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CASE REPORT

Treatment of tardive dystonia due to risperidone use with single-dose botulinum toxin

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ABSTRACT

Late-onset dystonia occurs after long-term antipsychotic treatment or after discontinuation of treatment. Being young, male gender, mental retardation, and mood disorder are risk factors. By considering the dystonic complaints and psychotic symptoms of the patient who had a diagnosis of schizoaffective disorder and had risperidone 8 mg/day tablet use for 3 months, it was planned to continue treatment with clozapine. When the dystonic complaints did not improve, botulinum toxin was applied and recovery was achieved. In most cases, botulinum toxin can provide a dramatic improvement in the treatment of tardive dystonia, which is very difficult to treat and causes significant loss of functionality and poor quality of life. For this reason, botulinum toxin application should come to mind in the treatment of tardive dystonia.

Keywords: Botulinum toxin, risperidone, tardive dystonia

INTRODUCTION

Late dystonia (LD) is one of the dystonic symptoms that occur following long-term antipsychotic treatment or after discontinuation of treatment. It can be seen in the form of involuntary, fast, or slow abnormal movements in the arms and legs, choreoathetosis-like wiggles, and throws in the neck and body. If it is not very severe, it can be stopped voluntarily for a short time (1). LD, which develops more rapidly than tardive dyskinesia, is painful, can be focal, segmental, or generalized. It often begins in the cranial and cervical regions (2).

Retrocollis and torticollis are most common in the neck (1). LD, which tends to spread more rapidly at younger ages, is classified as a variant of tardive dyskinesia. Although its pathophysiology is not fully known, it is focused on changes in the cholinergic system (2).

LD is a chronic disorder, but spontaneous recovery can also be seen. Anticholinergic agents or dopamine-depleting drugs such as reserpine and tetrabenazine can be used in the treatment of LD. Agents in these two groups are reported to be effective in 50% of patients with LD. Clonazepam and clozapine are the other agents reported to be effective in the treatment of LD. Also, deutetrabenazine and valbenazine, which have a role in the treatment of chorea, tics, and tardive dyskinesia, might be used in patients with dystonia, particularly those with tardive dystonia. Deutetrabenazine and valbenazine seem to have a better pharmacologic and side effect profile than

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tetrabenazine (3). Botulinum toxin injection can be applied especially in focal LD cases that do not respond to medical treatment (2).

In this case report, our aim is to draw attention to the characteristics, management, and treatment of LD due to risperidone use and to demonstrate the therapeutic effects of only single-dose botulinum toxin injection. Informed consent was obtained from the patient and his family for the case presentation and publication.

CASE

The patient was 22 years old, single, secondary school graduate, unemployed, exempt from military service, living with his family. He was brought to the emergency service by his older brother with complaints of running away from home, irritability, talking to himself, and suspiciousness. He was taking olanzapine 10 mg/day, risperidone 1 mg/day, sodium valproate 500 mg/day, and biperiden tb. 2 mg/day. He was admitted to the service. Before the hospitalization, he broke the windows at his home and tore his clothes. He also described difficulty in sleeping for 2 weeks prior to admission. He said that he felt "very depressed" and heard male voices criticizing him. He thought that people were jealous of him because of being handsome. He said that God invited him to the wedding in Istanbul.

When the patient's father was interviewed, it was learned that his complaints had started 3 years ago. At that time, he had been very aggressive, he had talked to the mirror, he had not communicated with people. According to his medical records, he had been hospitalized due to schizoaffective disorder. After using risperidone 8 mg/day for 3 months, contractions in his neck and stiffness in his arm had started for 1 year.

The patient did not have any comorbid medical disease. He did not use alcohol, substance, or cigarette. There was not any psychiatric disease identified in the family. During the psychiatric examination, he was conscious and oriented. His self-care had decreased, and his speaking volume and speed had increased. His affect was inappropriate, and his mood was dysphoric. His associations were loose. He had grandiose, reference, persecution delusions, and auditory hallucinations. He had impaired reasoning. He had no insight. He had at least a 2-week period of psychosis without prominent mood symptoms, and full mood disorder episodes have been present for the majority of the illness. With the help of these symptoms, the patient's diagnosis of schizoaffective disorder was made.

