Myoclonic seizures induced by antipsychotic drugs: A case series and literature review

Antipsikotik ilaçların neden olduğu miyoklonik nöbetler: Bir olgu dizisi ve literatür incelemesi

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SUMMARY

Introduction: The true frequency of myoclonic seizures caused by antipsychotics is unknown. Myoclonus associated with clozapine and other antipsychotics has been shown less frequently than tonic-clonic seizures in the literature and the treatment protocol is controversial. In this study, we have compiled current literature data by presenting our clinical experiences in patients who developed myoclonic seizures with antipsychotic use. **Case Series:** The patients were followed up in the inpatient service of Gazi University Hospital, Department of Psychiatry between 2014-2019. Demographic data, clinical variables, imaging methods and response to treatment of 10 patients with myoclonic seizures were analyzed. After clinical evaluation, psychiatric diagnoses were clarified according to DSM-5. Psychotropic drugs and doses, EEG, MRI examinations and follow-up data were recorded in these patients with myoclonic seizures.

While 6 of the patients (60%) were receiving clozapine treatment, other patients using olanzapine, amisulpride and quetiapine were seen as 2 (20%), 1 (10%) and 1 (10%), respectively. The mean chlorpromazine dose-equivalent of the antipsychotics used by all 10 patients was 876.66 mg per day. In addition to antipsychotic change, valproic acid was used (most frequently) for the control of myoclonic seizures in 8 of the patients (80%), due to insufficient response. **Conclusion:** Myoclonic seizures may be misdiagnosed as sudden falls resulting from generalized tonic-clonic seizures, dyskinesia, and clozapine induced hypotension. In patients with myoclonic seizures, use of antipsychotic drugs should be kept in mind, especially in additional medical conditions such as renal failure, as well as direct central nervous system pathologies.

Keywords: Myoclonic seizures, myoclonus, antipsychotics, schizophrenia, atypical antipsychotics

ÖZET

Giriş: Antipsikotiklerle oluşan miyoklonik nöbetlerin gerçek sıklığı bilinmemektedir. Klozapin ve diğer antipsikotiklerle ilişkili miyoklonus, literatürde tonik-klonik nöbetlere göre daha az sıklıkla gösterilmiş ve tedavi protokolü tartışmalıdır. Bu çalışmada antipsikotik kullanımı ile miyoklonik nöbet gelişen hastalarımızda klinik deneyimlerimizi sunarak güncel literatür verilerini derlemiş bulunmaktayız. **Olgu Sunumları:** Hastalar Gazi Üniversitesi Hastanesi Psikiyatri Anabilim Dalı' nda 2014-2019 yıllarında takip edilmiştir. Miyoklonik nöbetleri olan 10 hastanın demografik ve klinik verileri, görüntüleme yöntemleri ve tedavi yanıtları incelendi. Klinik değerlendirme sonrası DSM-5'e göre psikiyatrik tanıları netleştirildi. Miyoklonik nöbet görülen bu hastaların tedavilerinde yer alan psikotrop ilaçlar, dozları, EEG, MRG sonuçları ve takip verileri kaydedildi. Hastaların 6'sı (% 60) klozapin tedavisi alırken, olanzapin, amisülpirid ve ketiapin kullanan diğer hastalar sırasıyla 2(% 20), 1(% 10) ve 1(% 10) olarak görüldü. Kullanılan antipsikotiklerin ortalama klorpromazin doz eşdeğeri günde 876.66 mg olarak hesaplandı. Hastaların 8'inde (% 80) miyoklonik nöbetlerin kontrolü için antipsikotik değişimine ek olarak, yeterli cevap sağlanamaması nedenli, valproik asit (en sık olarak) kullanıldı. **Sonuç:** Miyoklonik nöbetler; jeneralize tonik-klonik nöbetler, diskinezi ve klozapine bağlı hipotansiyondan kaynaklanan ani düşmeler olarak yanlış tanı alabilmektedir. Miyoklonik nöbetleri olan hastalarda direkt santral sinir sistemi patolojilerinin yanı sıra -özellikle böbrek yetmezliği gibi ek tıbbi durumlarda- antipsikotik ilaç kullanımı akılda tutulmalıdır.

Anahtar kelimeler: Miyoklonik nöbetler, miyoklonus, antipsikotikler, şizofreni, atipik antipsikotikler

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INTRODUCTION

Myoclonus is defined as sudden, jerky, generally non-rhythmic, involuntary movements. It can present either a movement disorder or a seizure (1). Myoclonic seizures are characterized as the same, brief, jerking spasms of muscles with loss of consciousness in generalized types. On the other hand, consciousness is preserved in focal myoclonic seizures (2).

Some medications and multidrug usage predispose to these conditions. Among first-generation antipsychotics, the greatest seizure risk is considered to be chlorpromazine [3,4]. Among second-generation antipsychotics, clozapine is the one with the greatest risk for myoclonic conditions (5,6). Only a few reports of myoclonus induced by olanzapine, quetiapine is available in the literature (7,8).

