

# Acute Dystonia due to Aripiprazole Use in Two Children with Autism Spectrum Disorder in the First Five Years of Life

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## SUMMARY

Autism spectrum disorders (ASD) are neuropsychiatric disorders characterized by impairment in social interactions, in verbal and non-verbal communication, and restricted and stereotyped patterns of interest and behavior within the first 3 years of life.

Pharmacologic interventions may be needed for the treatment of temper tantrums, aggression, hyperactivity, and stereotypes in children with ASD. The approval of aripiprazole by the United States Food and Drug Administration (USFDA) for the treatment of temper tantrums in children and adolescents with ASD has gained increased interest for the use in these patients. Aripiprazole is a partial agonist for the dopamine D2, serotonin 5-HT1A receptors, and an antagonist for 5HT2A receptors. Because aripiprazole is a partial agonist, it has been speculated that aripiprazole has a protective effect for extrapyramidal side effects, movement disorders, and metabolic problems. But the increased use in children and adolescents is associated with an increase in the number of case reports related with such problems. Nevertheless, our review of the literature uncovered limited data regarding the association between acute dystonia and aripiprazole use in ASD children under five years of age is. In this paper, we present two cases of autistic spectrum disorder children with ages under 5 years that developed acute dystonia taking aripiprazole.

**Key words:** Dystonia, aripiprazole, child

## INTRODUCTION

Antipsychotic drugs are known to be effective in the treatment of temper tantrums, aggressive behaviors, hyperactivity, stereotypes and self destructive behaviors in the children and adolescent with ASD (Chavez et al. 2007, Stigler et al. 2003). USFDA has approved the use of risperidone and aripiprazole for the treatment of temper tantrums in ASD children and adolescents. Aripiprazole, a new antipsychotic drug, is a partial agonist for the presynaptic and postsynaptic dopamine D2 receptor, strong agonist for D3 receptor (Burris et al. 2002, Deleon et al. 2004), and serotonin 5-HT1A receptor partial agonist, 5-HT2C receptor agonist and 5-HT2A receptor antagonist (Jordan et al. 2002). Acute dystonic reaction

is an extrapyramidal system (EPS) side effect that usually arises first with antipsychotic use and presents dramatically. Dystonia causes involuntary, continuous, or spasmodic muscle spasms (Annagür and Tamam 2008). Aripiprazole has been reported to cause less EPS side effects, movement disorders, and metabolic disorders in comparison to other antipsychotic drugs due to its partial agonistic property (Saha et al. 2001, Yeung et al. 2001).

Dystonia presented in two of our cases under 5 years of age due to low dose aripiprazole treatment. The importance of this case report is the limited case reports of acute dystonic reaction (ADR) with aripiprazole in children with ASD under 5 years.

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## CASES

CASE I: A 4 year old girl patient who has been followed up in our polyclinic was diagnosed with ASD by a child and adolescent psychiatrist in a university hospital. Therefore, the patient was directed to special education. Six months after the initial diagnosis, the patient was admitted to our polyclinic with complaints of hyperactivity, temper tantrums, and self destructive behaviors. Aripiprazole (0.5 mg/day) was administered to the patient based on her weight (32 kg), height (110 cm), and body mass index (26.4 kg/cm<sup>2</sup>). The aripiprazole dose was increased to 1mg/day because no significant recovery from the complaints at the 1 month follow up was observed. The symptoms were found to be ongoing at the second follow up in the second month and aripiprazole dose was increased to 2mg/day. Three days following the last follow up, the patient was referred to our emergency department unable to walk with contraction in the right leg and pulling her right leg towards her abdomen. Her physical examination revealed contraction in her right leg. The neurologic and other system examinations were found to be normal other than the findings above. The contraction in the right leg was thought to be a drug induced dystonic reaction and 2mg intramuscular biperidene treatment was administered. A near total recovery of the complaints was observed in 30 minutes. Aripiprazole was stopped and difenhidramine 37.5mg/day treatment was started. The patient was called for a follow up visit 3 days later. In the follow up visit, she was able to walk easily and right leg contraction was absent. Since no complaint was present, difenhidramine was stopped. The family did not approve any other medical treatment. The patient has been followed in our polyclinic with 3 month intervals.