Figure 1. Torticollis was remarkably observable before botulinum toxin administration.

Schizophrenia, bipolar disorder, and psychotic depression were ruled out.

The effect of torticollis on daily functionality was remarkable (Fig. 1). Major pathology was not detected in routine examinations. Sodium valproate 1000 mg/day and quetiapine 100 mg/day (he took quetiapine if he had insomnia) were started on the patient with a preliminary diagnosis of schizoaffective disorder. Clozapine 25 mg/day was added to the treatment, and the dose was increased up to 400 mg/day. Clozapine 400 mg/day, sodium valproate 1000 mg/day, and quetiapine 100 mg/day (if necessary) were used for 22 days before botulinum toxin administration.

The diagnosis of cervical dystonia was confirmed by neurology, and botulinum toxin administration was planned. Before the application, the Abnormal Involuntary Movements Scale (AIMS) was administered to the patient, and he scored 22 points. The AIMS, which was performed 1 week after botulinum toxin administration, was evaluated as 10 points. It was

observed that the cervical dystonic contractions of the patient also decreased clinically.

During clinical follow-up, regression of symptoms of his delusions and hallucinations was observed. The serum valproate level was 60 µg/mL during hospitalization, and sodium valproate was increased to 1250 mg/day. The patient was discharged with sodium valproate 1250 mg/day, clozapine 400 mg/day, and quetiapine 100 mg/day after 33 days of treatment.

The patient came to our hospital for regular outpatient controls after discharge. During his outpatient controls, he was taking his medicines regularly. However, he did not come to his outpatient control before hospitalization. After 5 months, the patient was hospitalized for the second time due to treatment refusal and exacerbation of his psychotic symptoms for 10 days. He was irritable and talking to himself. He was suspicious of his family. He was telling that he hated his family. He was exhibiting a negative attitude. Olanzapine 20 mg/day, clozapine 25 mg/day, sodium valproate 500 mg/day were started. Olanzapine was tapered off gradually and discontinued. Amisulpride 400 mg/g was added to the treatment of the patient who did not show sufficient improvement by taking clozapine 450 mg/day. Amisulpride was discontinued when dystonic contractions restarted in the patient's neck. This treatment did not change the metabolic parameters and weight of the patient. Daily vital monitoring (blood pressure, pulse, and fever) was made. He did not have a cardiac problem because of drugs.

Electroconvulsive therapy (ECT) was initiated for the patient due to persistent persecution delusions and homicidal ideas. The patient used clozapine 400 mg/day and quetiapine 200 mg/day (if necessary) during ECT. The patient, whose complaints regressed after 6 ECT sessions, was discharged with clozapine 400 mg/day and quetiapine 200 mg/day (if necessary). Valproate was discontinued before ECT, and it was planned to add valproate to the treatment during outpatient controls. The AIMS, which was applied both at the time of admission and at the time of discharge, was evaluated as 1 point.

DISCUSSION

Acute dystonic reactions, conversion disorder, Wilson's disease, primary dystonia, and dystonia due to other drugs should be excluded in the differential diagnosis of LD. Clinically, it should be distinguished from dystonia caused by infections, metabolic diseases, or structural lesions of the brain. LD happens involuntarily and cannot be prevented by the patient. In this respect, imitation should be distinguished from mannerism and tic (4). In our case, the diagnosis of LD was made as a result of the exclusion of these diagnoses.

Risperidone binds to 5-HTA2A, 5-HT2C, D2, and H2 receptors with high affinity and to D1 with low affinity (5). Because of pharmacological action of risperidone in the dopamine–serotonin relationship, it causes reduced dopamine blockage in striatal dopaminergic neurons and fewer extrapyramidal symptoms (EPS) are seen compared to typical antipsychotics. However, it is known that there is a risk of developing EPS and tardive dyskinesia during risperidone treatment. Risperidone-induced LD cases have been reported in the literature (6,7). After treatment with risperidone 2–4 mg/day, EPS was not observed. EPS emerged with risperidone 5–8 mg/day. Risperidone can cause EPS in a dose-dependent way, and this risk increases with doses beyond 6 mg/day (8).

