

# Acute Dystonia Caused by Clomipramine: a Case Report

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## ABSTRACT

### Acute dystonia caused by clomipramine: a case report

Drug-induced acute dystonia is a movement disorder that occurs most often with neuroleptics, though there are many drugs in its etiology. The exact mechanism of antidepressant-associated extrapyramidal side effects (EPS) is not known. However, hypotheses including inhibition of dopaminergic function in the nigrostriatal pathway, impaired balance between dopaminergic, serotonergic, noradrenergic or cholinergic activity, and serotonergic inhibition of dopaminergic functions in the striatum leading to extrapyramidal side effects have been suggested. The number of cases with acute dystonia during clomipramine use is low. We wish to draw attention to this rare side effect of clomipramine and to contribute to the literature by presenting a case of acute dystonia on the 5<sup>th</sup> day of clomipramine treatment in a 19-year-old male patient.

**Keywords:** Antidepressants, clomipramine, dystonia

## ÖZ

### Klomipraminin neden olduğu akut distoni: Bir olgu sunumu

İlaç kullanımıyla ortaya çıkan akut distoni, etiyolojisinde birçok ilacın olduğu ama en sık nöroleptiklerle ortaya çıkan bir hareket bozukluğudur. Antidepresan kullanımı ile ortaya çıkan ekstrapiramidal yan etkilerin oluş mekanizması tam olarak bilinmemektedir. Ancak, dopaminergik fonksiyonların nigrostriatal yolda inhibe edilmesi, dopaminergik, serotonergik, noradrenergik veya kolinerjik aktivite arasındaki dengenin bozulması, striatumda dopaminergik fonksiyonların serotonin tarafından inhibisyonunun ekstrapiramidal yan etkilere yol açması ileri sürülen hipotezlerdendir. Literatürde klomipramin kullanımı sonrasında akut distoni gelişen vaka sayısı nadirdir. Biz 19 yaşındaki erkek hastamızda klomipramin kullanımının 5. gününde ortaya çıkan akut distoni gelişimi olgusunu sunarak klomipraminin nadir görülen bu yan etkisine dikkat çekmek ve literatüre katkıda bulunmak istedik.

**Anahtar kelimeler:** Antidepresan, klomipramin, distoni



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## INTRODUCTION

Dystonia is defined as an acute tonic muscle spasm, often affecting tongue, jaw, eyes, and neck, sometimes seizing the entire body. It sets on suddenly and is uncomfortably painful for the patient. The condition is more frequently seen in young persons. The spasms in the neck can present as opisthotonus or torticollis. Spasms in the ocular muscles can turn the eyes sidewise or upwards (oculogyric crisis). The tongue may be enlarged and extend outwards in a laryngospasm or jaw dystonia (1). While the physiopathological mechanisms have not yet been fully explained, it is assumed that an imbalance

between the striatal dopaminergic and cholinergic systems due to a sudden and extreme blockage of the dopamine receptor is responsible for this presentation. Drug-induced dystonia mostly originates from substances blocking dopamine activation, especially those blocking dopamine D2 receptors in the caudate, putamen, and globus pallidus (2,3). Other drugs causing dystonia are those changing the balance between serotonin and dopamine or dopamine and acetylcholine in the basal ganglia (4-6). Clomipramine is a tertiary amine tricyclic antidepressant with specific D2 antagonist activity and strong serotonin reuptake inhibitor properties. The most important side effects reported are vertigo, hypokinesia, headache,

irritability, constipation, increased appetite, nausea, dryness of the mouth, increased perspiration, and cardiac side effects. Other potential side effects are convulsions and an increased disposition for convulsions (7). By contrast, our paper presents a patient developing dystonia with clomipramine.

## CASE

A 19-year-old single male university student had seven months previously began developing complaints of shortness of breath, a sensation of chest pressure, palpitation, and pain in back and arms. With these complaints, he presented at the policlinics for pulmonary medicine and cardiology. The complaints recurred in paroxysmal form once every 15-20 days. Around 4 months previously, fainting and paresthesia in the limbs developed in addition to the earlier complaints. The patient presented at the neurology policlinic; however, no neurological findings were determined. As the complaints did not recede, one month previously the patient attended the psychiatric policlinic, receiving a diagnosis of anxiety disorder and conversion disorder. He was prescribed sertraline 50mg and alprazolam 0.5mg. As the complaints did not resolve within one month, the patient was admitted to the psychiatry ward with complaints of distress, palpitation, breathing difficulties, syncope, and paresthesia in hands and feet. He was diagnosed with conversion disorder and anxiety disorder according to DSM-5 (8). The patient was started on clomipramine 50mg/day and alprazolam 1mg/day. On the 3<sup>rd</sup> day of hospitalization, the clomipramine dose was increased to 75mg/day. However, on the 5<sup>th</sup> day of hospitalization, spasms in the neck and inward contractions and flexions in arms and legs set in. Hemogram and blood biochemistry (Na, K, Ca, Mg, urea, creatinine, etc.) had been normal during hospitalization. An emergency reassessment did not result in any pathological findings. A neurological consultation was requested to investigate the potential presence of an organic disease. The results of the neurological examination did not suggest any organic etiology. Thus it was decided to reassess the patient

