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Letter to Editor

Sertraline-Induced Stuttering in an Adolescent with Autism Spectrum Disorder

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ABSTRACT

There is also evidence that stuttering is caused by an adverse reaction to various medications. Antiepileptic drugs, antidepressants, antipsychotics, and methylphenidate have all been linked to drug-induced stuttering. The patient was 13 years old (male) and was diagnosed with autism spectrum disorder, attention deficit hyperactivity disorder, and mild mental retardation. The patient had language development and was able to form sentences of 4-5 words. Atomoxetine 50 mg/day and aripiprazole 15 mg/day treatment was used. Sertraline 50 mg/day treatment was initiated because of repeated questioning, order-symmetry compulsions and repetitive behaviors. Approximately one month after the initiation of sertraline treatment, the patient came for a follow-up visit and it was found that the compulsions of the patient had decreased, but one week after sertraline treatment, it was learned that the patient started to have word blocks, prolongation of words and repetitions during speech. No pathology was found in the examination, hemogram and biochemistry tests, brain MRI and EEG tests. After sertraline treatment was discontinued, the stuttering of the patient gradually decreased and improved within 2 weeks. Both serotonergic and dopaminergic effects of sertraline as well as autism spectrum disorder (white matter anomalies) are thought to contribute to sertraline-induced stuttering.

Keywords: stuttering, sertraline, autism, adolescent, antidepressant

Dear Editor,

Stuttering is defined as a disruption of the normal flow and timing of speech characterized by the repetition of sounds, syllables, or words, the prolongation of sounds, and interruptions in speech known as blocks [1]. Stuttering is usually classified into developmental and acquired stuttering [1]. Acquired stuttering can occur later in life, often as a side effect of certain neurological conditions, medications, or psychological trauma in some cases where stuttering first occurs [2]. There is also evidence that stuttering is caused by an adverse reaction to various medications [1]. Antiepileptic drugs, antidepressants, antipsychotics, and methylphenidate have all been linked to drug-induced stuttering [1, 3]. As a result of drug-induced stuttering, the time between initiation of the causative drug and the onset of stuttering, or between reducing the dosage of the drug and the relief of stuttering, is short. This suggests that drug-induced stuttering may be caused by neurochemical changes in the brain [4]. In

this case report, a 13-year-old patient with autism who started stuttering after sertraline treatment was presented. There are few cases in the relevant literature. To the author's knowledge, this is the first patient who developed sertraline-induced stuttering during adolescence and was diagnosed with autism.

Patient Information

The patient was 13 years old (male) and diagnosed with autism spectrum disorder, attention deficit hyperactivity disorder, and mild mental retardation. The patient also had complained irritability, behavioral problems, and harm to others and objects. The patient was attending individual special education, and no chronic medical disease or speech problems such as stuttering-articulation disorder, were found in the patient's medical history. The patient had language development and could form sentences of 4-5 words. The patient's father had a diagnosis of obsessive-compulsive disorder and there was no family history of stuttering. Atomoxetine and aripiprazole were started as drug treatment and gradually increased to 50 mg/day and 15 mg/day, respectively. The patient was followed up regularly in our outpatient clinic for about 5 months. Sertraline 50 mg/day treatment was initiated because of repeated questioning, order-symmetry compulsions, and repetitive behaviors. Approximately one month after sertraline treatment, the patient came for a follow-up visit and it was found that the patient's compulsions had decreased. However, one week after sertraline treatment, it was learned that the patient started having word blocks, word prolongation and repetitions during speech. It was learned that these complaints occurred almost every day, often during speech. Stuttering was considered in the patient who was also observed with these complaints during the interview. Clonic stuttering was considered in the case and no movement disorder accompanying stuttering was observed or detected. In the evaluation, it was not found that there was no sibling birth, moving, loss, or any stressful situation or change at school or home before stuttering**.** He was referred to Ear-Nose-Throat and Pediatric Neurology physicians for organic etiology. No pathology was found in the examination, hemogram and biochemistry tests, brain MRI and EEG tests. Stuttering was thought to be due to sertraline and sertraline treatment was discontinued. After sertraline treatment was discontinued, the patient's stuttering gradually decreased and improved within 2 weeks. The patient was then started on fluoxetine treatment and no stuttering-like side effects were observed in follow-up. The patient received fluoxetine treatment for about 6 weeks, but his symptoms persisted, and fluoxetine treatment was discontinued and escitalopram treatment was started. With escitalopram 20 mg/day treatment, obsessive-compulsive symptoms decreased, and no stuttering-like side effect was observed in follow-up. Written and informed consent was obtained from the patient's parents.

DISCUSSION

Stuttering has not been sufficiently characterized in terms of its etiology and pathogenesis. A number of factors contribute to stuttering, including differences in brain anatomy, particularly in the auditory and motor cortex and the substantia nigra. In addition, there are differences in dopaminergic function and regulation [5]. Medications can treat stuttering, but they can also cause stuttering as a side effect. For example, although there are promising results with atypical antipsychotic drugs such as risperidone and olanzapine in the treatment of stuttering [6], there are also case reports of induced (antipsychotic drugs) by drugs used in the treatment of stuttering [7].

