Aripiprazole in ADHD with Tic Disorder and in ADHD with Tourette Disorder: Two Case Reports

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We report the effect of aripiprazole in attention deficit hyperactivity disorder (ADHD) with tic disorder and in ADHD with Tourette disorder, which are very common in clinical settings, but are not supported by theory. We administered 15 mg of the dopamine partial agonist aripiprazole, which led to the obvious improvement of symptoms in ADHD patients with tic disorder or Tourette disorder.

KEY WORDS: Aripiprazole; Attention deficit hyperactivity disorder (ADHD); Tic disorder; Tourette disorder.

INTRODUCTION

Chronic tic disorders and Tourette disorder are common neuropsychiatric disorders characterized by involuntary motor and vocal tics. Chronic tic disorders and Tourette disorder affect 1–3% of school children. Attention deficit hyperactivity disorder (ADHD) is a childhood-onset neuropsychiatric disorder with an estimated prevalence of 4–7.6% in Korean children. ADHD is a clinically heterogenous disorder characterized by hyperactivity, impulsiveness, and inattention. ADHD and tic disorders commonly co-occur. According to a community-based study, the reported prevalence rates of ADHD and tic symptoms in children aged 6–12 years were 4.3%; in this study, 27% of children with ADHD had tic disorders, while 55% of children with tic disorders also had ADHD. Similar results have been reported for Tourette disorder, with an estimated 50–80% of patients also having ADHD.

ADHD accompanied by Tourette disorder makes medical treatment for patients more difficult than for either disorder alone. This is due to the traditional use of antipsychotics to treat Tourette disorder and of dopamine reuptake blockers to treat ADHD. Tics in particular can be exacerbated when dopamine reuptake blockers are administered.

Aripiprazole (Abilify) is a novel atypical antipsychotic agent with dopamine partial agonistic characteristics. The U.S. Food and Drug Administration (FDA) has approved its use for the treatment of schizophrenia and bipolar disorder.

ADHD is caused by decreased levels of dopamine in the frontal lobe, whereas Tourette disorder is caused by increased dopamine in the basal ganglia. Antidopaminergic drugs often lead to an improvement in the symptoms caused by Tourette disorder. It is of interest, therefore, that a few case reports indicate the effectiveness of a partial dopamine agonist, aripiprazole, in treating Tourette disorder.

Here, we report two cases of ADHD with Tourette syndrome, which is very common in clinical settings, but is not supported by theory. We administered a dopamine partial agonist, aripiprazole, which led to an obvious improvement in attention and tic symptoms in ADHD patients with Tourette disorder or tic disorder.

CASE

Case 1

An 8-year-old boy presented with complex motor tics and vocal symptoms, including coprolalia and hyperactivity, leading to a diagnosis of Tourette disorder and ADHD. Diagnostic criteria were met for ADHD combined type using both the DSM-IV and the K-SADS-PL-K (Kiddie-Schedule for Affective Disorders and Schi-
zaphrenia, Present and Lifetime, Korean Version) in interviews by child psychiatrists.\textsuperscript{11} A score of 17 on the Abbreviated Conners Parent-Teacher rating Scale-Revised (ACRS) was noted. Omission/Commission on the visual TOVA was 71/91 (converted score) and Omission/Commission on the auditory TOVA was 52/81.\textsuperscript{14,15} The score was 83 for hyperactivity on the Korean Personality Inventory for Children (K-PIC) scale.\textsuperscript{16} No obvious symptoms of depression or anxiety were found. On the Child Behavior Check List, Korean version (CBCL) score was 68 and the aggressiveness scale score was 89.\textsuperscript{17} A score of 27 on the Kovac Children’s Depression Inventory (CDI) indicated a mild depressed status.\textsuperscript{18}

The patient had been on 1 mg of risperidone and OROS methylphenidate 18 mg for 2 months with little improvement of the symptoms of ADHD or the tic symptoms. We then increased the dose of risperidone to 2 mg for 2 months, but the tic symptoms showed little improvement and the symptoms of ADHD still caused severe impairment. Because the tic symptoms remained problematic, this was our main clinical focus. With the consent of the parents, we stopped risperidone treatment and began administering 15 mg of aripiprazole.

While on risperidone, the Yale Global Tic Severity Scale score was 18 for vocal tics and 16 for motor tics.\textsuperscript{19} The patient was found to be in moderate distress with a severe overall impression. Self-reported Tic Disorder scores were 17 for the vocal tic and 11 for the motor tic.

Two weeks after beginning the 15 mg of aripiprazole regimen, the score decreased to 15 for the vocal tics and 14 for the motor tics. However, the patient showed no change in the level of symptoms of tic disorder or overall impression. His self-reported scores for vocal and motor tics were 9 and 10, respectively. According to the parents’ observations, the patient’s aggressiveness was diminished and peer relationships were improved after administration of aripiprazole. The patient scored 108/104 for Omission/Commission on the visual TOVA, and 70/86 on the auditory TOVA, representing an exacerbation of ADHD. We conducted a study of sleep patterns using the Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI). Sleep time was somewhat shorter, but there was no change in the quality of sleep.

In the interview and examination 1 month following the administration of 15 mg of aripiprazole, the severity level for the vocal and motor tics had decreased to 9, with a minor level of suffering with an overall impression of slight impairment. The self-reported score was 2 for vocal tic symptoms and 5 for motor tics. Although the patient still exhibited temper tantrums at school, his overall school life showed improvement. The homeroom teacher also commented that the patient’s study ability had improved and that he could pay attention in class for much longer periods. No worsening of ADHD symptoms was observed after 6 months of aripiprazole administration.

