Transient febrile reaction after electroconvulsive therapy in treatment resistant schizophrenia: A case report

Bilge Targıtay Öztürk[1], Ayşenur Alp Balat[2], Koksal Alptekin[3]
[1]M. D., [3]Prof., Dokuz Eylul University Faculty of Medicine, Department of Psychiatry, Izmir, Turkey
https://orcid.org/0000-0002-8524-5204-https://orcid.org/0000-0002-7601-9002
[2]M. D., Dokuz Eylul University Faculty of Medicine, Department of Child and Adolescent Psychiatry, Izmir, Turkey
https://orcid.org/0009-0006-2586-3429

SUMMARY

Electroconvulsive therapy has been used safely for many years, especially in treatment resistant schizophrenia. Studies to date have identified nausea, headache, myalgia, amnesia and confusion as common side effects associated with electroconvulsive therapy. In recent years, there have been case reports of transient, benign and generally paracetamol-responsive fever following electroconvulsive therapy. This article presents in detail the fever reactions observed after electroconvulsive therapy sessions in an 18-year-old case of treatment-resistant schizophrenia. After excluding life-threatening conditions in the patient, the identified risk factors and possible underlying mechanisms, it has been concluded that transient benign febrile reactions were associated with electroconvulsive therapy.

Keywords: Electroconvulsive therapy, fever, schizophrenia, side effect

INTRODUCTION

Electroconvulsive therapy (ECT) is now widely used in the treatment of many severe psychiatric and neurological diseases, such as mood disorders, schizophrenia, catatonia, Parkinson's disease, neuroleptic malignant syndrome (NMS) etc. (1). Although the action mechanism of ECT is still not clearly known, it is a biological therapeutic method based on the principle of creating a seizure through external electrical stimulation. The procedure has been demonstrated to be fast, highly effective and safe in clinical practice for many times (2). However, some adverse effects can be observed in patients despite modern ECT applications. Nausea, headache, myalgia, anterograde amnesia and confusion are the most common side effects of ECT. Cardiac and respiratory complications are generally mild to moderate, increase with age and occur most often in patients with preexisting comorbidities (3). Fever has not formally been described as a side effect of ECT, but a few cases of transient benign febrile reactions after ECT have been reported to date (4–10). In a study in which the fever status of patients receiving ECT was evaluated retrospectively for 15 years, it was stated that approximately 8.8% of patients had fever more than once and 1.5% of ECT sessions caused fever (11). Therefore, we consider of interest the description of a patient who was recently treated in our psychiatry inpatient unit and presented with transient, recurrent and self-limited febrile reactions after ECT sessions.

Case history

An 18-year-old female patient first experienced persecutory delusions and disorganized behaviors 2 years ago. Over time, auditory and visual hallucinations were added to these symptoms. At the age of 17, after the onset of symptoms such as echolalia, grimacing, waxy flexibility, mutism and negativism, the patient was admitted to the child and adolescent psychiatry inpatient unit with a diagnosis of catatonic schizophrenia. Risperidone 4 mg/day, aripiprazole 5 mg/day, alprazolam 6 mg/day and biperiden 2 mg/day treatment was administered. During the hospitalization, catatonia symptoms completely resolved and psychotic symptoms partially regressed. The patient was discharged without completing the treatment in accordance with her family's request. She did not use her medications regularly and attend outpatient clinic check-ups after discharge. Six months after hospitaliza-