with MR imaging, cerebral venography, and EEG under hypnosis. Considering that the patient might have developed an acute drug-related dystonia, clomipramine treatment was discontinued and biperiden 5mg IM was administered. Within one hour, a reduction in the patient's complaints of spasms was observed. The side effects were assessed according to Naranjo's Adverse Drug Reaction Probability Scale, which measures to what degree an adverse drug effect is likely to be drug-related rather than caused by other factors (9). Our patient scored a total of 8 points on the scale, which corresponds to a highly probable relation. The patient's treatment was set to tablet escitalopram 10mg/day, tablet biperiden 4mg/day, and tablet diazepam 10mg/day. Results of MR imaging, cerebral venography, and EEG under hypnosis as well as a neurological reassessment found no pathologies, which suggests that the spasms may have been drug-related. As the spastic complaints decreased, the biperiden dose was reduced to 2mg/day and the complaints resolved after one week of progressive reduction. Given that the general complaints also decreased quickly, it was planned to phase out biperiden. On the 12<sup>th</sup> day of hospitalization, the patient was discharged with a medication plan of biperiden 2mg/day and diazepam 5mg/day. During the follow up examination it was seen that the patients had no contractions, and the treatment rearranged.

## DISCUSSION

Acute dystonia can be caused by a number of triggers, the most commonly seen cause being a drug-related side effect. In the literature, the following drug classes are reported as triggers for acute dystonia: neuroleptics, antiemetics, tricyclic antidepressants, monoamine oxidase inhibitors (MAO inhibitors), selective serotonin reuptake inhibitors (SSRIs), serotonin antagonist and reuptake inhibitors (SARIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), antiepileptic drugs (phenytoin, carbamazepine, diazepam), and antimigraine drugs (sumatriptan) (4-6,10-13). For typical antipsychotics, a 2.3 to 60% risk to develop acute dystonia has been reported (14),

while for atypical antipsychotics, a risk between 2 and 3% has been found (15). Antidepressants are also known to cause dystonia, though not at the level of antipsychotics. A case series reported that the SSRI group entailed a higher risk than other antidepressants (3,16). It is known that an increased blood level of SSRIs like paroxetine and fluvoxamine can increase the risk of acute dystonia (17). Gill et al. (3) reviewed studies examining extrapyramidal side effects related to cyclic antidepressants, determining an occurrence of akathisia in 26% of tricyclic antidepressant (TCA) use cases, dystonia in 17% of cases, reversible dyskinesia in 52%, and neuroleptic malignant syndrome in 4% of cases.

TCAs block serotonin and noradrenaline reuptake pumps and, to a lesser degree, dopamine reuptake pumps as well. Some TCAs (such as clomipramine) are more powerful inhibitors of serotonin reuptake pumps; others are more selective for noradrenaline than for serotonin (desipramine, maprotiline, nortriptyline, protriptyline). However, most TCAs block serotonin as well as noradrenaline reuptake (18). While older sources generally state that extrapyramidal side effects in TCA use are rarely seen, studies and case reports published in recent years suggest that extrapyramidal side effects in TCA use are frequent but often go undiagnosed because of insufficient recognition (5). The first case reports describing antidepressant-related extrapyramidal side effects appeared in the 1950s. In 1959, Foster and Lancaster (19) presented a number of cases describing coarse tremor as a result of imipramine use. In the mentioned review article on TCA-related extrapyramidal side effects, it was determined that these effects were not frequently seen and not related with age but rather dose-dependent (3). A study made in 2002 showed that extrapyramidal side effects with the use of TCAs were dose-dependent and resolved with a reduction of the drug dose or its discontinuation (5). These side effects were reported to be related with advanced age, female sex, cytochrome P2D6 (CYP2D6)-inhibiting drugs, and the presence of D2 receptor polymorphism (4). As far as we could see, there are only a small number of reports about incidents with clomipramine use in the literature, like one case with clomipramine (20) and one with a joint use of haloperidol and clomipramine (21).

Ninety percent of acute dystonias occur within the first 3 days after drug use (1). In our case, involuntary spasms and flexions in hands and feet and neck spasms began after a short time, around five days after starting clomipramine. When the treatment of acute dystonia is started early, response is usually quick (12,22). Our patient was given 5mg biperiden IM. His complaints of spasms decreased within one hour. IM injection of anticholinergic drugs resolves symptoms within a few minutes, and repeat injections are usually not required. In oral treatment with anticholinergic drugs, it is important to continue for a period between 48 hours and 7 days to prevent recurrence of symptoms (22). In our case, after a single dose of 5mg biperiden IM and a subsequent therapy with 4mg/day biperiden orally the patient's complaints of spasms progressively decreased over the course of one week, and he was discharged with a reduced dose of biperiden (2mg) with recommended follow-up examination one week later.

TCAs are a group of antidepressants frequently used in the treatment of a number of psychiatric diseases. By presenting a case with acute dystonia, a rarely seen side effect of these drugs, we want to draw the clinicians' attention to this TCA side effect and contribute to the literature.

| Contribution Categories |                                   | Author Initials          |
|-------------------------|-----------------------------------|--------------------------|
| Category 1              | Concept/Design                    | S.B.                     |
|                         | Literature review                 | S.B., M.F.T.             |
|                         | Data analysis/Interpretation      | S.B., M.F.T.             |
|                         | Case follow-up (if applicable)    | S.K., M.A.               |
| Category 2              | Drafting manuscript               | M.F.T., S.B.             |
|                         | Critical revision of manuscript   | S.K., M.A.               |
| Category 3              | Final approval and accountability | S.B., M.F.T., S.K., M.A. |
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