

Aripiprazole-induced Tardive Dyskinesia in 13 Years Old Girl Successfully Treated with Biperiden: A Case Report

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In the last years second-generation antipsychotics are increasingly prescribed in the pediatric population for the treatment of several psychiatric disorders. Among the long term adverse effects, extrapyramidal symptoms (EPS) are less reported compared to first-generation antipsychotics. Tardive dyskinesia (TD) is a iatrogenic rare syndrome characterized by persistent slow writhing and sudden involuntary movements mainly involving the oral-buccal-lingual area with masticatory movements. We report a young girl with mood disorders accompanied by mild intellectual disability and behavioral problems who had TD after treatment with Aripiprazole, which responded to Biperiden therapy.

KEY WORDS: Antipsychotics; Drug side effects; Tardive dyskinesia; Movement disorders; Pediatrics.

INTRODUCTION

Tardive dyskinesia (TD) is a rare syndrome characterized by persistent slow writhing and sudden involuntary movements mainly involving the oral-buccal-lingual area with masticatory movements.^{1,2)} TD is considered a iatrogenic disorder mostly associated with long-term use of first generation antipsychotics and most often observed in women and middle-old aged patients after a minimal interval of exposure of 3 months.^{1,3-5)} In the last years, it has been accepted that TD may appear relatively early in the course of treatment with dopamine receptor blocking agents (DRBAs).¹⁾ However, such extrapyramidal symptoms (EPS) are less reported in patients undertreated with second-generation antipsychotics (SGAs).⁶⁾ Aripiprazole is an atypical antipsychotic with partial dopamine D2 receptor agonist, 5HT 1A agonist and 5HT 2A antagonist properties.⁷⁾ The high occupancy of D2 receptors occurs without inducing EPS in the majority of subjects since partial agonism induces a lower functional antagonism of

D2 receptor-mediated neurotransmission, rather than full antagonists.⁸⁾ To date, few cases of TD have been reported in patients treated with aripiprazole and most of them were adults in association with other manifestations such as parkinsonism or after long-term treatment and exposure to many different drugs.^{5,9-13)} Here we present a case report of a 13-years-old girl who developed TD after a 3-weeks-treatment with aripiprazole.

CASE

A 9-years-old girl was referred, for the first time, to our unit for behaviour and mood disorders accompanied by mild intellectual disability. The patient had a history of slight delayed motor, language and social milestones. According to mother she was a difficult child to manage during infancy as she had behaviour problems. Learning difficulties and verbal speech impairment had been managing with special education programs, cognitive therapy and logotherapy. The neurological examination failed to reveal major pathological signs. A complete diagnostic work-up for intellectual disability was performed including: routine laboratory investigations, coagulation and metabolic exams that resulted to be unremarkable. Neurophysiological investigations including electroencephalography (EEG), visual evoked potential and auditory brainstem response (ABR) were normal. Karyotype was 46,XX. Array-CGH failed to show any abnormalities.

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Brain magnetic resonance imaging scan was normal. At age of 11 she showed a worsening of behavioural problems characterized by marked irritability, mood instability characterized by frequent fluctuations of mood over time, changes in eating, compulsive self-biting and obsessive thoughts, several sleep-related movement disorders included bruxism, body rolling and enuresis. She was treated with valproate and topiramate for around six months with no effect. Valproate and topiramate were discontinued while risperidone was introduced at starting dose of 0.5 mg/day and then increased to 2 mg/day, with improvement of behavioral symptoms. Nevertheless, one year later, the patient presented a worsening of mood instability and of temper outbursts (verbally and behaviorally). Thus, risperidone was gradually withdrawn and quetiapine was started at initial dose of 100 mg/day up to 300 mg/day with beneficial. One year later, due to a further relapse of psychiatric symptoms, the patient was referred to another clinical center where quetiapine was stopped and aripiprazole was started at 7.5 mg/day as initial dose. After 3 weeks, the girl displayed involuntary movements of her mouth and slurred speech. For this reason her parents abruptly suspended aripiprazole. After 2 days she was referred to our unit for the occurrence of fine and rhythmic lips movements, along the vertical axis. Also the tongue was involved with constant rhythmic dystonic contractures. The clinical examination did not reveal any other EPS.

