

Tardive Dystonia Related with Aripiprazole

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Tardive dystonia is characterized by sustained, generally slow involuntary twisting movements. It is estimated to occur at a frequency of 1% to 4% among patients who are taking an antipsychotic agent. Unlike the first generation antipsychotics, the second generation antipsychotics are less likely to cause neuroleptic-induced movement disorder. For aripiprazole, only a few cases have been reported for tardive dystonia. We present a young male, who developed a severe tardive dystonia after taking aripiprazole for 5 years. The patient was admitted to the treatment of both his dystonic and psychotic symptoms. Olanzapine was administered instead of aripiprazole and while his psychotic symptoms improved, the dystonic symptoms were continued. Therefore, olanzapine was switched to clozapine while augmenting with benzodiazepine, anti-cholinergic, and ginkgo biloba to control his tardive dystonia. After 2 weeks of treatment, the dystonic movement decreased remarkably.

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Key Words Aripiprazole, Clozapine, Tardive dystonia, Schizoaffective disorder, Ginkgo biloba.

INTRODUCTION

With the introduction of the second generation antipsychotics, the incidence of neuroleptic-induced movement disorders has been decreased dramatically.¹ Tardive dystonia (TD), a late side effect of the antipsychotics, was also reduced. Although TD has been far less reported than tardive dyskinesia, it is frequently more disabling than dyskinesia.¹⁻³ Whereas complete remission of tardive dyskinesia had been reported in a case series,⁴ no complete remission occurred in a series of 29 TD patients.⁵

TD is a persistent syndrome of sustained muscle contraction that produces twisting and repetitive movements or abnormal postures.⁶ It usually involves the head and neck, producing torticollis, retrocollis, or anterocollis, but sometimes TD involves back muscles, resulting opisthotonus and gait disturbances.²

Aripiprazole is known to have a low risk of extrapyramidal symptoms, because of its partial agonistic activity at dopa-

mine receptor D₂ and serotonin receptor 5HT_{1A}.⁷ However, aripiprazole was reported to be associated with tardive dyskinesia.⁸⁻¹⁰ Furthermore, several cases of TD have also been reported with the use of aripiprazole.¹¹⁻¹⁴ Herein, we report a rare case of TD related with aripiprazole in a patient with schizoaffective disorder.

CASE

A 28-year-old male admitted to the department of psychiatry, Uijeongbu St. Mary's Hospital, Catholic University of Korea for torticollis and exacerbated psychotic symptoms of persecutory delusion and auditory hallucination. He was taking aripiprazole from 5 years ago due to his schizoaffective disorder, and the dose was increased from 10 mg/day to 20 mg/day 3 years ago. Half year later, his psychotic symptoms improved, but he began to complain about dystonia of his neck towards right side and also dystonic symptom on the left arm including abduction. His torticollis improved slightly by increasing benzodiazepine (lorazepam to 3 mg/day) and anticholinergic (bentropine to 3 mg/day) while reducing the aripiprazole dose, but the movement disorder was not fully diminished and worsening of the psychotic symptoms occurred.

After admission, aripiprazole was switched to olanzapine and the dosage was titrated up to 20 mg/day on the 7th hospital day. Lorazepam and bentropine were both increased to 4 mg/day. To further mitigate the dystonic symptoms, aman-

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tadine 200 mg was also added. Whereas the psychotic symptoms improved, his torticollis and involuntary abduction of the left arm showed only limited response. Upon thorough physical and neurological examinations, he did not demonstrate any other dyskinesic or dystonic movements. The magnetic resonance imaging of the brain revealed no abnormality that could be associated with his dystonic symptoms. In addition, there was no familial history of movement disorders.

After 2 weeks of applying olanzapine, it was switched to clozapine in order to improve the dystonia. Clozapine was slowly built up to 300 mg/day with the 1 mg/day of lorazepam and 3 mg/day of benztropine. While the dystonic symptom improved mildly without worsening of psychotic symptoms, aspiration pneumonia and confused mental status suddenly occurred at his 28th hospital day. The patient had to be transferred to the pulmonology department and treated with intravenous antibiotics for 2 weeks. During that period, all of the psychotropics including the clozapine were stopped and the dystonic symptoms were greatly aggravated. After the improvement of the aspiration pneumonia and the delirium, he was re-transferred to psychiatric department. Clozapine was carefully reapplied and benztropine was readministered. Diazepam and ginkgo biloba, an anti-oxidant, were given to additionally relieve TD. After 2 weeks of treatment regimen composed of clozapine 200 mg/day, valproic acid 1000 mg/day, benztropine 1 mg/day, diazepam 30 mg/day, and ginkgo biloba 240 mg/day, the dystonic movement decreased remarkably and the patient was discharged at his 56th hospital day.

