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Case Report / Olgu Sunumu

Can Aripiprazole Cause Parkinsonism? Two Cases with Aripiprazole-Induced Parkinsonism

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ABSTRACT

Can aripiprazole cause Parkinsonism? Two cases with aripiprazole-induced Parkinsonism

The association between aripiprazole and Parkinsonism has not been well demonstrated. Our patients' present complaints started several weeks after the initiation of aripiprazole only. We present two female cases who developed extrapyramidal syndrome (EPS) after administration of aripiprazole. Neither of them had ever used any antipsychotic agent except aripiprazole and the EPS disappeared within less than a week after administration of an anticholinergic drug. The severe Parkinsonism in our cases is associated with aripiprazole. Our report emphasizes the need for careful monitoring for the development of Parkinsonian features in patients treated with aripiprazole.

Keywords: Aripiprazole, Parkinsonism, secondary syndrome

ÖZ

Aripiprazol Parkinsonizm sebebi olabilir mi? Aripiprazol ile Parkinsonizm gelişen iki olgu

Aripiprazol ve Parkinsonizm ilişkisi çok iyi gösterilememiştir. Olgularımızın yakınmaları sadece aripiprazol kullanımı ile ilaç başlandıktan bir kaç hafta sonra başlamıştır. Aripiprazol sonrası ekstrapiramidal sendrom (EPS) gelişen iki kadın olgu sunuyoruz. Bu olguların ikisinin de daha önce aripiprazol dışında hiç bir antipsikotik kullanımı yoktu ve EPS, antikolinerjik tedavi ile yaklaşık bir haftada geriledi. Olgularımızdaki ciddi Parkinsonizm aripiprazol ile ilişkilidir. Raporumuz aripiprazol başlanmış hastalarda Parkinsonian bulgu gelişimi açısından yakın izlem gerektiğini vurgulamaktadır.

Anahtar kelimeler: Aripiprazol, Parkinsonizm, ikincil sendrom

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INTRODUCTION

Aripiprazole develops a partially agonist activity at dopamine D2 receptors, distinguishing it from all other currently available antipsychotics, which are D2 antagonists. Preclinical studies have shown that aripiprazole has D2-antagonist activity under hyperdopaminergic conditions, which is believed to be associated with control of psychotic or positive symptoms, and D2-agonist activity under hypodopaminergic conditions, which is thought to be associated with improvement of negative symptoms and cognition and minimizing extrapyramidal syndrome (EPS) and prolactin changes (1). The relationship of aripiprazole and Parkinsonism is poorly defined. Our patients' present complaints started several weeks after the initiation of aripiprazole only. We present two female cases who developed EPS after administration of aripiprazole. Neither of them had ever used any antipsychotic agent except aripiprazole and the EPS disappeared within less than a week after administration of an anticholinergic drug. Therefore, the severe Parkinsonism in our cases is associated with aripiprazole.

CASE 1

A 19-year-old female patient was admitted to our psychiatry clinic with psychotic illness characterized by unmanageable agitation, hallucinatory behaviour, loosening of associations, delusions of persecution and reference, and labile mood for 4 months. After detailed work-up, a diagnosis of schizophrenia was made. The patient was receiving aripiprazole 5mg/day in our outpatient clinic. After one week, she still had significant psychotic features. The dose of aripiprazole was increased to 30mg/day. She reported severe backache and constipation a week later. Two weeks later, she developed severe EPS. The patient had marked significant bradykinesia, masked face, loss of associated movements, and difficulty in maintaining a straight posture. There were no rigidity and tremor. We detected nothing else in her neurological examination either. Her modified Hoehn-Yahr stage was 3 (2). All metabolic, infectious, and autoimmune markers were negative in the laboratory. The patient's MRI scans were normal. In our opinion, backache and constipation were non-motor symptoms of Parkinsonism. We administered 4mg/day biperiden per os. After two days, the patient was almost completely free of Parkinsonian symptoms.

