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Antipsychotic Drugs Rechallenge in Multi-antipsychotic Drug Induced Atypical Neuroleptic Malignant Syndrome: A Case of Cotard's Syndrome

Çoklu Antipsikotik İlaç Kullanımı ile Tetiklenen Atipik Nöroleptik Malign Sendromda Antipsikotik İlaç Başlama Güçlükleri: Cotard Sendromu Olgusu

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ABSTRACT

Neuroleptic malignant syndrome (NMS) is an uncommon but potentially fatal idiosyncratic reaction to neuroleptics and characterized by a distinctive clinical syndrome of mental status change, rigidity, fever, and dysautonomia. Cotard's syndrome is characterized by the appearance of nihilistic delusions concerning one's own body or life. By presenting this case, we aim to discuss the differential diagnosis and treatment plan of a patient with catatonia and Cotard's syndrome, which were noted after NMS, in light of the literature.

Keywords: Neuroleptic malignant syndrome, Cotard's syndrome, atypical neuroleptic malignant syndrome, nihilistic delusions, electro-convulsive therapy

ÖZ

Nöroleptik malign sendrom (NMS), nöroleptik ajanların kullanımıyla ortaya çıkan, bilinçte değişiklikler, rijidite, ateş yüksekliği ve otonomik değişiklikler ile karakterize olan, nadir fakat ölümcül bir idiosenkratik reaksiyondur. Cotard sendromu ise, kişinin bedeni ya da yaşamı ile ilişkili nihilistik sanrılarla karakterize bir sendromdur. Bu olgu sunumu ile, NMS sonrasında katatoni ve Cotard sendromu gelişen hastada, ayırıcı tanıları ve tedavi planını literatür eşliğinde tartışmayı amaçladık.

Anahtar Kelimeler: Nöroleptik malign sendrom, Cotard sendromu, atipik nöroleptik malign sendrom, nihilistik sanrı, elektrokonvülsif terapi

Introduction

Neuroleptic malignant syndrome (NMS) is an uncommon but potentially fatal idiosyncratic reaction to neuroleptics, characterized by a distinctive clinical syndrome of mental status change, rigidity, fever, and dysautonomia (1).

Cotard's syndrome (CS) is characterized by the appearance of nihilistic delusions concerning one's own body.

"We report a case of a 17-year-old boy with catatonia and nihilistic-paranoid delusions, which were noted after multi-antipsychotic drug treatment induced atypical NMS."

Case Report

A 17-year-old boy was admitted to the psychiatry clinic because of incoherent speech which emerged after somatic pains, irritability, temper outbursts, and initial insomnia. The patient was prescribed olanzapine (10 mg per day) in Ege University Faculty of Medicine Adult Psychiatry inpatient service. After admission to the clinic, risperidone 2 mg per day, biperiden 2 mg per day, olanzapine 5 mg per day were added to his treatment. Due to hyper salivation,

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bradykinesia, cogwheel phenomenon, and dysphagia, the dose of biperiden was increased to 6 mg per day, risperidone treatment was stopped, clozapine 12.5 mg per day was initiated. One week later, he was admitted to the intensive care unit because of hyperthermia, confusion, irregular pulse and blood pressure, vomiting, hemoptysis, dyspnea, wheezing and laboratory abnormalities such as elevation of creatine kinase (CK) (five times the upper limit of normal), lactate dehydrogenase, liver transaminases, troponin T, and leukocytosis, but urine myoglobin was negative. Posterior-anterior chest radiography and echocardiography were consistent with pulmonary edema and ventricular failure, respectively. A presumptive diagnosis of NMS was made. Anti-psychotic treatment was discontinued and supportive care was initiated afterwards (biphasic positive airway pressure, dopamine, milrinone, furosemide, intravenous hydration and alkalinization), amantadine and bromocriptine were started. His general condition improved and pulmonary edema and cardiac failure rapidly decreased within the fifth day. He was transferred to child and adolescent psychiatry inpatient service with a treatment of digoxin 0.125 mg per day and carnitine 1 g per day.

On admission, he was agitated, depressive and had nihilistic and bizarre delusions (he was convinced that he was dead and at the same time immortal; and that his body and his teeth had melted) and was suicidal. He exhibited parkinsonism signs, including tremor, bradykinesia and unsteady gait, he also had catatonic features including catalepsy, negativism, posturing, mutism. The patient was diagnosed with CS with underlying major depressive disorder with psychotic features and catatonia. During the first three days, he received a total of 2.5 mg lorazepam. On the fourth day, escitalopram 2.5 mg per day and lorazepam 2.5 mg per day were added to his treatment schedule. The following day, due to cramping pain in his neck and inappropriate laughter, increase in his motor activity, and statements like "his entire body was melting except for his penis"; acute dystonia and behavioral disinhibition were suspected and escitalopram treatment was stopped, and the dose of lorazepam was increased to 7.5 mg per day. He was rechallenged with quetiapine two weeks after the resolution of NMS without the recurrence of the symptoms. But quetiapine was not sufficient to control the symptoms, and increasing its dose rapidly could have caused the recurrence of NMS. Hence, we transferred the patient to another clinic for the purpose of electro-convulsive therapy (ECT) implementation.

Discussion

In this case report, the differential diagnosis and treatment plan of a patient with catatonia and CS, which were noted after NMS, were discussed.

NMS is a rare but potentially fatal complication of anti-psychotic pharmacotherapy (1). Incidence and mortality of NMS has declined in recent years owing to the awareness on the disorder. Estimated incidence is about 0.01-0.02% for patients treated with anti-psychotics, but it has not yet been clarified for children and adolescents (2,3).

