CASE REPORT

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Tardive Oculogyric Crisis Due to Aripiprazole Treatment in an Adolescent Patient Diagnosed with Bipolar Disorder

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Abstract

Antipsychotics usage in children and adolescents is becoming widespread. One of the extrapyramidal side effects associated with long-term antipsychotic drug use follow-up is an oculogyric crisis (OGC). OGC is defined as a dystonic reaction commonly observed after typical antipsychotic drug administration. However, there are rare cases which report OGC after atypical antipsychotic use. In this report, we present an adolescent with bipolar disorder who developed OGC after 2 years of aripiprazole and quetiapine use. To best of our knowledge, this case report has been the first case to present the clinical presentation of tardive OGC due to aripiprazole treatment in an adolescent patient. It is important to note that OGC might be observed in the acute phase and it might be as a result of chronic use detected during a clinical follow-up. Safety, tolerability and efficiency of aripiprazole in pediatric populations should be further analyzed in the future studies.

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INTRODUCTION

This case report aims to present the clinical course of a 16-year-old adolescent patient diagnosed with Bipolar Disorder, who had developed oculogyric crisis (OGC). OGC is identified among various extrapyramidal system (EPS) side-effects due to medication with delayed onset in case of treatment with aripiprazole + quetiapine combination. This case is different from previous cases as it has been the first adolescent case reported in the relevant literature who have developed tardive-OGC due to aripiprazole use.

CASE

Our case was a 14-year-old female adolescent patient who came to the children's psychiatry unit of our hospital as an outpatient. Initial clinical interview with the case and her family revealed that they went to another children's psychiatry clinic due to her decreased total sleeping time, increased physical violence towards others, irritability, agitation and aggressiveness. The patient was diagnosed with Bipolar Disorder. The case was admitted to the inpatient unit. She received a follow-up in the inpatient unit. The treatment of the case started with oral aripiprazole 15 mg/day combined with quetiapine 150 mg/day. The unit reported that she had clinical improvement with this regimen. The case was followed up in the inpatient unit for another month following significant symptomatic relief. After the case was discharged from the clinic, she was referred to our unit to be followed up as an outpatient with the request of the patient and her family. In her regular follow-up for 2 years, her medication regimen was the same. There was no episode experienced in this period and the patient was euthymic. At the end of 2nd year in treatment (on January 2018), the case was 16 years old. At this time, the case started to experience involuntary crossing vertical deviation and continuous upward position of her eyes. Initially, these symptoms appeared once a week and lasted for approximately 2 hours. According to the information collected from the patient, there was no history of medication intake above recommended and prescribed dosage. Neurological examination, electroencephalography and Magnetic Resonance Imaging results were normal. In this process, a thorough differential diagnostic process and Naranjo Adverse Drug Reactions Probability Scale [1] with a total score of 6-points were applied. Based on these processes and applications, the case received formal OGC diagnosis induced by aripiprazole. The patient was self-admitted to the hospital with OGC. In this period, OGC-related symptoms of the patient had decreased without any other treatment. Medication dose was reduced to 10 mg/day. As

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there was no significant clinical improvement regarding the observed side effects, aripiprazole was discontinued and the treatment regimen was applied with quetiapine alone. When the treatment was revised and replaced as 450 mg/day quetiapine, the patient had no experience of an OGC episode or any effective episode.

DISCUSSION

Aripiprazole is a third-generation atypical antipsychotic drug. The drug has a partial agonistic effect over Dopamine D2, D3 and serotonin 5HT1A receptors and antagonistic features on serotonin 5HT2A receptors. Due to this complex dual action mechanism, aripiprazole has been reported to have fewer EPS side-effect profile compared to other antipsychotic drugs [2]. Some studies showed the efficacy of aripiprazole to treat tardive dyskinesia which is an EPS side – effect, induced by other antipsychotic drugs due to this complex dual action mechanism [3,4,5].

