CASE REPORT

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Inflammation-Related Non-Infectious Febrile Reaction Induced by Electroconvulsive Therapy in a Young Female with Bipolar Disorder: A Case Report and Literature Review

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ABSTRACT

Electroconvulsive therapy (ECT) has been employed as an effective treatment for refractory psychiatric disorders worldwide. Despite its extensive use, the occurrence of a fever following ECT has been rare and seldom documented. The reasons behind a post-ECT fever could vary; instances solely attributed to inflammation have been scarcely reported. We present the case of a 27-year-old woman diagnosed with bipolar disorder who experienced multiple fever episodes after having ECT. Diagnostic tests revealed elevated C-reactive protein (CRP) levels with no other infectious focus or possibility of neuroleptic malignant syndrome. We propose that this febrile reaction without real infection was related to inflammatory response triggered by ECT, with the release of various neurotransmitters into the brain and changes in the microsystems. Under this impression, we can speculate that it is a benign and reversible process, allowing us to continue ECT and achieve therapeutic efficacy. This might be the first report to suggest that an ECT-induced fever is related to inflammatory reactions.

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INTRODUCTION

Electroconvulsive therapy (ECT) has been used as a safe procedure for individuals with refractory psychiatric disorders. While ECT can have adverse effects, ranging from headaches to fatal cardiovascular events,[1] a fever after having ECT has been infrequent in practice. Various factors could cause febrile reactions, including infection or malignant hyperthermia.[2,3] Nevertheless, rare reports have focused solely on the inflammatory reaction during and post-ECT. Numerous studies have examined fever occurring after ECT, but a few have investigated potential non-infectious inflammatory responses associated with the procedure.[4] In this study, we present the case of a 27-year-old female diagnosed with a depressive episode of bipolar disorder, who experienced recurrent benign febrile episodes following ECT. We further discuss the potential mechanisms underlying her fever.

CASE PRESENTATION

Informed consent was obtained from the patient. A 27-year-old female had bipolar disorder over the past 2 years. She had a history of thalassemia. Her in-charge psychiatrist has prescribed various medications, and she had previously undergone psychotherapy. During her manic episodes, she was treated with risperidone and sodium valproate. For her depressive episodes, she was prescribed lurasidone, lamotrigine, quetiapine, and trazodone. Her mood symptoms have fluctuated, with periods of exacerbation and remission.

In March 2023, the patient experienced a depressive episode. Medication adjustments were made during outpatient visits. After hospitalization, there was no remarkable improvement in the patient's depressive mood and intense suicidal ideation. The main medications prescribed were Quetiapine (50 mg/day) and Trazodone (100 mg/day). Given the diagnosis of refractory depression, a unanimous decision was made to proceed with ECT, a treatment the patient had not previously undergone.

Electroconvulsive therapy was initiated on the eighth day of hospitalization, with a planned course scheduled every other day. Before starting ECT, a comprehensive

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assessment was conducted, including a chest x-ray, electrocardiogram, and various laboratory tests, such as complete blood count, liver and renal function, and electrolytes. Most test results were normal, except for mild anemia and low mean cell volume, suspected to be thalassemia-related. The patient had no fever since admission. Electroconvulsive therapy was performed with bitemporal electrode placement by using a Thymatron system IV machine under the following settings for this patient: brief pulse width, 0.5 ms; frequency, 60 Hz; duration, 0.5/0.9/1.4 s; and electric current, 900 mA. The range of energy charge was 25.1 mC–75.6 mC. Thiamylal sodium was intravenously administered for anesthesia. The duration of seizures induced by the ECT ranged from 12 s to 55 s.

Following the first ECT session, the patient remained fever-free. However, after the second ECT session, the patient developed a fever of 38.8°C. No signs of infection were observed, and diagnostic tests revealed elevated C-reactive protein (CRP) levels (7.71 mg/L, normal range: < 5mg/L), with a normal white blood cell (WBC) count and a normal neutrophil percentage. Chest x-ray revealed no active lung lesion and urine test showed no bacteriuria. Antibiotics with Amoxicillin 500 mg/clavulanic acid 125 mg and celecoxib were administered to alleviate both the postictal headache and febrile state. Her fever was resolved with medication treatment.

During the third ECT session, a recurrent fever (38.2°C) occurred. The patient had been prescribed antibiotics, and the fever subsided.

On the 14th day of admission, the fourth ECT session resulted in another fever (38.1°C). Laboratory tests showed an elevated CRP (42.27 mg/L) but normal WBC and percentage of neutrophil, while the fever reduced later.

The fifth and sixth ECT sessions did not cause a fever.

During the seventh session, the patient experienced a brief fever (38.5°C) after ECT. The fever was accompanied by an elevated CRP (41.55 mg/L), with normal WBC, neutrophil percentage, creatine phosphokinase (CPK), and myoglobin levels. The patient was discharged with a significant improvement in depressive symptoms and a reduction in suicidal thoughts after completing 7 ECT sessions. We have created a table (Table 1) that summarizes the patient's clinical timeline and responses to treatment interventions.

MAIN POINTS

- Fever is rarely reported as a side effect of ECT.
- A temporary disruption in the blood-brain barrier during ECT leads to the release of various neurotransmitters into the brain, changes in the microsystems, and cytokines responsible for generating a fever.
- If the febrile reaction is related to inflammation, we may speculate that it is a benign and reversible process, and we can continue ECT and achieve therapeutic efficacy.

