

Clozapine and Aripiprazole-Induced Stuttering: A Case Report of Turner Syndrome with Schizophrenia

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ABSTRACT:

Clozapine and aripiprazole-induced stuttering: a case report of turner syndrome with schizophrenia

Turner Syndrome (TS) is the most common chromosomal anomaly in women. Its psychiatric manifestations have not been clearly defined. Occurrence of schizophrenia is higher in patients with TS than in the normal population. The literature has reported instances associating stuttering as a side effect of antipsychotic drugs, particularly clozapine-induced stuttering. We found only one case report describing aripiprazole-associated stuttering. In the present case report, we present a female patient with TS-diagnosed schizophrenia who had been treated with aripiprazole because she developed stuttering during treatment with clozapine and then developed dose-dependent stuttering with aripiprazole.

Keywords: clozapine, aripiprazole, stuttering, turner syndrome

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INTRODUCTION

Turner Syndrome (TS), which is among the most prevalent chromosomal anomalies in women, is caused by X-monosomy, 45X/46XX-mosaicism, and other X-chromosomal structural abnormalities. TS is characterized by dwarfism, gonadal dysgenesis, and various external malformations, such as short stature, webbed neck, broad chest, cubitus valgus, and dysmorphic face¹.

Stuttering is defined as a disturbance in the normal fluency and pattern of speech in which a person tends to repeat sounds and syllables or whose speech includes sound prolongations and broken words². Two types of stuttering have been described: iatrogenic and developmental. Iatrogenic stuttering is caused by drug side effects generally in patients who have a developmental disorder or have a family history of stuttering. Stuttering associated with antipsychotics is a rarely encountered side effect. A number of studies have

indicated that stuttering may occur as side effects of antipsychotic drugs, such as chlorpromazine, trifluoperazine, fluphenazine, levomepromazine, olanzapine, risperidone, and clozapine^{3,4}. We found only one case report for aripiprazole-associated stuttering⁵.

With regard to the etiology of iatrogenic stuttering, one study's PET images showed that hypo-metabolism in the striatum was generated by high dopamine levels⁶. Another study determined that high numbers of dopamine (D2) receptors located in a section of basal ganglia could be one of the underlying genetic characteristics. This study also observed that dopamine activity in stutterers was found to be 50–200% higher than that in persons who were not stutterers³. Some studies have suggested that dopamine/ acetylcholine balance may be related to the suppression and exacerbation of stuttering in susceptible persons, like seen in other extrapyramidal side effects. The neuroleptics reportedly suppress and aggravate stuttering⁷. Clozapine, which is defined as a prototype of atypical antipsychotics, is an antagonist of D2 and serotonin 2A (5-HT_{2A}) receptors, and it is the first antipsychotic partial agonist of 5-HT_{1A} receptors⁸. Aripiprazole is a partial agonist of pre- and post-synaptic dopamine D2 receptors. This drug has an intense affinity for the D3 receptor and moderate affinity for the D4 receptor. It is also a partial agonist of serotonin 5-HT_{1A} and 5-HT_{2C} receptors and an antagonist of the 5-HT_{2A} receptor⁹. We found no information to confirm whether these characteristics are included in the etiology of stuttering.

In the present case report, we report a female patient with TS and schizophrenia who had been treated with aripiprazole because she developed stuttering during treatment with clozapine and then developed dose-dependent stuttering with aripiprazole.

CASE

Miss B, a 21-year-old, single woman who had been diagnosed with TS when she was 6 years old was admitted to our clinic because of auditory

hallucinations. Three months earlier, when presented at our clinic with symptoms of fear, laughing and talking to herself, not communicating with her family, not eating, not sleeping, and shouting, we prescribed risperidone 1 mg/day. However, she stopped taking risperidone because of side effects and was hospitalized because of continuing symptoms. After she was discharged from the hospital, we prescribed olanzapine 15 mg and biperiden 4 mg which improved her sleep problems but auditory hallucinations continued and she experienced rigidity. We increased olanzapine to 20 mg and biperiden to 6 mg, but her rigidity continued. During her follow-up examination 15 days later, she showed an increase in rigidity, and we decided to admit her to the hospital. A mental status examination at admission revealed sub-depressive mood, auditory hallucinations, visual hallucinations, persecutory delusion, social withdrawal, and avolition. Her orientation was intact for time, place, person, and situation. She scored a total of 60 points on the Positive and Negative Syndrome Scale (PANSS) with the following subsection scores: positive symptoms = 14, negative symptoms = 18, and general psychopathology = 28. Her intelligence level was 80 (in the average range). We detected no alcohol or substance abuse and no use of any medication. Her family history revealed schizophrenia in her mother's uncle. Her physical examination revealed short stature, mane neck, and cubitus valgus (symptoms associated with TS), and she had no breast development. According to her mother, Miss B began to talk when she was 3 years old, and she experienced no speech problems and stuttering before the present clozapine treatment. She relied on a hearing aid because of an 80% hearing loss in both ears. Her neurological examination was normal as were her EEG and cranial MRI examinations.