DISCUSSION

The patients exhibited torticollis after taking aripiprazole for 5 years, and it was improved after administering clozapine, diazepam, benztropine and ginkgo biloba. Aripiprazole has been associated with low risks for weight gain, metabolic disturbances and hyperprolactinemia, but it has been related with dose-dependent extrapyramidal symptoms.¹⁵ Moreover, in several studies for aripiprazole use in mood disorder, the risk for akathisia was significantly higher than placebo.¹⁶

TD has been understood in the similar pathophysiology of tardive dyskinesia, antipsychotics having a causative role with dopamine hypersensitivity.^{17,18} Still, they differ in several areas: different phenomenological manifestations (torticollis -displayed in our case), different risk factor (young and male predominance -also correlating to our case), and different reactions to anti-cholinergics which can improve tardive dystonia but may exacerbate tardive dyskinesia.¹⁹

TD can be related with severe life-threatening complications such as aspiration pneumonia due to laryngeal dystonia.¹⁴ In this case, there is also a possibility that the aspiration

pneumonia was induced by TD since the dystonic symptoms involved his neck and as he had no other specific risk factors for aspiration. Therefore an extra caution should be taken when a patient with dystonic symptoms shows signs of aspiration such as cough, fever shortness of breath, dysphagia and etc.

Aripiprazole has been known as dopamine partial agonist, but it has high affinity for D₂ receptors with weak affinity for D₁ receptors, and this receptor profile can lead to an imbalance between D₁- and D₂-mediated striatal outputs.^{12,17} As a result, chronic use of aripiprazole may potentially cause TD as well as tardive dyskinesia. On the contrary, there were also case reports of tardive symptoms being improved by aripiprazole for both TD^{20,21} and tardive dyskinesia.^{22,23} Therefore, not only the antipsychotic agent but also the individual factors may play a role in the pathogenesis of TD.

While chronic neuroleptic usage results in high D₂ receptor blockade, lower occupancy for D₁ receptors may lead to sensitization of the D₁-mediated striatal output, which in turn leads to abnormal movement.¹⁷ In a prior meta-analysis, clozapine showed lower D₂ receptor occupancy (61.7%) than other atypical antipsychotics (82.9–96.5%) except for quetiapine (49.1%).²⁴ Compared to typical antipsychotics, clozapine has relatively higher D₁ receptor occupancy and this may contribute to the restoration of the D₁ and D₂ imbalance.^{14,17} Worsening of TD had been observed in our case with the discontinuation of clozapine, suggesting breach of partially restored D₁-D₂ balance. Clozapine was stopped temporally in the treatment course due to the concerns of clozapine-induced sialorrhea exacerbating the aspiration pneumonia. The authors speculate that the improvement of TD that occurred following the re-introduction of clozapine owes to the restored D₁ and D₂ imbalance by blockage of over-sensitized D₁-mediated striatal output. As in our case, there was also a report of aripiprazole-induced TD resolved by clozapine previously.²⁵

Once developed, TD usually persists. The conventional approaches to control TD symptoms include administration of benzodiazepine, anticholinergic, dopaminergic or dopamine-depleting agents (amantadine or tetrabenazine). According to a recent evidence-based guideline for tardive syndromes, clonazepam and ginkgo biloba were suggested for tardive syndromes (both level B).²⁶ In the same review, the level of evidence for amantadine was lower (level C). Yet, there was another double blinded randomized control trial that demonstrated a positive result,²⁷ but not included in the review.²⁸ Although the evidence was limited for TD, we additionally prescribed amantadine as our case was regarded potentially life threatening due to aspiration pneumonia in association with TD. If refractory, botulinum toxin injection, electroconvulsive therapy, and pallidal deep brain stimulation can also be considered as a treatment modality. In this case, patient's

dystonic symptoms were successfully controlled with clozapine 200 mg, diazepam 30 mg and ginkgo biloba 240 mg for 2 weeks.

In conclusion, although it is not frequent, aripiprazole may cause tardive dystonia. Therefore, a careful monitoring is advised when prescribing aripiprazole in order to detect TD early and to prevent accompanying complications.

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