We present our clinical experiences in ten patients who developed myoclonic seizures with the use of antipsychotics.

CASE SERIES

Subjects

All of the patients were followed up in the inpatient service of Gazi University Hospital, Department of Psychiatry between 2014-2019. Verbal consent was obtained from all patients and data were analyzed retrospectively. The diagnoses of the patients were evaluated according to DSM-5 after a clinical interview. However, Schizophrenia subtypes were also defined in order to provide partial detail in the diagnostic contents. Psychotropic drugs and doses, EEG (electroencephalography) and CT (computerized tomography), MRI (magnetic resonance imagining) diagnostic methods, drug therapies initiated, and clinical findings were recorded during the myoclonic event. Tests such as complete blood count, liver, kidney function tests, thyroid function tests, glucose, iron, folate, and vitamin B12 levels were performed to exclude other medical causes other than myoclonic seizures. The diagnosis and treatment of the patients were conducted in a multidisciplinary manner by psychiatry and neurology physicians. The patients did not have a primary neurological disease. However, sufficient information on medical comorbidities that may trigger myoclonic seizures could not be obtained in all patients because the relevant records could not be accessed adequately.

Statistical analysis

SPSS 23.0 version was used in the analysis of patient data. Sociodemographic and clinical characteristics of the patients were evaluated using descriptive statistical methods such as percentage, number, mean and standard deviation.

Case Analysis

The demographic characteristics, drug data, electrophysiological and radiological features of patients are summarized in Table 1. There were 10 patients with myoclonic epileptic seizures under antipsychotic treatment. Neither they nor their family had an epilepsy history. Two (20%) of the patients were female and 8 (80%) were male. The mean age was 24.2 years. Seven (70%) of them had a diagnosis of undifferentiated schizophrenia while 2 (20%) of them had a diagnosis of treatment-resistant schizophrenia and 1 (10%) was diagnosed as disorganized schizophrenia.

The mean duration of the disease was found to be

Table 1. Myoclonic seizure cases triggered by antipsychotics

Case number	Age/ Gender	Education	Marital Status	Dx	Duration of disease	Used Antipsychotic/ Dose during myoclonic seizure	CLP equivalent**	Used antiepileptic drug	Dose of antipsychotic after seizure	EEG/ Neuroradiological studies
1	21/M	University	Single	Undif. Sch	9 months	Clozapine/ 400 mg	800 mg	Valproic acid 800 mg	300 mg	Partial onset epileptic activity No acute cranial pathology on MRI
2	23/M	University	Single	Dez Sch	1 year	Clozapine/ 425 mg	850 mg	Valproic acid 600 mg	325 mg	Normal EEG findings No acute cranial pathology on MRI
3	20/M	University	Single	Undif. Sch	8 months	Olanzapine/ 15 mg	300 mg	Clonazepam 1 mg	10 mg	Bilateral synchronous symmetrical spike and polyspike and slow wave discharges No acute cranial pathology on MRI
4	23/F	Primary School	Single	Undif. Sch	1 year	Olanzapine/ 15 mg	300 mg	Lorazepam 2 mg	10 mg	Intermittent generalized slow wave activity (Larger amplitude in frontal electrodes) No acute cranial pathology on MRI
5	35/M	Secondary School	Married	Undif. Sch	5 years	Clozapine/ 450 mg	900 mg	Valproic acid 1000 mg	350 mg	Paroxysmal, bilateral synchronous symmetrical spikes No acute cranial pathology on MRI
6	21/F	Secondary School	Single	Undif. Sch	9 months	Clozapine/ 400 mg	800 mg	Valproic acid 1000 mg	300 mg	Normal EEG No acute cranial pathology on MRI
7	22/M	Secondary School	Single	Undif. Sch	4 years	Amisulpride/ 400 mg Quetiapine/ 800 mg	300 mg 1066.66 mg (Total: 1366,66mg)	Valproic acid 1000 mg	400 mg 400 mg	Paroxysmal, generalized high amplitude spike and slow wave activity No acute cranial pathology on MRI
8	27/M	Secondary School	Single	TR Sch	8 years	Clozapine/600 mg	1200 mg	Valproic acid 1000 mg	600 mg	Normal EEG No acute cranial pathology on MRI
9	22/M	Secondary School	Single	TR Sch	2.5 years	Clozapine /350 mg	700 mg	Valproic acid 1000 mg	350 mg	Normal EEG No acute cranial pathology on MRI
10	28/M	Secondary School	Married	Undif. Sch	6 years	Haloperidol/ 15 mg Quetiapine/ 600 mg	750 mg 800 mg (Total: 1550 mg)	Valproic acid 1000 mg	15 mg 300 mg	Normal EEG No acute cranial pathology on MRI

M: Male, F: Female, Dx: Diagnosis, Undif. Sch: Undifferentiated schizophrenia, Dez Sch: Disorganized schizophrenia, TR Sch: TreatmentResistant schizophrenia, CLP: Chlorpromazine, MRI: Magnetic resonance imaging, EEG: Electroencephalography