DISCUSSION

Electroconvulsive therapy is a procedure using artificial electrical stimulation to produce a generalized seizure. It is indicated for the treatment of various conditions, including severe depression.[5] ECT is highly effective in alleviating depressive symptoms with fewer adverse effects.[5] Although ECT is well-tolerated, some side effects may occur, including headache, nausea, myalgia, and postictal confusion with transient amnesia. Most of them are self-limiting and can be managed symptomatically.[1,5] However, fever or hyperthermia is rarely reported as a side effect of ECT.

The precise mechanism underlying febrile reactions after ECT remains unclear. Various factors could cause a fever. Among them, infection, including aspiration pneumonia or infection at the site of intravenous access, is the most common cause.[2,6] Aspiration pneumonia and adult respiratory distress syndrome can be complications of ECT.[1] Anesthesia for ECT may induce fever. Malignant hyperthermia can occur in response to certain anesthetic agents and muscle relaxants characterized by a hypermetabolic state.[1,5] A propofol-induced drug fever should be considered in cases of fever of unknown origin when propofol has been administered during ECT.[3]

We conducted a comprehensive literature review of febrile reactions following ECT, including 8 papers (1 research article and other 7 case reports).[4,6-12] The research article showed that approximately 8.8% of patients receiving ECT had fever more than once, and 1.5% of all individual ECT sessions experienced fever.[8] The findings of higher WBC count, slightly elevated CRP, higher CPK, and myoglobin level in the fever sessions were suggested as a reaction caused by muscular damage. However, the conclusion was limited by the retrospective design with some missing data.

Among the case reports in the literature review, 3 found leukocytosis, elevated CRP, or elevated polynuclear lymphocyte, which may be associated with infectious etiology.[6,12] Some articles mentioned the possibility of respiratory infection, supported by chest x-ray findings.[6] Two case reports revealed increased CPK levels and malignant hyperthermia could not be completely ruled out.[4,12]

Compared to other cases, we conducted a complete blood test to rule out potential factors for the fever. Additionally, we made our best effort to explore a novel possible mechanism in our patient. In our case, the patient underwent 7 ECT sessions and experienced a febrile reaction in 4 of them. After the fever episodes, the patient's CPK and myoglobin levels were within a normal range, and no muscle rigidity was elicited. It is not likely the febrile reactions resulted from malignant hyperthermia. Specifically, we assume post-ECT fever in our patient was not due to thiamylal because she was under the same

Table 1. The Patient's Clinical Timeline and Responses to Treatment Interventions

Response Toward Treatment Intervention	Before Admission	First Week of Admission (1st-4th ECT)	Second Week of Admission (5th-6th ECT)	Third Week of Admission	Fourth Week of Admission	Fifth Week of Admission (7th ECT)	Sixth Week of Admission (Discharge)
PHQ-9	24	22	16	15	15	14	10
SAS	48	40	32	28	27	24	21
CGI-S	5	5	4	4	4	4	3

CGI-S, Clinical Global Impressions Scale; ECT, electroconvulsive therapy; PHQ-9, Patient Depression Questionnaire; SAS, Suicide Assessment Scale.

anesthetic agent in all sessions. During the surveys of the second, fourth, and seventh ECT sessions, the laboratory results reported normal WBC and neutrophil counts, with elevated CRP levels. Diagnostic studies, including chest x-rays and urine tests, revealed no specific findings. Based on these reports, we suspected the patient's fever was not caused by an infection. We proposed that the post-ECT febrile response in this patient was an inflammatory reaction.

During the ictal phase of ECT, there is a temporary disruption in the blood-brain barrier due to a surge in blood pressure, which only occurs when repeated electronic stimulation is applied.[13] Brain edema after ECT was noticed via image studies, perhaps resulting from the breakdown of the blood-brain barrier. This disruption leads to the release of various neurotransmitters into the brain and changes in the micro-systems,[14] and cytokines are responsible for generating a fever. We infer that this is related to a febrile phenomenon following ECT; that is, the febrile reaction observed in our case is associated with an inflammatory response. Additionally, CRP is an inflammatory marker that shows increased expression during inflammation and has the potential to regulate inflammatory processes.[15] Nevertheless, the exact mechanism behind the post-ECT febrile reaction in relation to inflammation necessitates further elucidation. The potential cause of this uncommon condition might offer insights into current therapeutic strategies and propose potential changes in clinical practice based on our discoveries. Prospective studies in the future are required to gain a deeper understanding of this phenomenon.

The limitations of this study include: Firstly, the patient experienced fever episodes in 4 ECT sessions but remained fever-free in the other 3 sessions. The reason for this discrepancy could not be clarified in our manuscript. Secondly, during the third ECT session with fever, we did not collect lab data or conduct other surveys, including imaging studies. We should have conducted comprehensive evaluations during each fever episode.

To our knowledge, this is the first report to indicate that an ECT-induced fever is related to inflammatory reactions with only elevated CRP. After differentiating the etiologies of post-ECT febrile reaction, if the febrile reaction, just like in our case, is related to inflammation, we may speculate that it is a benign and reversible process, and we can continue ECT and achieve therapeutic efficacy.

We propose that in the future if a patient develops post-ECT fever without displaying any infectious symptoms, it would be advisable to consider supportive treatment and postpone the use of antibiotics. Furthermore, we infer that our study presents pure laboratory findings of elevated CRP with normal WBC, CPK, and myoglobin levels. These findings can shed light on the possible mechanisms underlying the inflammatory reaction.

Informed Consent: Written informed consent was obtained from the patient who agreed to take part in the study.

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