In a study evaluating the efficacy of second-generation antipsychotics for the treatment of LD, which is known to be very difficult to recover, risperidone was found to be effective in 47% of cases, but it was reported to be less effective than other second-generation antipsychotics (clozapine, quetiapine, aripiprazole, olanzapine, ziprasidone, and amisulpride) (9). On the contrary, by considering our case with LD triggered by the use of risperidone, it was thought that personal differences determined this risk.

In a study, it was reported that tardive dyskinesia and LD were observed in 35% of patients using risperidone, amisulpride, olanzapine, aripiprazole, ziprasidone, and clozapine. It has been found that tardive dyskinesia is mostly around the mouth tongue, tardive dystonia is mostly in the form of torticollis, and the time between the start of treatment and the observation of movement disorder symptoms is 15 months for tardive dyskinesia and 43 months for LD (10). In our case, LD in the form of torticollis was observed on the neck after using risperidone 8 mg/day for 3 months. Although the average onset time for LD is reported as 43 months in the literature (10), our case shows that LD symptoms can begin after 3 months of use.

LD diagnosis is made according to four criteria; presence of chronic dystonia, exposure to chronic antipsychotics during dystonia, negative test results to rule out other causes of dystonia, and absence of a family history of dystonia. Greene (11) reported that a diagnosis of LD is possible after 3–6 months of exposure

to antipsychotics. Unlike acute dystonia, a previous history of dystonia is not considered a risk factor for LD (11). Our case also meets these four criteria. It was observed that our patient had had dystonia lasting for 1 year after using risperidone 8 mg/day for 3 months, and there was no history of dystonia in his family or himself.

According to the studies, the hypodopaminergic state in the nigrostriatal dopaminergic pathway and its relationship with the serotonergic system are thought to play a role in the development of LD. While tardive dystonia responds to anticholinergics in some patients, dopamine antagonists improve symptoms in others (6).

Antipsychotic treatment should be discontinued, if possible. Anticholinergics can be used for the treatment of LD. It has been reported that LD caused by pimozide and thioridazine was successfully treated with benztropine in one case (12). If there is no response to anticholinergics, botulinum toxin injection, tetrabenazine, or baclofen can be considered as an alternative in focal dystonia (12,13). Although clozapine is a good option for the prevention and treatment of LD, it has been reported that the most effective treatment is botulinum toxin injection, but there may be cases that do not respond to botulinum toxin treatment (13). The paralytic effect of botulinum toxin subsides over a period of 2–3 months (14). Also, deep brain stimulation of the globus pallidus internus is a safe, effective long-term LD treatment (15), and 33%–90% improvement of AIMS score was observed after up to 7 years (16). In our patient, clozapine treatment was started, but there was not enough improvement, and botulinum toxin was applied to the cervical region and it was planned to be repeated every 3 months if necessary. After the botulinum toxin injection, 40% improvement was detected in the first week. After 5 months, botulinum toxin was not repeated as planned. However, 100% improvement was detected.

According to one case, the development of dystonia after 2 years of olanzapine 5 mg daily in an older person with Alzheimer's dementia was observed. After diphenhydramine treatment, the dystonia resolved. However, the patient became delirious. Clozapine was not a favorable alternative because of the need for laboratory monitoring. In our case, there was no improvement before botulinum toxin injection (17).

Risk factors for LD can be listed as follows: being young, male gender, mental retardation, and mood disorder (2). When LD first developed, it seemed that our patient met most of the risk factors, as he was 20 years old, male, and his clinic was accompanied by a mood disorder.

Our case draws attention to the onset of LD symptoms in a short period of 3 months after using risperidone 8 mg /day. Although it had lasted for a year, almost complete recovery of LD with single-dose botulinum toxin injection was observed. LD can develop even in a very short time, especially in young, male patients in the affective spectrum. Botulinum toxin injection can be applied especially in focal LD cases that do not respond to medical treatment (2). Although clozapine 400 mg/day was given to our patient, there was no effect on LD. However, it responded quickly to single-dose botulinum toxin injection. Our patient was young and LD affected the quality of his life. It should be kept in mind that this side effect, which is known to be very difficult to treat, can be successfully treated with single-dose botulinum toxin in some cases. Botulinum toxin should be used more frequently during the treatment of LD.

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