Aripiprazole Can Improve Apraxia of Eyelid Opening in Parkinson’s Disease

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Abstract

We herein report three cases of Parkinson’s disease associated with difficulty in eyelid opening, referred to as apraxia of eyelid opening (AEO), which improved after aripiprazole treatment. In case 1, aripiprazole was administered as a psychiatric treatment. It proved to be effective in AEO with blepharospasm. In case 2 and case 3, the patients experienced AEO without blepharospasm, and a significant improvement was observed after aripiprazole treatment. In this study, the aripiprazole dosage ranged between 3 and 9 mg/day. This is the first report of aripiprazole as a potentially effective treatment for AEO in Parkinson’s disease.

Key words: Parkinson’s disease, apraxia of eyelid opening, aripiprazole

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Introduction

Apraxia of eyelid opening (AEO) is a nonparalytic movement disorder characterized by transient difficulty in initiating voluntary eyelid opening or in response to command (1). AEO is observed in idiopathic Parkinson’s disease (PD) and other extrapyramidal diseases (1, 2). Botulinum toxin injection into the orbicularis oculi muscles improves AEO and blepharospasm, however, this is effective only for about 4 months (1-3). Aripiprazole, which is a partial agonist of dopamine D2 and D3 receptors and of the serotonin 5-HT1A receptor, and a serotonin 5-HT2A receptor antagonist, is an antipsychotic drug, which has been proven effective in the treatment of patients with schizophrenia and for symptoms of depression. A number of studies have evaluated the efficacy of aripiprazole, a relatively novel antipsychotic agent, in treating the psychiatric symptoms of PD (4-6). This paper is the first to show that aripiprazole was effective against AEO in patients with idiopathic PD.

Case Reports

Case 1

A 74-year-old woman who was diagnosed with PD at 48 years of age, whose symptoms fulfilled the UK PD Society Brain Bank Clinical Diagnostic Criteria (7), began experiencing hallucinations from 72 years of age. Magnetic resonance imaging (MRI) findings of the brain were normal. After the reduction of her antiparkinsonian dosage, quetiapine, donepezil, and haloperidol were initiated. However, these antipsychotics were discontinued due to worsening motor symptoms and invalidity. The patient spent most of the day with her eyelids closed with blepharospasm and she was diagnosed as having AEO without blepharospasm at 73 years of age (Table 1). At 74 years of age, aripiprazole treatment was initiated at a dosage of 1.5 mg/day to treat hallucinations. This dosage was gradually increased to 9 mg/day. After 14 days of aripiprazole treatment, AEO improved. In response to a request from the patient, the dosage was reduced to 6 mg/day, and this reduced dosage remained effective for AEO. Although hallucinations manifested on occasion, they occurred less frequently. Thereafter, the aripiprazole dosage was reduced to 3 mg/day, which resulted in AEO recur-
rence. After increasing the dosage back to 6 mg/day, improvement in AEO was observed within a few days.

Compared to the patient’s scores according to the Unified Parkinson’s Disease Rating Scale (UPDRS) before aripiprazole treatment, those for speech, handwriting, food cutting, dressing, action tremor, finger tapping, palm movement, leg agility, gait, and dyskinesia (duration and pain) improved after 3 months of treatment with 6 mg/day of aripiprazole (Table 2). However, the sensory complaints worsened. The severity of AEO was ranked according to a clinical rating scale of functional disability due to AOE or blepharospasm developed by Krack et al. (functional status of AEO) (2). The patient’s functional status of AEO (2) improved from 3 before treatment to 1 with 9 mg/day of aripiprazole (Table 2). Nine mg/day of aripiprazole continued to be effective for AEO over 12 months.

**Case 2**

A 78-year-old man fulfilling the diagnostic criteria (7) developed PD at 73 years of age. The brain MRI findings were normal. At 76 years of age, AEO without blepharospasm manifested (Table 1). He began closing his eyes more frequently, particularly during meals. He was able to open his eyes by manual elevation of the lids. The Ethic Committee approved the aripiprazole treatment and informed consent was obtained. Treatment with 3 mg/day of aripiprazole began at 77 years of age. However, no improvement in AEO was observed. After 6 months, the dosage was increased to 6 mg/day, however, no symptom change was observed. Therefore, the dosage was further increased to 9 mg/day. After 3 days of the 9 mg/day treatment, an improvement in AEO was finally observed. Although mild swelling of the lower limbs occurred, no other adverse effects were observed.