33.5 months (between 8 and 96 months). Six (60%) of the patients were under clozapine treatment while others using olanzapine, amisulpride, and quetiapine, haloperidol, and quetiapine were found to be 2 (%20), 1 (%10), and 1 (10%) respectively. The average dose of clozapine use during myoclonic activity was found to be 437.5 mg per day. It was 15 mg per day for those using olanzapine. On the other hand, the average chlorpromazine dose equivalent of antipsychotics used by all 10 patients was found to be 876.66 mg per day. Those treated by clozapine were using 875 mg chlorpromazine equivalent antipsychotic per day while the chlorpromazine equivalent doses of those using olanzapine, amisulpride + quetiapine, and haloperidol + quetiapine were found to be 600 mg, 1366.66 mg, and 1550mg per day respectively. In 8 (80%) of the patients, valproic acid was used for the treatment of the myoclonic states. Lorazepam and clonazepam were the other two choices in two patients. After the myoclonic event, the average dose of clozapine use was found to be 370.8 mg per day, while this dose for olanzapine was 10 mg per day.

DISCUSSION

Myoclonic seizures are observed in patients with specific myoclonic epileptic syndromes or occur as a result of hypoxic, infective, inflammatory, neurodegenerative, and toxin/ drug-associated conditions (9,10). The percentage of drug-related myoclonic seizures is substantial. Besides, it is frequently encountered, especially as one of the reasons for frequent consultation from non- neurologist physicians (10).

Older ages, neurodegenerative comorbidities, history of epilepsy, impaired renal functions, electrolyte imbalance, drugs (opioids, levodopa, quinolones, phenytoin, carbamazepine, amantadine, etc.), and multidrug usage predispose to this condition (9,10).

We detected that this situation occurred under the use of atypical antipsychotics in 9 patients and both typical and atypical antipsychotic combinations in 1 patient. Atypical antipsychotics lower the seizure threshold more and they are preferred more in clinical practice nowadays (11).

Six patients were using clozapine. Clozapine is known as the antipsychotic that reduces the epilepsy threshold mostly (12). It has also been reported to create any kind of seizure activity, and it is known to cause focal awareness seizures, focal impaired awareness seizures, atonic, tonic-clonic, or myoclonic seizures (3,5). Although generalized tonic-clonic seizures are frequently observed, we want to emphasize that myoclonic seizures may occur and may be encountered in daily practice (2).

While all patients who had a seizure with clozapine experienced these seizures at doses of 400 mg and above, in two patients using olanzapine seizures were seen on 15 mg doses. Seizures were observed in one patient using amisulpride 400 mg and quetiapine 800 mg; and in another patient, using 15 mg haloperidol and 600 mg quetiapine. In previous studies, with high doses (1,000 mg/day chlorpromazine equivalent), seizures were seen in 9% of the patients; with moderate doses, in 0.7% patients; and with low doses 0.3% of the patients (200 mg/day chlorpromazine equivalent) (13,14). Although rare, epileptic seizures can be observed even with low doses of antipsychotics, depending on the patient's epilepsy threshold and additional factors. In a report, status epilepticus was documented with minimal doses of CPZ (~1000 mg/d) in patients (15). The equivalent dose of chlorpromazine in which myoclonic seizures occurred was found to be 850 mg per day. This result seems to be consistent with the findings in the literature. Nevertheless, these EEG changes and seizures have been generally believed to be related to both the dose and plasma concentration. Also, it is possibly happening with rapid drug titration (1-4). EEG changes corresponded to the myoclonic events time wisely, especially in seizures. EEG recordings can be normal in these conditions (1).

In the treatment of these myoclonic events, the priority should be to reduce the dose or change the triggering drug (10). However, in daily practice, drug switching is compelling because the psychotic conditions of these patients were resistant, an agent such as clozapine had been switched on intentionally. So, we reduced the doses of these antipsychotics, and valproic acid (500-100mg/ day) was added to the treatment in 8 patients, benzodiazepine (lorazepam 2mg/day, clonazepam 1mg/day) in 2 patients. As with other seizure types, the use of GABAergic drugs has been effectively treated these myoclonic seizures due to the assumption that the underlying pathology is GABAergic inhibition (16,17). Levetiracetam is also used in myoclonic conditions, but it is rarely preferred with these psychiatric patients because of the dose-independent aggression and/ or psychotic side effects (18,19,20).

Our access to some data in our cases (time of onset of the seizure, comorbidities) was incomplete due to various reasons (time-lapse, wrong remembering, missing notes, etc.). The incompleteness of these data creates a limitation and the results should be interpreted carefully in this direction.

CONCLUSION

It shouldn't be forgotten that myoclonic seizures may occur in the form of sudden, jerky, involuntary movements. Symptoms of myoclonic events can sometimes be misdiagnosed as tonic-clonic seizures, dyskinesia, and sudden falls that result from hypotension. Antipsychotic drug usage has to be kept in mind in a patient with myoclonic states besides primary central nervous system pathologies.

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