CASE II: A 3.5 year old male patient was diagnosed with ASD by a child and adolescent psychiatrist in a state hospital, and directed to special education. Due to the hyperactivity, intense temper tantrums, and stereotypic behaviors, aripiprazole (0.5mg/day) was started. The boy was referred to our polyclinic by his relatives because of the lasting complaints. The aripiprazole treatment was increased to 1mg/day. In the first month follow up, the symptoms were still present; therefore, aripiprazole dose was increased to 2mg/day. Because that the complaints were partially reduced at the second month follow up control, aripiprazole was increased to 3mg/day. Two days after the last follow up visit, the patient was admitted to the emergency department with contraction in the neck and chin on the right side. The patient was unable to close his mouth and his physical examination revealed torticollis and oromandibular dystonia. This situation was thought to be drug induced dystonia and 2mg intramuscular biperidene was applied to the patient. A near total recovery of the complaints was observed in 60 minutes. Aripiprazole was stopped and difenhidramine 37.5mg/day treatment was started. The patient was evaluated in the follow up visit one week later, and no dystonia was detected and difenhidramine was stopped. The family did not accept other treatment regimen and the

patient was dropped from the follow up because he did not come to regular follow up visits.

## DISCUSSION

Early age, male gender, previous dystonia history, the first episode of the psychiatric disorder, the first usage of the antipsychotic drug, the high potency of the antipsychotic drug, and the high dose at the initial treatment have been accepted as risk factors for antipsychotic induced dystonia development (Keepers and Casey 1991). Aripiprazole may have a protective effect against EPS side effects due to its partial agonistic property. However, case reports related with these side effects have been reported due to increased use in child and adolescents (Singh et al. 2007, Goga et al. 2012, Gökçen et al. 2014, Varkula and Dale 2008). The acute dystonic reactions that have been reported in the literature are mostly in the cases who are between 10-20 years of age and the drug dose was in 5-15mg/day intervals (Singh et al. 2007, Goga et al. 2012, Gökçen et al. 2014, Varkula and Dale 2008). In two 3 year old cases, aripiprazole use by accident was reported. One case took 15mg and the other took 30mg aripiprazole causing severe EPS side effects in both of the cases (Schonberger et al. 2004, Thabet et al. 2013).

Aripiprazole dose was 2-3 mg/day in our 0-5 year age group cases. In the first case, aripiprazole was selected by considering metabolic side effects due to the patient's obesity issues. In the second case, aripiprazole was started by another child and adolescent psychiatrist who first evaluated the patient. Since the patient was on treatment in the time of referral to our polyclinic, the treatment was continued only by dosage titration. Drug side effects were assessed with Naranjo's Adverse drug reaction (ADR) probability scale. According to this scale, 9 and above points were evaluated as definite, 5-8 points probable, 1-4 points possible and 0 point was evaluated as doubtful (Naranjo et al. 1981). When we assessed our cases according to this scale, presence of previous literature reports of aripiprazole induced dystonia (1 point), development of dystonia after the use of suspected drug (2 point), recovery of the side effect after the use of specific antagonist (1 point), absence of other effect that could cause dystonia (2 point) and the approval of dystonia by an objective evidence (1 point) were obtained. This data makes us think that these side effects were highly probably aripiprazole induced.

Although 5-18 years of age effectiveness and safeness data for aripiprazole is present, literature data for the use in children smaller than 5 years of age is lacking. Because of this, case reports on open label and double blind studies are needed in this age group. Also, it should be kept in mind that EPS side effects may arise with low-dose aripiprazole use in this age group, contributing to clinical symptom severity and abnormal involuntary movements which should be checked regularly.

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