Bildik et al. investigated the efficacy and tolerability of aripiprazole and the authors found that aripiprazole treatment was generally well tolerated. However, adverse reactions were more common in the pediatric population in general. It was observed that there was a relatively low rate of discontinuation due to adverse reactions and there were no known suicide or death cases [6]. A relevant meta-analysis conducted in 2016 has revealed that children and adolescents using aripiprazole were sensitive towards EPS side effects caused by the drug similar to the adults taking the same medication. Furthermore, it was noted that aripiprazole significantly increased the risk of developing EPS side effects compared to placebo [7]. Since our case has a relatively young age, this might be counted as a risk factor for developing tardive OGC.

There have been two reported adult cases with aripiprazole related acute onset OGC in the related literature [8,9]. However, only one adult case with tardive OGC as a form of dystonic reaction has been reported until now. This case report showed the clinical presentation of a 23-year-old male who developed OGC at 9th month of his aripiprazole monotherapy. The researchers believed that this side effect that was observed at a late phase of treatment was due to a disrupted balance between D1 and D2 mediated striatal output [10]. All of these three cases that aripiprazole related OGC have been cases of adult patients. There has been only one adolescent case with tardive OGC reported in adolescents [11], but it was induced by risperidone. No adolescent case with aripiprazole-induced tardive OGC has been reported in the related literature.

Although the exact pathophysiology of tardive dystonia remains unclear, alterations in dopaminergic and cholinergic neurotransmission have been frequently stressed, along with a discussion over the similarity to the pathophysiology of tardive dyskinesia [12]. While aripiprazole has poor D1 receptor affinity, it has a strong affinity for D2 receptors (95%) [13]. This might cause an imbalance between D1 and D2 mediated striatal output [10,14]. While chronic neuroleptic use leads to high levels of D2 receptor blockage, over time lower levels of D1 receptor occupation by the agent might cause abnormal mobilization via sensitization of D1 mediated striatal output [14]. This aforementioned condition might potentially have caused the tardive – OGC. A previous meta-analysis had reported lower levels of D2 receptor occupation with quetiapine (49.1%) and clozapine (61.7%) compared to other antipsychotics (82.9-96.5%) [15]. In our case, OGC was completely eliminated when aripiprazole was discontinued. Additionally, no further OGC episodes were observed despite increased quetiapine dosage and regular use of the drug for 1 year. This might be explained by the hypothesis of lower rates of D2 receptor occupation with quetiapine compared to aripiprazole, and the possible prevention of D1 mediated striatal output sensitization. Similar to our case, many adult cases have been reported in the literature that clozapine and quetiapine have been used as therapeutic in patients with tardive dyskinesia or dystonia due to aripiprazole which leads to lower D2 receptor occupancy rate [16-19].

Aripiprazole is metabolized in the liver with the agency of cytochrome p450 CYP3A4 and CYP2D6 enzyme systems. Renal clearance of aripiprazole is at minimum levels [20]. Our case had no history of any hepatic or renal disease. Metabolism of quetiapine occurs via the CYP3A4 enzyme system [20].Aripiprazole acting as a substrate in the same enzyme systems might have caused competitive inhibition, in turn, leading to an increase in plasma aripiprazole concentration.

Individuals treated with a stable dose of the medication throughout their adolescence might experience a temporary increase in plasma concentrations of the drug. Other possible explanations of this phenomenon might be that gonadal hormones and drugs competed for microsomal enzymatic systems of the liver [21]. Changes that occur in receptor density values according to developmental stages of an individual are commonly known. Such changes might be the rapid increase in D1 and D2 receptor density in 2 years which is followed by a tendency to decline. After 10 years of age, such decrease might be 3.2 and 2.2 for every decade, respectively [22]. Such changes observed due to adolescence as it was in our case might have also played a role in the tardive – OGC developing process. In addition to this, the effects of aripiprazole on D3 receptors as well as on 5-HT6 and 5-HT7 receptor antagonism are unknown. This further indicates that these receptors might have a possible role in the etiology of OGC.

CONCLUSIONS

Our case is the first adolescent case in the literature for tardive OGC due to aripiprazole use. It is important to note that OGC might be observed in the acute phase and it might be a result of chronic use which is detected in clinical evaluation. Safety, tolerability and efficiency of aripiprazole in pediatric populations should be further analyzed in the future studies.

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