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) identified the core features of NMS as hyperthermia, rigidity and CK elevation after exposure to a dopamine antagonist within 72 hours. Neurological signs (e.g., tremor, sialorrhea, akinesia, dystonia, trismus, myoclonus, dysarthria, dysphagia, rhabdomyolysis), changes in mental status, autonomic instability (e.g., tachycardia, blood pressure elevation or fluctuation, urinary incontinence, pallor, and tachypnea) may accompany these features. It is stated in DSM-5 that NMS is often heterogeneous in onset, presentation, progression, and outcome. In our case report, hyperthermia and elevated CK levels were detected although muscle rigidity was absent, consistent with negative urine myoglobin. Pulmonary edema and ventricular failure considered as cardiorespiratory failure, are complications of NMS.

Non-specific laboratory abnormalities such as leukocytosis, elevation of transaminases, lactate dehydrogenase, and alkaline phosphatase can be observed in NMS besides CK level elevation, and we determined all of these laboratory abnormalities in our case (1,2).

The symptoms of NMS initiates between 24 hours to 30 days after anti-psychotic drug intake and resolves within 7-10 days subsequent to discontinuation of the inducing agent (4-6). In our case report NMS could have been triggered by olanzapine, risperidone or clozapine because all of these neuroleptics were initiated within 14 days before the diagnosis of NMS. Besides, NMS resolved on the fifth day after the discontinuation of anti-psychotic drugs.

Some risk factors have been reported for NMS, such as increased and rapidly titrated anti-psychotic doses, agitation, dehydration, physical restrain, iron deficiency, history of previous NMS, parenteral administration routes, excessive alcohol consumption (1,2,6-9). We detected iron deficiency, agitation, and dehydration as risk factors in our case.

NMS is a diagnosis of exclusion, so it should be differentiated from other conditions, including infection of central nervous system (CNS), agitated delirium, malignant catatonia, serotonin syndrome, malignant hyperthermia (2,10). There was neither prodromal viral illness nor other neurological signs, so we excluded the infection of the CNS. Due to the absence of history of using serotonergic agents or getting general anesthesia; serotonin syndrome and malignant hyperthermia were excluded, respectively. Although malignant catatonia is a differential diagnosis of NMS, it might be hard to distinguish the two conditions because of the associated clinical (e.g. rigidity, hyperthermia, autonomic instability, stupor) and laboratory findings (e.g., elevated CK levels, reduced serum iron level, electroencephalography abnormalities). Moreover, residual catatonia can persist for weeks after the resolution of NMS (5,11). In our case, catatonia was not detected before the patient was admitted to the intensive care unit, so we excluded malignant catatonia, and diagnosed him with atypical NMS induced with multiple neuroleptics.

Identification of the syndrome is the keystone for NMS treatment. The first step of the treatment is discontinuation of the anti-psychotic agent. After that, supportive therapy must be initiated (e.g., aggressive rehydration and restoring electrolyte balance, alkaline fluids, physical cooling, careful monitoring of complications, including aspiration pneumonia, acute renal failure, cardiac arrest, pulmonary embolism, disseminated intravascular coagulation) and specific agents such as amantadine, bromocriptine and dantrolene must be used in order to reduce the mortality rate (6,12,13).

Due to the high possibility of NMS recurrence, at least 2 weeks should elapse after recovery; low doses of low-potency anti-psychotics should be titrated gradually after a test dose; and patients should be carefully monitored for early signs of NMS when psychotic symptoms persist (6). We initiated low dosage quetiapine treatment after recovery from NMS and titrated it very slowly. If residual symptoms and catatonia persist after NMS, or supportive treatment and specific agents do not control NMS, ECT might be considered as a treatment option (12).

CS was first identified by James Cotard in 1880 as a new form of depression composed of anxious melancholia, ideas of damnation or rejection, insensitivity to pain, delusions of nonexistence concerning one's own body, and delusions of immortality. There is insufficient data about the prevalence and incidence of the syndrome (14). CS is described as a cluster of symptoms as part of an underlying disorder, mostly depressive and bipolar (15-18). Although our initial diagnosis was major depressive disorder with psychotic features, patients must be followed closely for bipolar disorder because of manic symptoms after treatment with escitalopram, and an increased risk of bipolar disorder during adolescence with CS (17). The most frequent symptoms of CS are depressive mood (89%), nihilistic delusions concerning one's own body (86%), nihilistic delusions concerning one's own existence (69%), anxiety (65%), delusions of guilt (63%), delusions of immortality (55%), and hypochondriac delusions (58%) (19). Our patient was convinced that he was dead, that his body and his teeth had melted and he felt very anxious because he was guilty, and this delusion caused extreme suffering and suicidal thoughts. However, at the same time he was convinced that he was immortal. Therefore, all symptoms were consistent with CS. Yamada et al. (20) divided the course of CS into three stages in 1999. The first stage, "the germination stage", is characterized by significant hypochondriasis and a depressive mood. The second stage, "the blooming stage", which is more specific to Cotard symptom, includes nihilistic and immortality delusions. Ultimately, the last stage, "chronic stage", is divided into two forms: a depressive and a paranoid type (20). The first two stages were present in our case. Prognosis and treatment is based on the underlying disorder, and monotherapy, combination therapy, or ECT can be used as a treatment option (14). Thus, we both prescribed anti-psychotics and planned to imply ECT in the course of our treatment.

In summary, anti-psychotic treatment is a challenge after NMS, and ECT might be considered as a treatment option in these cases.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Helin Yılmaz, N. Burcu Özbaran, Sezen Köse, Concept: Helin Yılmaz, N. Burcu Özbaran, Sezen Köse, Design: Helin Yılmaz, N. Burcu Özbaran, Sezen Köse, Data Collection or Processing: Helin Yılmaz, N. Burcu Özbaran, Sezen Köse, Literature Search: Helin Yılmaz, Writing: Helin Yılmaz.

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