Successful Treatment of Tardive Diaphragmatic Flutter in an Elderly Man with Aripiprazole☆

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SUMMARY

Tardive dyskinesia (TD) is a severe adverse effect induced by prolonged treatment with antipsychotics. The development of TD is usually associated with advanced age, female sex, prior extrapyramidal adverse effects, and a longer duration or an intermittent course of antipsychotic treatment. Older age, however, is the most robust risk factor for TD. Tardive diaphragmatic flutter is an uncommon form of TD and may lead to great distress in the patient’s life. No effective treatment advice for tardive diaphragmatic flutter has been suggested. We herein report the case of a 65-year-old male with bipolar disorder who suffered from tardive diaphragmatic flutter associated with the long-term usage of risperidone. The diaphragmatic flutter remitted for 2 years under the monotherapy with aripiprazole. Potential mechanisms, such as the dopamine stabilization in aripiprazole, are discussed.

KEYWORDS:
Aripiprazole, clozapine, elderly, tardive diaphragmatic flutter, tardive dyskinesia

1. Introduction

Focal uncontrolled writhing abdominal movement is not common and only a few case reports were found in the literature. Diaphragmatic flutter is one type of such involuntary movement. It can be paroxysmal or continuous, and the terms “belly dancer syndrome” and “Leeuwenhoek’s disease” were coined to describe it. The clinical manifestations of diaphragmatic flutter are heterogeneous, including shortness of breath, inspiratory stridor, fatigue, epigastric pulsations, chest pain and abdominal wall pain. The rhythmic movements usually disappear during sleep and increase with respiratory maneuvers (e.g., deep inspiration). The symptom may be restricted to the diaphragm but frequently involves the accessory respiratory muscles, such as the scalenes and intercostals. The term “respiratory myoclonus” is therefore also suggested. The diagnosis of respiratory myoclonus is based mainly on the clinical presentation, chest fluoroscopy, and electromyographic exam.

2. Case report

A 65-year-old male, diagnosed with bipolar disorder and alcohol use disorder at 20, was admitted to the psychiatric ward in June 2008 due to progressive abdominal dyskinesia for 5 months. He had referred rhythmic involuntary movements episodically over the right upper quadrant abdomen, with tightness and respiratory difficulty. The duration and frequency of dyskinetic episodes increased gradually and progressed to swallowing dyskinesia, episodic neck jerks with head nodding, hand tremor, lip pursing, tongue protruding and squirming. The abnormal involuntary movement scale (AIMS) score was 18 at admission.

During the period from January 2006 to May 2008, his bipolar symptoms and drinking problems remitted under risperidone 3 mg/day and oxcarbazepine 600 mg/day. In January 2008, he first developed the intermittent abdominal involuntary movement. He thereafter had a feeling of tight throat, hoarseness, and shortness of breath. The movement symptoms appeared nearly every day and each episode lasted for 1 hour. The episode would happen spontaneously and mainly while he was in sitting or lying positions. The movement-related pain also affected his daily life. The evolution of symptoms during an episode usually began with dyskinesia over the upper quadrant a few minutes after lying down. The intensity then increased slowly while in the same position, followed by abdominal tightness, subjective respiratory difficulties, and hyperventilation. Finally, the elevated anxiety would make the patient stand up to end the symptoms.

At admission, we gave him biperiden 2.5 mg by intramuscular injection, but the abdominal dyskinesia got worse 15 minutes later. Haloperidol 2.5 mg was then injected intramuscularly, and the...
chronic use of antipsychotics; (ii) damage to the striatal...increasing age. Our case also had simultaneous orolinguo-

older age. The antipsychotic-induced tardive symptom may...movements was related to the prolonged use of risperidone and...decreased from 18 at admission to 5 at discharge in July 2008. The tardive diaphragmatic...improved partially in severity and frequency. The AIMS score...one week later, the overall abdominal dyskinesia had...improvement of 5-hydroxytryptamine 1A and D2 receptors, and antagonism of 5-hydroxytryptamine 2A receptors. Some have suggested...that D2 partial antagonism may normalize D2-receptor function in patients with TD. Aripiprazole causes “functionally selective” activation of D3 (and possibly D2)-dopamine receptors,

and thus acts like a dopamine system stabilizer. Aripiprazole exhibits activity as a dopamine agonist in relation to the hypo-
dopaminergic condition, while acting like a dopamine antagonist when at the hyperdopaminergic status. The evidence shows that the use of aripiprazole causes little D2 receptor up-regulation. Therefore it may be used to prevent or treat the TD.

In summary, our report provides a possible way to manage diaphragmatic flutter and TD. We demonstrated a successful switch from clozapine to aripiprazole to treat an elderly patient’s mental disorders and involuntary movements.

