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Letter to the Editor (Case report)

Tardive dystonic symptoms associated with aripiprazole treatment

1. Introduction

Oculogyric crisis is one of the common side-effect of anti-psychotics (Dorevitch, 1984). It is frequently recognized as acute dystonic reaction primarily involving the ocular muscles, although other movements including retrocollis, blepharospasm, contraction of the frontalis, and jaw opening may be associated as well (Owens, 1990; Sachdev, 1993).

Tardive oculogyric crisis refers to delayed onset ocular muscle dystonia in chronically antipsychotic-treated patients and usually reported as a subtype of tardive dystonia (Adityanjee et al., 1999). Most reports of tardive dystonia have been originated in cases with typical antipsychotics as well as with atypical antipsychotics such as risperidone, olanzapine, clozapine ziprasidone and aripiprazole (Dave, 1994; Dunayevich and Strakowski, 1999; Rota et al., 2007; Vercueil and Foucher, 1999; Ziegenbein et al., 2003).

Given a characteristic receptor binding profile that combines partial agonistic activity at D₂ and 5HT_{1A} receptors, aripiprazole may have benefits in the treatment of tardive syndromes (Duggal, 2003). It has been known that the risk of aripiprazole for movement disorder has been considered lower than that of other atypicals, although two case reports of tardive dystonia associated with aripiprazole have been available to date (Oommen et al., 2006; Pinninti et al., 2006).

We here present the case of a patient with mental retardation who developed a reversible tardive oculogyric crisis after treatment with aripiprazole monotherapy.

2. Case report

A 23-year-old man was brought to the Department of psychiatry Kangnam St. Mary's Hospital for increasingly aggressive and disruptive behavior, persecutory delusion and auditory hallucination. He had been diagnosed with Down syndrome and mental retardation at an early age. The persecutory delusion and hallucination had been begun since his age 20. Thus, his diagnosis was axis I: schizophrenia paranoid type, axis II: mental retardation and axis III: down syndrome by DSM-IV-TR criteria. Although the aggression began earlier in childhood, he was becoming progressively more dangerous in his community because of his increasing size and the increasingly frequent and indiscriminate nature of his assaultive behavior. He did not take any psychiatric treatment for his symptoms.

Aripiprazole was begun at 10 mg/day in our clinic and maintained. On the day 7 of the treatment, he complained mild tremor on his left hand, however this symptom was subsided by the next day. In spite of the spontaneous remission of the tremor, we could not exclude the possibilities of extrapyramidal symptom (EPS) by aripiprazole treatment. Therefore, 5 mg/day procyclidine, an anticholinergic agent was added because of prevention of EPS of aripiprazole. Shortly thereafter, his psychotic symptoms began to improve, with decreased aggression, persecutory delusion, auditory hallucination and social withdrawal. After 2 month of treatment, he complained urination difficulty, therefore procyclidine was discontinued promptly and bethanechol chloride 15 mg/day was added. His urination difficulty was subsided by the 1 week of bethanechol treatment. Thereafter, the bethanechol treatment was discontinued.

By the 9th month of treatment, he began to experience recurrent dystonic reactions characterized by fixed upward gaze and hyperextended neck. The involuntary conjugate ocular deviations was fixed to the upper right side and lasted for 1 h with the frequency of 2–3 times per week. His ocular symptom was not precipitated by any psychiatric symptoms such as delusion or hallucination nor any other physical symptoms such as fatigue. His ocular deviation was associated with the symptom torticollis, the hyperextension of the right cervical muscles. The duration and the frequency of the torticollis were similar to that of the ocular muscle deviations. Upon examination, he did not have any other dyskinetic and dystonic movements. There was no familial history of movement disorder. A thorough neurological examination and brain imaging revealed no other abnormalities. These oculogyric crises were relieved by lorazepam 1 mg/day and procyclidine 5 mg/day and occurred much less frequently when we decreased the aripiprazole dosage to 5 mg/day. After 1 week of lorazepam, procyclidine treatment and dose reduction of the aripiprazole, the frequency and duration of the dystonic symptoms had been changed from 2–3times per week and 1 h to 1 time per week and less than 20 min.

Two months later, he did not complain any event of oculogyric crises and dystonic movements. After numerous discussions with him and his parents about the risks and benefits of aripiprazole, he continues to take aripiprazole at 5 mg/day, along with procyclidine, 5 mg/day, and lorazepam 1 mg/day. He continues to benefit behaviorally from the drug regimen.

3. Discussion

There have been a few case reports where aripiprazole has been found to improve symptoms of tardive dyskinesia in patients

previously treated with other neuroleptics, with a D₂ partial-agonism balancing a D₂ receptor function in patients with tardive dyskinesia (Duggal, 2003). However, as indicated in the previous case reports, aripiprazole has also shown the risk of tardive dystonia during a combination therapy with other medication such as lithium and ziprasidone (Oommen et al., 2006; Pinninti et al., 2006). In line with previous reports, our case calls for further clinicians' attention about a potential risk of tardive oculogyric crisis during aripiprazole monotherapy as well. In the present case, the clear temporal relationship between commencement and reduction of aripiprazole, and the reduction of abnormal involuntary movements after administration of anticholinergic agents, suggests that aripiprazole may be attributable to the development of the tardive dystonic movements.

Although the pathophysiology underlying tardive dystonia remains unclear to date, it has been understood in the continuum of the pathophysiology of tardive dyskinesia, with particular emphasis on the alteration in dopaminergic and cholinergic neurotransmission (Adityanjee et al., 1999). Based on a proposed kindling model, repetitive stimulation of the D1 receptor leading to a sensitization of the D1-mediated striatal output in the presence of D2 receptor blockade, may be a plausible mechanism for tardive dyskinesia (including tardive dystonia) (Trugman et al., 1994). Endogenous dopamine may stimulate D1 receptors during chronic antipsychotic treatments, while D2 receptors are occupied by antipsychotics. Hence chronic treatment with aripiprazole may disrupts the normal coordination of balance between D1- and D2-mediated striatal outputs by selectively blocking D2 receptors, despite of the partial agonist activity in D2 receptor.

Reflecting our patient, well-documented risk factors of tardive dystonia were included in the present case: young, male gender, and mental retardation (Adityanjee et al., 1999). The prevalence of cerebral insults (including mental retardation) in the tardive dystonia estimated to be 7%–48% (Davis et al., 1988; Kang et al., 1986). Therefore, aripiprazole should be administered cautiously especially to the patients who have potential risk factors of the tardive dystonia.

In conclusion the present report clearly suggests that aripiprazole may also have a propensity to develop a tardive movement disorder regardless of the type of administration, monotherapy or combination treatment.

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