Miss B's symptoms of auditory hallucination, visual hallucination, persecutory delusion, social withdrawal, avolition, and impairment in functionality were prevalent longer than six months. This episode of symptoms was not due to the direct physiological effects of a substance or a

general medical condition. According to the Diagnostic and Statistical Manual of Mental Disorder, fourth edition (DSM IV), Miss B's diagnosis (2) was schizophrenia. After we began clozapine (which we increased to 100 mg), decreased and stopped the olanzapine, and stopped the biperidene, her auditory hallucinations and rigidity subsided, social communication improved, and she returned to her pre-morbid level of functionality.

Her PANSS score at discharge was a total of 40 points with the following subsection scores: positive symptoms = 9, negative symptoms = 11, and general psychopathology = 20. During her 8th week follow-up examination, we noted stuttering and referred her to otolaryngology and neurology specialists for evaluation. Since the evaluation revealed no organic cause for the stuttering, we suspected it might be associated with the clozapine and began to decrease its dosage, and we also added aripiprazole 5 mg to the treatment. We noted that her stuttering disappeared but auditory hallucinations recurred when aripiprazole was increased from 5 to 7.5 mg. We noted also that the stuttering returned with the 7.5 mg aripiprazole only to disappear when we decreased to 5 mg.

DISCUSSION

The psychiatric manifestations observed in TS have not been clearly defined. Moderate mental retardation, attention and memory problems, anxiety, visuospatial processing problems, deficits in fear recognition, impairments in social cognition, and motor functioning problems are among the manifestations observed in patients with TS¹⁰. In addition, the occurrence of schizophrenia is higher in these patients than in the normal population. The authors hypothesized an "inherent genetic vulnerability" to psychotic syndromes in TS, triggered by stressful situations¹¹.

Stuttering usually improves with reduction in clozapine dosage. Two studies showed that stuttering generally occurred with increases in dosage in case reports where stuttering had been associated with clozapine^{12,13}. In the present study,

stuttering occurred when a 100 mg/day fixed dosage of clozapine was continued. In some case reports; stuttering was detected in patients taking clozapine and patients had experienced dystonia and dyskinesia¹⁴ and rigidity, an extrapyramidal side effect similar to the rigidity experienced by our patient.

In the majority of the patients who developed stuttering due to clozapine, abnormalities were detected in EEG, or an epileptic attack episode was reported^{12,13,15}. After our patient's EEG was normal and she had no epileptic episode stuttering had developed because of clozapine, we decreased the clozapine dosage. Because the stuttering continued, we added aripiprazole to the treatment. The stuttering stopped but after an increase at aripiprazole dosage, the stuttering returned. Stuttering also occurred following an increase in aripiprazole dosage from 15 mg to 30 mg in another case study of aripiprazole-associated stuttering⁵. However, stuttering appeared to be associated with a lower dosage of aripiprazole in our case report. In one case report, a 38-year-old man was diagnosed with stuttering when he was 4 years old. However, he had no psychiatric disorder and had been treated with aripiprazole¹⁶.

The dysfluency problem may be a manifestation of akathisia in some patients who developed drug-induced stuttering¹⁷. Stuttering with phenothiazines has been reported as well but was paired with desipramine in one case and lithium in the other. To treat two patients who had developed akathisia and stuttering, researchers administered propranolol. Propranolol alleviated the stuttering and akathisia in these two patients, but these symptoms returned when propranolol was interrupted. Following retreatment with propranolol, the symptoms were again alleviated. Other reports indicated that akathisia and stuttering may be closely related¹⁸. It is well-known that aripiprazole is associated with akathisia¹². In the present case report, we detected no akathisia in our patient who experienced drug-induced stuttering.

We found no information in the literature on stuttering development after antipsychotic usage in

patients with TS. The present case report is unique from other case reports on antipsychotics because our patient is the first (to our knowledge) to be diagnosed with both schizophrenia and TS and to develop stuttering after treatment with aripiprazole.

In conclusion, although stuttering caused by antipsychotic medication is a rare side effect, the possible mechanisms causing the occurrence of stuttering in this situation are not known. Etiologic studies are required to clarify this matter.

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