References
dyskinesia improved thereafter. The results of laboratory testing, including complete blood count, biochemistry, thyroid profile, vitamin B12, folate levels, and metabolic and immunological panel were within normal limits. Electromyographic exam over the abdominal muscles showed regular bursts of muscle contraction of about 1 Hz, mainly from the diaphragm, which spread to the abdominal wall. The diaphragm tremor was impressed. Study of the nerve conduction velocity demonstrated possible right phrenic nerve palsy. The results of cerebral and spinal cord magnetic resonance imaging, electrocardiography, abdominal echography and abdominal computed tomography scan were unremarkable.

We first switched risperidone 3 mg/day to quetiapine 200 mg/day to attempt to manage the tardive diaphragmatic flutter. The dyskinesia persisted, however, and quetiapine was switched to clozapine gradually 11 days later, and oscarbazepine was discontinued. One week later, the overall abdominal dyskinesia had improved partially in severity and frequency. The AIMS score decreased from 18 at admission to 5 at discharge in July 2008. During the follow-up at outpatient clinic, monotherapy with clozapine 100 mg/day continued and adverse effects developed, including hyper-somnolence, sialorrhea, fatigue, and body weight gain. The tardive diaphragmatic flutter worsened 4 months after discharge, and the AIMS score was 7. Due to the intolerable side effects of clozapine and worse control of tardive diaphragmatic flutter, aripiprazole was chosen to treat the patient’s bipolar disorder and tardive dyskinesia. In December 2008, we switched clozapine to aripiprazole in a period of 4 weeks and the dosage of aripiprazole was titrated to 10 mg. The AIMS score became 3 after using aripiprazole for 4 weeks. No involuntary limb movement and respiratory difficulty were found at this time. In March 2009, monotherapy with aripiprazole 15 mg/day was established. In the subsequent 2 years, the patient adhered to the monotherapy without diaphragmatic flutter and his bipolar disorder was in remission.

3. Discussion

Typical risk factors associated with the development of tardive dyskinesia (TD) include older age, pre-existing movement or neurodegenerative disorders, female sex, the presence of affective illness, and antipsychotic exposure for longer than 6 months. Older age, however, is the most robust risk factor for TD. Over the age of 65 years, the prevalence of TD is five to six times greater than in younger patients. In this case, the emergence of the abnormal movement was related to the prolonged use of risperidone and older age. The antipsychotic-induced tardive symptom may become permanent and irreversible, and is less likely to resolve with increasing age. Our case also had simultaneous orolinguo-buccal stereotypes, indicating that the patient’s diaphragmatic flutter was a variant of TD. It was therefore aggravated by the use of an anticholinergic drug, biperiden, and ameliorated with the antidopaminergic agent haloperidol.

The pathophysiological mechanisms of TD include: (i) supersensitivity of the nigrostriatal dopamine D2 receptors under the chronic use of antipsychotics; (ii) damage to the striatal γ-amino butyric acid interneurons; and (iii) damage to the striatal cholinergic interneurons. These mechanisms, however, cannot explain why only a proportion of patients develop TD during exposure to the similar antipsychotic. In this case, differential responses to the therapies with anticholinergic and antidopaminergic agents implied that the abdominal dyskinesia might be associated with higher dopaminergic tone. The supersensitive dopaminergic function would become worse due to the reduced acetylcholine status. Despite there being no consensus in the treatment of TD, the common approach is to withdraw the offending antipsychotic if possible. In the present report, the tardive diaphragmatic flutter was eventually treated by switching from clozapine to aripiprazole. It showed that aripiprazole was beneficial and improved diaphragmatic flutter and tardive dyskinesia. Aripiprazole, a dihydroniquinolinone agent, has been reported to treat cases with TD and improved the involuntary symptoms through its unique mechanism of action. The effect might arise from the partial agonism of 5-hydroxytryptamine 1A and D2 receptors, and antagonism of 5-hydroxytryptamine 2A receptors. Some have suggested that D2 partial antagonism may normalize D2-receptor function in patients with TD. Aripiprazole causes “functionally selective” activation of D3 (and possibly D2)-dopamine receptors, and thus acts like a dopamine system stabilizer. Aripiprazole exhibits activity as a dopamine agonist in relation to the hypodopaminergic condition, while acting like a dopamine antagonist when at the hyperdopaminergic status. The evidence shows that the use of aripiprazole causes little D2 receptor up-regulation. Therefore it may be used to prevent or treat the TD.

In summary, our report provides a possible way to manage diaphragmatic flutter and TD. We demonstrated a successful switch from clozapine to aripiprazole to treat an elderly patient’s mental disorders and involuntary movements.