**Case 2**

An 11-year-old boy presented to the outpatient clinic with ADHD. Diagnostic criteria for ADHD combined type and chronic vocal tic disorder were documented by a child psychiatrist using both the DSM-IV and K-SADS-PL-K. A score of 22 on the ACRS was noted. Omission/Commission on the visual TOVA was 48/75 (converted score) and Omission/Commission on the auditory TOVA was 52/81. On the K-PIC scale, the score was 80 for anxiety, 69 for hyperactivity, and 76 for depression. The CBCL scale score was 64 for attention problems. No obsessive-compulsive disorder comorbidity was found. A CDI Score of 9 was noted.

In the early stage of treatment, the patient was prescribed methylphenidate. Tic symptoms were noticed after 1 year of pharmacotherapy. Only a simple vocal tic, but no motor tic, was reported. The patient had experienced a stressful school situation at that time. With the consent of the parents, we decided to start drug treatment and administered 15 mg of aripiprazole.

On the Yale Tic Disorders Test,\textsuperscript{20} the severity score was 14 for vocal tics, 0 for motor tics, a medium distress level for tic disorder, and an overall severe impression. The Self-reported Tic Disorder scores were 3 for vocal tic and 0 for motor tic.

To control symptoms, 15 mg of aripiprazole was given for 4 weeks. Thereafter, we conducted an interview with the patient and his guardians. The results of the Yale Tic Disorders Test showed a severity of symptoms score of 10 for vocal tics, 0 for motor tics, and very mild distress levels for tic severity. The overall impression status was changed to mild. The Self-reported Tic Disorder score showed no change, with a score of 3 for vocal tic and 0 for motor tic. Omission/Commission on the visual TOVA was 62/77 (converted score) and Omission/Commission on the auditory TOVA was 64/59. Because of concerns about the sedating effects of atypical antipsychotics, sleeping patterns were tested using PSQI and ISI; no significant difference was observed before aripiprazole administration.

**DISCUSSION**

The treatment of psychiatric comorbid conditions such as when treating ADHD symptoms often poses a problem in the medical treatment of Tourette syndrome. In the past,
There have been minor concerns that the administration of methylphenidate may have exacerbated tic symptoms in cases of ADHD accompanied by tic disorders.21,22) By similar reasoning, the administration of antidopaminergic agents for Tourette disorder with ADHD symptoms might also lead to the worsening of ADHD symptoms.23) However, a recent study of ADHD in children with Tourette syndrome suggested that the administration of methylphenidate did not exacerbate tic disorders.24) A study involving 136 children who received methylphenidate for 16 weeks revealed that the worsening of tic symptoms was due to receiving both MPH (20%) and placebo (22%). The study also demonstrated that MPH therapy does not exacerbate existing tic disorders: neither the dose of the stimulant nor the duration of treatment showed statistical significance.24)

It is currently recommended that psychostimulants be used to treat ADHD with simple tic, but not to treat Tourette disorder with ADHD symptoms.25) A partial agonist, aripiprazole has an antagonistic action on the D2 receptor. It decreases the levels of dopamine in the mesolimbic pathway, which accounts for its lower activity in the nigrostriatal, tuberoinfundibular pathway. Aripiprazole acts to increase D2 receptors by increasing levels of dopamine in the mesocortical pathway, although its mechanism in vivo is not yet well known.26)

A shortcoming in this case II was not observing the effect of aripiprazole for a sufficient period of time. The symptoms of tic disorder generally show various changes with a typical waxing and waning of tic severity. Therefore, a thorough observation of the symptoms of tic disorder for a lengthy period is essential for an accurate evaluation.

Singer27) suggested that a tonicphasic model of dopamine release represents a unifying hypothesis of Tourette disorder: a reduction in tonic (basal) dopamine, thought to be due to an overactive dopamine transporter system, could result in a system with high concentrations of dopamine receptors and an increased phasic release of dopamine. Singer27) proposed that Tourette disorder is associated with excess nigrostriatal dopaminergic activity, either via hypersensitive dopamine receptors, dopamine hyperinnervation, or abnormal presynaptic terminal function.

These cases showed an exacerbation of ADHD symptoms in both Tourette disorder with ADHD and ADHD with tic disorder within 1 month of the administration of aripiprazole. However, no worsening of ADHD symptoms was observed after 6 months of aripiprazole administration in the first case. In addition, the parents reported improvements in aggression and irritability after 1 month of aripiprazole administration.

We hypothesize that the exacerbation of ADHD symptoms at the early stage of the administration of aripiprazole is due to the relief of excessive nigrostriatal dopaminergic activity and the decline in prefrontal dopaminergic activity produced by the drug. We suggest that thereafter, aripiprazole, which is a partial dopamine agonist, may induce a prefrontal hypodopaminergic state for ADHD, as well as decrease the subcortical hyperdopaminergic state for Tourette disorder. Cortico-striato-thalamo-cortical pathways have been recently suggested in the pathophysiology of Tourette disorder, which assumes their close relationship with the prefrontal dopamine abnormality of ADHD.28,29) This hypothesis agrees with the clinical impressions in the case studies examined here. However, a larger sample size is needed to control for confounding factors. The limitations of these case reports restrict the ability to generalize our findings.

The patient with both Tourette disorder and ADHD showed a temporary worsening of ADHD symptoms after treatment with 15 mg of aripiprazole, but exhibited some improvement in the tic disorder and aggressiveness. As time passed, some improvement was also observed in ADHD symptoms. Although our observations indicate that aripiprazole might be effective in the treatment of Tourette disorder with ADHD or in tic disorders with ADHD, further well-designed placebo-controlled trials are clearly needed to establish the efficacy of aripiprazole in these disorders.

REFERENCES