CASE 2

A 57-year-old female patient was admitted with severe left-sided rest tremor, minor bradykinesia, masked face, and hypophonic speech for seven months. Her modified Hoehn-Yahr stage was 1.5 (2). She had been diagnosed with Parkinson's disease and administered rasagiline mesylate 1mg/day in the previous hospital. As her complaints had not improved, 187.5mg/day L-dopa (3x1/2 levodopa/benserazide) had been added to her therapy. She was admitted to our neurology outpatient clinic with these treatments. Major depressive disorder and hypertension were recorded in her medical history. She was using duloxetine (60mg/day) and aripiprazole (15mg/day) for depressive disorder and enalapril (5mg/day) for hypertension. In our neurologic examination, she also had left-sided postural tremor. All metabolic, infectious, and autoimmune markers were negative in the laboratory. The patient's MRI scans were normal. Because postural tremor was accompanied by resting tremor, we suspected drug-induced Parkinsonism. When the history was detailed, we learned that all complaints had set in after starting the aripiprazole treatment. Rasagiline mesylate, L-dopa, and aripiprazole were stopped and 2mg/day biperiden was administered. Her complaints were reduced after a week.

DISCUSSION

The side-effects of antipsychotic medications are often associated with a reduced compliance to treatment, and movement disorders are an important concern. Well-reported adverse effects (AEs) of aripiprazole include insomnia, anxiety, headaches, nausea, vomiting, and somnolence (3). McEvoy et al. (3) reported that extrapyramidal side effects, which are common in patients receiving typical agents, were minimal with aripiprazole treatment and the incidence of EPS-related AEs was similar for patients receiving aripiprazole compared with those receiving placebo. Many studies have extensively described the EPS profiles of earlier atypical neuroleptics, namely clozapine, quetiapine, olanzapine, ziprasidone, and risperidone (4). However, the relationship between aripiprazole and Parkinsonism was poorly defined. Parkinsonism associated with aripiprazole has only been described in case reports and case series (5-8). The cases of Parkinsonism associated with aripiprazole reported in the literature were elderly females receiving multiple antipsychotic therapy. Our cases were also female, but they were not elderly, and their psychotic symptoms were under control with monotherapy. One of them was only 19 years old and aripiprazole was the first drug administered in her first psychotic attack. To our knowledge, non-motor symptoms have not been described in case reports of Parkinsonism associated with aripiprazole. Our first patient's complaints started with non-motor symptoms initially, while motor symptoms were added after a week.

One of our cases was bradykinesia-dominant and the other one was tremor-dominant and unilateral.

Various clinical types of Parkinsonism were also reported in the literature. Complaints of both patients started a few weeks after the use of aripiprazole and they improved within a few weeks, just as the cases in the literature.

As a differential diagnosis, all primary and secondary forms of Parkinsonism were screened. All metabolic, infectious, and autoimmune markers were negative in the laboratory. MRI scans of both patients were normal. Hereditary and idiopathic forms of Parkinsonism were excluded according to history and neurological examination. Patients with hereditary Parkinsonism usually present with a family history. The characteristic features of hereditary Parkinsonism are early disease onset, myoclonus, diurnal rhythm of symptoms, etc. The most widely known ones are associated with SCNA, parkin, and LRRK 2 genes. Patients with PARK 2 mutations leading to Parkinson's disease respond well to dopaminergic agents, but relief with biperiden is not expected (9). Our patients have no family history and they do not have features characteristic of genetic forms of Parkinsonism.

The EPS mechanism of aripiprazole is complicated. Friedman et al. (10) undertook an open-label flexible-dose pilot study to evaluate the safety and tolerability of aripiprazole in patients with psychosis associated with PD. They had no data to implicate any particular mechanism to explain the effect of aripiprazole on PD patients. In their opinion, PD patients represent the most powerful test of a drug's potential for inducing Parkinsonism. They assumed that cases of worsened Parkinsonism may be related to the effects on D2 receptors (10). In addition, some studies suggest that the antagonist effect of the drug on 5HT2A receptors would increase dopamine release in the basal ganglia via feedback. On the other hand, aripiprazole binds to D2 receptors more readily than 5HT2A receptors (4). Its low EPS side effects are explained by its partial agonist mechanism. In a recent paper, the mechanism of the drug is defined as 'functional selectivity' rather than partial agonism. This is explained as a mix of classic effects thorough activation or inhibition in a limited number of signal transduction pathways of the target receptor (11). However, the EPS mechanism of aripiprazole has not been explained clearly so far.

Even though the risk of EPS associated with the use of atypical antipsychotics is lower than with conventional agents, it is not zero (12).

Our report emphasizes the need for careful monitoring for the development of Parkinsonian features in patients treated with aripiprazole.

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Category 1	Concept/Design	H.U.E.
	Literature review	H.U.E.
	Data analysis/Interpretation	H.U.E.
	Case follow-up (if applicable)	H.U.E.
Category 2	Drafting manuscript	H.U.E.
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