A concomitant video-EEG recording failed to show epileptiform discharges. The patient was immediately treated with clonazepam (4 mg/day) for 3 days without efficacy. After further 3 days with antioxidants (vitamin E) supplementation, with poor results, we decided to start biperiden 2 mg/day. It induced rapid reduction and disappearance of clinical symptoms within 3 weeks.

DISCUSSION

In a recent systematic review, annual TD incidence rate in children was reported to be 0.35% with SGAs.¹⁴⁾ Although the occurrence of EPS seems to be less frequent with atypical antipsychotics, surveillance of their appearance is recommended, especially if specific risk factors such as pediatric age, female sex, affective disorder diagnosis do exist.¹⁵⁾ The incidence of EPS differs among SGAs with a major rate reported in patients treated with risperidone, to a lesser extent in those with clozapine and quetiapine.¹⁶⁾ The likelihood of developing EPS with a first-line SGA depends not only on the specific agent, but

also on the rapidity of dose escalation, the target dose, and the patient's intrinsic vulnerability to EPS.¹⁶⁾

To date, report of TD in patients treated with atypical antipsychotics is rare and, to the best of our knowledge, there are only few reported cases of TD related to aripiprazole.^{9-11,13)} All of the patients reported were adults and only in one case TD emerged after at least 2 months of aripiprazole therapy.¹³⁾ Conversely, some authors showed efficacy of aripiprazole to treat TD induced by other DRBAs.¹⁷⁻¹⁹⁾ These authors supported the use of aripiprazole according to its peculiar mechanism of action²⁰⁾ by which it exerts activity as a dopamine agonist in hypodopaminergic states, while it acts as a dopamine antagonist when dopaminergic activity is increased. In this view, it may play a role in both prevention and treatment of TD.

Our patient presented two risk factors for TD such as female sex and an affective disorder. Although the semiology of the movements was quite suggestive, her manifestations atypically started after short term aripiprazole treatment. Nevertheless, our patient received quetiapine as long term treatment before starting aripiprazole, thus, her chronic previous quetiapine-exposure could contribute to TD. TD must be distinguished from rabbit syndrome (RS). In fact, even if RS is also a iatrogenic disorder, the movements observed in RS are rapid and regular, not involve the tongue and cannot be voluntary suppressed by the patient.²¹⁾ Furthermore TD has to be distinguished from other movements involving the face and the mouth regions such as orofacial tics (e.g., Tourette's syndrome), orofacial tremors (e.g., parkinsonian tremors), orofacial dystonia (e.g., Meige syndrome) and orofacial chorea.¹⁾ Differential diagnosis is crucial to identify the appropriate treatment of TD. Bhidayasiri *et al.*²²⁾ find out three levels of evidence-based recommendations of treatment of TD, but most of the agents are not recommended for pediatric population.

Although aripiprazole and quetiapine are characterized by a relatively low incidence of EPS, the present case underlines that clinicians should screen for EPS all patients in treatment with SGAs, since the first weeks of drug exposure. According to the American Academy of Neurology guidelines²²⁾ after withdrawing aripiprazole therapy, we started clonazepam (Level B of recommendation). Since no improvements were gained, we could not prescribe another antipsychotic given the young age of the patient. After failing antioxidant supplementation, we decided to start biperiden (both Level U of recommendation). Although it is not specifically recommended in treatment of TD, efficacy of biperiden has been pre-

viously reported in a young girl with severe dyskinesia induced by phenytoin.²³⁾

In conclusion, our 13-years-old patient with TD induced by aripiprazole showed rapid and complete improvement with biperiden treatment. Although few reports in the literature support this evidence, treatment with biperiden would be considered to manage TD in paediatric population. Moreover, video-EEG reports of such patients may be useful to improve diagnostic accuracy of this rare EPS in childhood.

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