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tion, her psychotic symptoms exacerbated, and she was admitted to the child and adolescent psychiatry inpatient unit for the second time. She was first administered risperidone 6 mg/day perorally, then risperidone consta 50 mg once every 2 weeks intramuscular treatment was prescribed due to treatment non-compliance. Additionally, aripiprazole 7.5 mg/day, diazepam 10 mg/day and biperiden 4 mg/day were used. Since the patient is over 18 years of age, she was transferred to the Adult Psychiatry Clinic in May 2024 to organize her treatment and follow-up. She had persecutory and reference delusions, visual and auditory hallucinations, disorganized behaviors and agitation while she was admitted to the psychiatric ward. She had no past or current history of smoking, alcohol or substance abuse. No clinical condition that would meet the criteria for catatonia was observed in the patient during her hospitalization. Routine tests performed on admission revealed leukopenia (white blood cell (WBC): 3000/μL, reference range: 4000-10000/μL) and neutropenia (absolute neutrophil count (ANC):200/μL, reference range: 2000-6000/μL) in the patient. Detailed examinations by the internal medicine department carried out no reason to explain the neutropenia. Therefore, it was initially considered that the neutropenia might be related to antipsychotic drugs. However, when past medical records were reviewed, it was observed that the patient had already been neutropenic in tests performed during periods when she was drug naive. It was decided that the patient had idiopathic neutropenia and frequent hematology follow-up was recommended. Long-acting paliperidone palmitate 150 mg intramuscular injection once monthly was started to apply due to the noncompliance with treatment. After the injections in the appropriate dose and for the sufficient duration, the patient's agitation disappeared and her disorganized behavior decreased, but her psychotic symptoms persisted. Therefore, olanzapine was added to the treatment and the dose was increased to 20 mg/day. Despite using olanzapine 20 mg/day for approximately 4 weeks, no response was obtained. The patient was considered to have treatment-resistant schizophrenia. It was decided to gradually taper off olanzapine treatment and perform ECT while continuing monthly long-acting paliperidone palmitate 150 mg intramuscular injection. Bitemporal ECT sessions were carried out by a psychiatrist and an anesthesiologist in a well-equipped set-up. Sessions were planned to be performed thrice weekly under standard anesthetic protocol using propofol as a general anesthetic agent, rocuronium as a muscle relaxant and sugammadex. The first ECT session was applied with a charge of 15 joules and led to a convulsion lasting 46 seconds. No complications were observed after the first session. The second ECT session was applied with a charge of 15 joules and led to a convulsion lasting 32 seconds. Within the first 6 hours after the second session, the patient had a fever of 39.3^{o}C. At this time the patient was physically asymptomatic and clinical examination was unremarkable. In order to investigate the etiology of fever, hemogram, routine biochemistry tests, complete urine analysis, blood-urine-stool and sputum cultures were performed. No difference was observed in the results compared to the previous results except WBC: 3100/μL ANS: 700/μL, C-reactive protein (CRP): 6.2 mg/L (refe-rence range: 0.2-5 mg/L), creatine kinase (CK): 67 U/L (reference range: 0-145 U/L). Ceftriaxone 2 g/day was started to be administered intravenously to the patient with neutropenia upon the recommendation of the infectious diseases department. A few hours after paracetamol 1000 mg was administered intravenously, the patient's body temperature returned to the normal range. Antibiotic therapy was continued for 7 days, no growth was detected in the patient's cultures and body temperature did not rise again. With the recommendation of the anesthesia department, ECT was suspended for 10 days after the antibiotic treatment. The third ECT session was applied with a charge of 20 joules and led to a convulsion lasting 25 seconds. Within the first 6 hours after the third session, the patient had a fever of 39.1^{o}C. No difference was observed except WBC: 4600/μL and ANC: 2700/μL in the laboratory explorations. No clinical symptoms were determined in the patient and the patient's fever decreased with paracetamol 500 mg tablets. Further ECT was discontinued after the third session. She was prescribed lurasidone after ECT and the dose was increased to 160 mg/day. Despite using the appropriate dose and duration of lurasidone, her psychotic symptoms persisted. In the recent period, it was planned to use clozapine and lithium treatment with close monitoring for neutropenia.

DISCUSSION

Infection, NMS, malignant catatonia and anesthe-

tic drug-associated fever could be considered as the different causes of fever observed after ECT sessions. Neutropenic fever and possible concomitant infections were ruled out in our patient. Because there was no growth in cultures, the fever resolved rapidly after a single dose of paracetamol and there were no other accompanying physical examination findings.

There are a limited number of studies showing that blood-brain barrier permeability temporarily increases after ECT applications (12). Altered permeability may increase the transition of psychotropic drugs into the central nervous system and enhance the possibility of developing NMS. Since paliperidone long-acting injection therapy was continued during ECT applications in our patient, she was evaluated for NMS. In addition, malignant catatonia was considered as a possible cause of fever due to history of catatonia in the past. It is noteworthy that most of the cases of ECT related febrile reactions reported in the literature have catatonic features (5,7,8,10). However, no other clinical or biochemical changes required for both NMS and malignant catatonia diagnosis were detected in the patient except fever. ECT is also indicated in the treatment of NMS and malignant catatonia.