Signals are sent from the basal ganglia to the thalamus to stimulate the cerebral cortex to initiate desired movements. This is based on motor, sensory, and cognitive input. Signals received by the input nuclei of the basal ganglia are transmitted through two pathways: a) directly and b) indirect. The direct pathway stimulates the cerebral cortex and activates the correct motor program, while the indirect pathway inhibits the cerebral cortex and all competing motor programs. Dystonia, dyskinesia, and stuttering can all be caused by disruption of these two pathways' coordination and cross-talk. Therefore, both increased and decreased dopamine neurotransmission in the striatum can disrupt the balance between direct and indirect pathways, leading to stuttering [4]. This suggests that an imbalance in dopamine levels involved in speech coordination may trigger various speech disorders such as stuttering [4]. Currently, in the etiology of drug-induced stuttering, drugs that potentiate the dopaminergic system or affect neurotransmission in the central nervous system are particularly emphasized [3]. However, it has been stated that in addition to increased dopamine levels, decreased GABA, the anticholinergic properties of drugs and changes in serotonin levels may also contribute to the development of drug-induced stuttering [1]. In many reports, selective serotonin reuptake inhibitors (SSRIs) have also been implicated, suggesting serotonergic mechanisms may be involved [8]. In a review of the literature, the drugs most associated with drug-induced stuttering were methylphenidate, topiramate and olanzapine, respectively [3]. However, there are some reported cases of stuttering associated with antidepressant drugs and the drugs with the highest relative risk ratio among

antidepressants are venlafaxine, citalopram and mirtazapine [3]. Sertraline is an antidepressant in the class of SSRIs with inhibitory effects primarily on presynaptic serotonin reuptake [9]. Several different mechanisms associated with sertraline-induced stuttering may be involved in this effect. Firstly, sertraline-induced stuttering may also be triggered by serotonergic inhibition of dopaminergic neurons. The ventral tegmental area contains these neurons' cell bodies. As a result, sertraline and other selective serotonin reuptake inhibitors cause stuttering by inhibiting dopamine pathways in the nigrostriatum [4]. SSRIs also cause more akathisia than other antidepressants, and akathisia is common in drug-related stuttering [8]. This supports that a similar mechanism may contribute to sertraline-induced stuttering [8]. It is thought that this mechanism may be related to stuttering by disrupting the dopamine balance involved in speech coordination. Second, sertraline also has minimal effects on dopamine levels and research has shown that it has greater dopaminergic activity than other drugs in the same SSRI category [10]. Sertraline increases dopamine levels in the striatum and nucleus accumbens by inhibiting dopamine transporters and this effect is higher than other antidepressants [10]. Considering that stuttering symptoms worsen with dopamine agonists and improve with dopamine antagonists [6], this effect of sertraline causing dopamine elevation may be related to stuttering and may be thought to cause stuttering by contributing to dopamine elevation, which is the most emphasized in the etiology of stuttering.

However, an alternative mechanism may also be involved in sertraline-induced stuttering in children with ASD. White matter (WM) abnormalities may also affect the connectivity between different areas of the brain involved in speech's motor control. Myelinated axons, which make up WM tracts, transmit signals between different brain regions, so they can coordinate their communication and functions [11]. Stuttering may result from the disruption of signal transmission between different areas of the brain that control speech and motor control by an agent that disrupts the normal activity of one or more neurotransmitters in the white matter [4]. Furthermore, abnormal functional connections in autism spectrum disorder have been shown to be defects in the integrity of white matter tracts, which include a collection of myelinated axon bundles that allow fast and efficient neuronal communication between different brain areas [12]. In patients with an underlying disorder, drugs that disrupt the normal balance of neurotransmitters in white matter may exacerbate white matter dysfunction.

In addition to sertraline, our patient was also receiving atomoxetine and aripiprazole treatment. Aripiprazole is a partial agonist of 5HT-1A and dopamine D2 receptors and antagonist of 5HT-2A receptors in the central nervous system. Aripiprazole and other antipsychotic drugs may cause extrapyramidal side effects and stuttering by disrupting the balanced and coordinated activity of dopamine pathways. In addition, increased dopamine neurotransmission in the prefrontal cortex as a result of serotonergic effects of aripiprazole may also lead to stuttering. Atomoxetine acts by increasing noradrenaline and dopamine concentrations in the prefrontal cortex. Rather than dopaminergic effects of atomoxetine, it increases activity in the subthalamic nucleus and consequently decreases the excitatory activity of the thalamocortical pathway [4]. This may cause stuttering as a result of inappropriate activation of orofacial muscles. In our case, the use of multiple drugs with activity on the dopaminergic pathway may have caused stuttering by affecting the dopamine balance.

In the present case, stuttering developed after initiation of sertraline treatment and gradually decreased after discontinuation of the drug. In 55.8% of cases with drug-induced stuttering attacks, the drug thought to cause stuttering was discontinued and stuttering was significantly reduced or completely recovered in all cases after discontinuation of the drug [4]. This finding is consistent with the improvement in stuttering after discontinuation of sertraline in the present case. This case report presents possible evidence for sertraline-induced stuttering and its etiology. Both the serotonergic and dopaminergic effects of sertraline as well as autism spectrum disorder (white matter anomalies) are thought to contribute to sertraline-induced stuttering. There are a limited number of studies on sertraline-induced stuttering in children and adolescents. Children in this age group with underlying disorders such as autism spectrum disorder are more susceptible to side effects, and should be monitored more closely for side effects such as stuttering.

Yours Sincerely,

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Conflicts of interest: The author declare not to have any conflict of interest.

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Ethics Approval: Ethics committee approval was not obtained because it was a case report. Written and verbal consent was obtained from the parents of the patient.

Author Contributions

Conceptualization: M.Ö.; Data acquisition: M.Ö.; Supervision: M. Ö.; Writing—original draft: M.Ö.; Writing—review & editing: M.Ö.

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