Compared to the patient’s UPDRS scores before aripiprazole treatment, scores for gait improved after 2 months of treatment with 9 mg/day of aripiprazole (Table 2). The patient’s functional status of AEO (2) improved from 3 before treatment to 1 with 9 mg/day of aripiprazole (Table 2). Nine mg/day of aripiprazole remained effective for AEO over 8 months.

**Discussion**

To the best of our knowledge, this is the first report to demonstrate that aripiprazole was effective against AEO with no major adverse effects on PD. The dosages of aripiprazole used in psychiatric disorders are usually ≥15 mg/day, while the dosages of treatment of AEO were 3 mg/day for case 2, 6 mg/day for case 1, and 9 mg/day for case 3. A lower dosage of aripiprazole may improve AEO.

AEO is often seen in extrapyramidal diseases, such as PD, progressive supranuclear palsy, and multiple system atrophy (1, 8). Many points remain unclear, including the anatomical lesion and its mechanism.

AEO may be associated with blepharospasm, and Krack et al. (2) have proposed that rather than a true apraxia, it may constitute a broad clinical spectrum of palpebral dystonias, ranging from sporadic twitches to obvious blepharospasm. Many researchers share the opinion that it is a type of dystonia rather than an apraxia (2, 9). In case 2 and case 3, AEO improved by massaging the eyelids or manual lift-
risperidone, quetiapine, olanzapine, and clozapine, with serotonin-dopamine antagonists (SDAs), such as mirtazapine, with aripiprazole 0.625 mg/day, and reported that dyskinesia improved in 10 out of 12 patients, suggesting that the modulatory effect of aripiprazole on the dopamine and serotonin systems may have been effective in improving dyskinesia. Lopez-Meza et al. (4) reported successful treatment of 3 patients with PD with psychosis with aripiprazole 15 mg/day without worsening of their motor symptoms. On the other hand, Fernandez et al. (5) reported that 2 out of 6 patients discontinued aripiprazole due to worsening motor symptoms.

Recently there have been reports about impulse control disorders such as gambling, hypersexuality, and compulsive shopping associated with aripiprazole treatment (16). Although no deterioration of Parkinsonism or severe adverse events were apparent in the present cases, we should monitor the adverse effects of aripiprazole with caution.

In the absence of other medications that are effective against AEO, aripiprazole can be effective in treating AEO.

Table 2. Changes of Symptoms during the Aripiprazole Treatment in Three Cases.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Date of UPDRS* examination</th>
<th>UPDRS Part 2</th>
<th>Part 2</th>
<th>Part 3</th>
<th>Part 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>Pre-treatment 9 28 40</td>
<td>68 13 3</td>
<td></td>
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<tr>
<td>Case 2</td>
<td>3 months after the treatment 1 11 12 22</td>
<td>7 3</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Case 3</td>
<td>Pre-treatment 1 12 13 21</td>
<td>4 2</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>2 months after the treatment 1 12 13 20</td>
<td>4 1</td>
<td></td>
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</tbody>
</table>

UPDRS*: Unified Parkinson’s Disease Rating Scale
**Functional status: Clinical rating scale of functional disability due to apraxia of eyelid opening or blepharospasm (2).
**Functional status: Clinical rating scale of functional disability due to apraxia of eyelid opening or blepharospasm (2).
1: Inconvenienced, but no functional disability.
2: Independent but disabled, e.g. for reading, watching TV or driving.
3: Dependent, disabled most of the time, unable to work, assistance to move outside needed.
4: Functionally blind, permanent eye closure.

Figure. Changes in the facial expression of case 2 before taking aripiprazole (A, B) and while taking aripiprazole 3 mg/day (C). A and B (before taking aripiprazole): Told to open the eyes after having been instructed to close the eyes. She had difficulty initiating eyelid opening with frontalis muscle contraction and levator muscle relaxation (A). She massaged her eyelids to open her eyes (B). C (while taking aripiprazole 3 mg/day): Told to open the eyes after having been instructed to close the eyes. She was able to open the eyes smoothly with slight contraction of the frontalis muscle. Informed consent for publication of photographs was obtained.

A B C
associated with PD; this finding has added another option for the treatment of AEO. Whether or not aripiprazole is effective in treating AEO in patients with disorders other than PD is a subject for future investigation and the mechanism whereby aripiprazole improves AEO should be clarified in the future.

The authors state that they have no Conflict of Interest (COI).

References