity (MMN), may serve as potential biomarkers of ECT response in schizophrenia, specifically changes in the amplitude and latency of these components have been associated with treatment response.[29,30] EEG-based connectivity measures, such as coherence and phase synchronization, can provide information about the functional connectivity between different brain regions. Alterations, in connectivity patterns, particularly in the frontal and temporal regions, have been linked to ECT response in treatment-resistant schizophrenia.[31] Lastly, Quantitative EEG (qEEG) measures, such as the frontal alpha asymmetry and the ratio of theta to beta power, may serve as potential biomarkers of ECT response in Schizophrenia.[32]

Genetic Biomarkers

The identification of specific genetic biomarkers of ECT response in treatment-resistant schizophrenia is an area of ongoing research. While the field is still evolving, several genetic factors have been investigated for their potential associated with ECT response in schizophrenia. Brain-derived neurotrophic factor (BDNF), is a protein that plays a crucial role in neuronal survival and plasticity.[33] Studies have suggested that genetic variations in the BDNF gene may influence ECT response in depression, the BDNF Val66Met polymorphism has been investigated in various psychiatric disorders, including schizophrenia, and may have implications for ECT response as well.[34,35] There are other serotonin, dopamine, and glutamate-related genes that have been implicated in treated response, however further research is needed to validate and replicate these findings to identify genetic biomarkers that may contribute to ECT response in this population.

DISCUSSION

In this review paper, we explored potential biomarkers of ECT response in treatment-resistant schizophrenia. Our findings suggest that clinical, neuroimaging, neurophysiological, and genetic markers may play a significant role in predicting ECT response. Neuroimaging findings suggest that structural and functional changes in specific brain regions, such as the prefrontal cortex, and limbic system may be associated with ECT response. Neurophysiological measures, such as resting-state EEG power and ERPs, also showed potential as biomarkers. Changes in these measures may reflect alterations in brain function associated with ECT response. However, the precise mechanism underlying these changes remains unclear and warrants further investigation. The potential genetic marker includes BDNF polymorphism, which may be associated with ECT response. This aligns with previous research suggesting that BDNF plays a crucial role in neuronal survival and plasticity, which may influence treatment response. However, the genetic basis of ECT response is likely to be complex and involve multiple genes, necessitating further research in this area. However, it is vital to acknowledge the limitations of the current research. The complexity of genetic factors, variability in neurophysiological measures, and the interpretation of neuroimaging data pose challenges in identifying robust and reliable biomarkers. Furthermore, the heterogenicity of schizophrenia and the need for a larger sample size and longitudinal studies limits the generalizability and clinical applicability of the findings. Future research should focus on addressing these limitations and further validating the potential biomarkers identified in this review. Replication studies with larger and more diverse samples are needed to establish the robustness and reliability of these biomarkers. Longitudinal studies are necessary to understand the temporal dynamics of these biomarkers and their predictive value over time. Additionally, efforts should be made to explore the clinical utility and feasibility of measuring these biomarkers in routine clinical practice. Despite these challenges, the identification of biomarkers of ECT response in treatment-resistant schizophrenia holds great promise for improving treatment outcomes and guiding personalized treatment approaches. By understanding the underlying biological mechanisms associated with treatment response, physicians may be able to optimize treatment selection and improve patient outcomes.

CONCLUSION

In conclusion, this review paper highlights the potential clinical, neurophysiological, neuroimaging, and genetic biomarkers in predicting ECT response in treatment-resistant schizophrenia. Further research and advancements in this field will contribute to the development of personalized and targeted interventions, ultimately improving the lives of individuals with treatment-resistant schizophrenia.

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