Possible febrile complications associated with the use of propofol were reviewed. Propofol infusion syndrome (PRIS) is a rare clinical condition with serious mortality and usually seen in children. In addition to hyperthermia, the main presenting signs of PRIS include rhabdomyolysis, cardiac arrhythmia, metabolic acidosis, hypotension, hyperkalemia, elevated liver enzymes and renal failure (13). PRIS is considered to be caused by the effect of propofol inhibiting mitochondrial fatty acid metabolism (14). It usually occurs when used for more than 48 hours as an infusion or at a dose greater than 4 mg/kg/hour (13). Another cause of propofol associated fever is susceptibility of propofol to environmental microbiological contamination due to its lipid-based structure (14). A new ampoule of propofol was opened immediately before ECT and a single dose of propofol was administered in a sterile manner to our patient just before the procedure. No febrile reaction was observed in other patients who received propofol and underwent ECT on the same days. Therefore, propofol-related fever was ruled out in our patient.

In a retrospective study evaluating ECT-related fever, female gender, young age, long seizure duration, thyroid diseases and low-dose quetiapine use were found to be associated with febrile reactions after ECT (11). Our patient is also a young woman and although she did not have a symptomatic or diagnosed thyroid disease, thyroid peroxidase (TPO) autoantibodies were detected positive. After she was scheduled to receive ECT, paliperidone long-acting injections were continued in her treatment and low doses of quetiapine were used intermittently for agitation or sleep problems. All these clinical features may have been predisposing factors for fever after ECT.

The causes of fever as a side effect of ECT are still not clearly known. However, it is suggested that mechanisms such as activation of the autonomic nervous system, disruption of thermoregulation due to the effect of ECT on the hypothalamus and triggering of the immune response may play a role in the etiopathogenesis of ECT associated fever (5,7–10). Autonomic system activity presents triphasic variation as parasympathetic-sympathetic-parasympathetic after exposure to electrical stimuli during ECT (15,16). The initial parasympathetic discharge lasts for 10-15 seconds and is immediately followed by sympathetic response of 5-7 minutes (5). Increased sympathetic activity can raise body temperature. However, in our case, the duration of the fever was much longer than the duration of sympathetic activity. Therefore, fever does not appear to be directly linked to increased transient sympathetic tone. Current research results suggest that ECT has a demonstrable impact on the structure and function of the brain (17). The principle thermoregulation center is located in the pre-optic hypothalamic region. It is stated that fever can be observed in the post-ictal period of partial and generalized seizures. It is also conceivable that the excessive neuronal activity of the seizure could transiently disrupt the function of the thermoregulatory control center in the anterior hypothalamus (18,19). It has been observed that even a single session of ECT temporarily triggers but repeated ECT applications suppress the immune response (20). Interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) are the most potent

endogenous mediators of fever (21). Higher WBC counts were reported in patients with fever after ECT compared to the control group without fever (11). Leukocytosis is accepted as a peripheral marker of the immune reaction. In our patient with idiopathic neutropenia, the transient increase in WBC and ANC after febrile ECT sessions may be a sign of a triggered immune response. In the light of all these findings, the cause of the patient's fever was primarily thought to be a benign febrile reaction related to ECT.

In our case report, we attempted to elucidate the causes of fever, which is one of the uncommon adverse effects of ECT. Before cases are accepted as benign febrile reactions related to ECT, other life-threatening etiologies must be excluded. Considering the increasing number of case reports in recent years, there is a need for clinical studies evaluating potential risk factors and possible mechanisms for ECT-associated transient fever. The results of these studies will guide whether ECT should be continued or discontinued.

Informed consent: Written informed consent was obtained from the patient and her parents to publish this manuscript.

Correspondence address: M.D., Bilge Targitay Ozturk, Dokuz Eylul University Faculty of Medicine, Department of Psychiatry, Izmir, Turkey btargitay90@yahoo.com

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