Donepezil-induced Cervical Dystonia in Alzheimer’s Disease: A Case Report and Literature Review of Dystonia due to Cholinesterase Inhibitors

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Abstract

We herein report an 81-year-old woman with Alzheimer’s disease (AD) in who donepezil, a cholinesterase inhibitor (ChEI), caused cervical dystonia. The patient had a two-year history of progressive memory disturbance fulfilling the NINCDS-ADRDA criteria for probable AD. Mini-Mental State Examination score was 19/30. The remaining examination was normal. After a single administration of donepezil (5 mg/day) for 10 months, she complained of dropped head. Neurological examination and electrophysiological studies supported a diagnosis of cervical dystonia. Antecollis disappeared completely at 6 weeks after cessation of donepezil. Dystonic posture can occur at various timings of ChEI use. Physicians should pay more attention to rapidly progressive cervical dystonia in ChEI-treated AD patients.

Key words: Alzheimer’s disease, cholinesterase inhibitor, donepezil, cervical dystonia, dropped head, Pisa syndrome

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Introduction

Tardive dystonia syndrome is known as the complication of prolonged treatment with antipsychotic medications, particularly classic antipsychotics. Pisa syndrome or pleurothotonus is a distinct form of tardive dystonia characterized by abnormal, sustained posturing with flexion of the neck and head to one side (1). This syndrome has been described primarily as an adverse effect of neuroleptic drugs (1-3). Cholinesterase inhibitors (ChEIs) are widely used in patients with Alzheimer’s disease (AD). This medication rarely causes Pisa syndrome in patients with dementia with Lewy bodies (4), multiple system atrophy (5) and AD (6, 7). We herein report a patient with AD who developed cervical dystonia after a single administration of donepezil and review the literature regarding ChEI-associated dystonia in AD patients.

Case Report

An 81-year-old woman developed a progressive global intellectual deterioration for two years and visited our department. The first score of Mini-Mental State Examination (MMSE) was 19/30. The remaining neurological examination was normal, showing no parkinsonism. The patient was diagnosed with probable AD according to the NINCDS-ADRDA criteria (8). There was no prior history of hallucination, depression, extrapyramidal disorders or medication with neuroleptics, antiepileptics or antiemetics. Treatment with donepezil (5 mg daily) was started, and the dementia remained stable for nine months. At that time, MMSE score was 18. Ten months after donepezil administration, the patient suddenly noticed dropped head. Antecollis worsened for two weeks. Neurological examination revealed a severe degree of anterior flexion and dystonic spasm in the neck (Fig. 1A). Other cranial nerves were normal. A slight degree of anterior flexion of the upper trunk was present at walk-
Figure 1. Photograph of cervical dystonia in the present patient. A) Marked anterior flexion of the neck during donepezil treatment. B) Normal neck position at 6 weeks after donepezil withdrawal.

We herein reported the case of an AD patient who developed cervical dystonia during a single administration of donepezil (5 mg/day) for 10 months. Dystonia was improved at 6 weeks after donepezil discontinuation.

Pisa syndrome (pleurothotonus) is an acquired, persistent truncal dystonia from the cervical to lumbar musculature that appears to be reversible. The distinct posture is characterized by an involuntary side flexion on either side of the body and head with a backward axial rotation. The patient looks like the leaning tower of Pisa. Ekbom et al. (1) first described this syndrome as a rare adverse effect of long-term classic neuroleptic medication. Pisa syndrome can be triggered by other medications, including antiemetics, valproic acid, lithium and atypical antipsychotics (9-11). The single or additional administration of ChEIs also causes this syndrome (6, 7, 12-22). Previous cases of ChEI-induced dystonia who had no other central nervous system (CNS)-acting medications are summarized in Table. Truncal dystonia, so-called Pisa syndrome, was present in 11 of 13 patients (6, 7, 13, 15-17, 20). Two patients developed cervical dystonia, resulting in antecollis (19) or torticollis (22). The underlying pathophysiology of drug-induced dystonia is complex. The functional imbalance between the dopaminergic and the cholinergic system could play a major role in the pathogenesis of Pisa syndrome. Acetylcholine and dopamine might contribute to axial muscle tone. Decreased dopaminergic neurotransmission and/or excessive cholinergic neurotransmission have been speculated to be present in patients with Pisa syndrome. Serotonergic or noradrenergic dysfunction has also been implicated in the dystonic mechanism. The frequency of ChEI-induced Pisa syndrome remains unclear because randomized clinical trials have not investigated the long-term adverse reactions of ChEIs. Highly selected patients who had younger age, better cognitive status and no other CNS-acting drugs are typically included in randomized trials of ChEIs. In general, the risk factors for developing Pisa syndrome include a female gender, old age, organic brain disease, combined pharmacologic treatment and previous treatment with classic neuroleptics (9, 23, 24). These clinical features are also comparable in patients with ChEI-associated dystonia (6, 7, 12-22). In contrast, the patient backgrounds in randomized ChEI trials seem to differ from the predisposing factors of Pisa syndrome. Only a few previous studies estimated the incidence or the prevalence of Pisa syndrome (16, 23, 24). A German study surveyed all newly admitted psychogeriatric patients over a 5-year period and reported a prevalence of 8.3%, 6.4% in men and 9.3% in women (23). A German study (22) showed 17 patients among a population of
45,000 psychiatric patients and the prevalence was 0.037%. With respect to the incidence of ChEI-induced Pisa syndrome, three patients developed this syndrome in an Italian cohort study of 7,395 ChEI-treated patients with mild to moderate AD. The incidence was estimated to be two per 10,000 patients per year (16). Otherwise, the frequency of cervical dystonia has not been studied in ChEI-treated AD patients. Only two Japanese patients were reported to develop cervical dystonia after a single administration of donepezil (19, 22). The present patient exhibited antecollis at 10 months after donepezil administration without other CNS-acting drugs. The distinct head falling appearance required differentiation from dropped head syndrome (DHS). DHS is characterized by severe neck extensor muscle weakness, resulting in a chin-on-chest deformity in the standing or sitting position. Dropped head is correctable with passive neck extension. This syndrome is caused by various etiological diseases, including motor neuron disease, peripheral neuropathy, myasthenia gravis, polymyositis, muscular dystrophy, neck extensor myopathy and Parkinson’s disease (25). Focal myositis in the neck was the most important differential diagnosis in the present patient. Gallium scintigraphy, the electrophysiological and MRI findings did not suggest inflammatory and myopathic changes in the cervical musculatures. Together with the recovery from antecollis, the persistent muscle contraction discharges vanished in the sternocleidomastoid, anterior scalenus and trapezius muscle. The clinicoradiological and electrophysiological course supported the diagnosis of cervical dystonia in the present patient.

Drug-induced Pisa syndrome is classified into acute and tardive dystonia according to the onset and prognosis. The duration of ChEI use is very variable from one day to 4 years (6, 7, 12-22). In the earliest onset of Pisa syndrome, dystonia was present at a few hours after the administration of donepezil (20). In most patients, ChEI-associated dystonia occurred within six months after ChEI administration (6, 7, 12-16, 18-20, 22). Four patients developed dystonia more than 1.5 years after ChEI treatment. Interestingly, other CNS-acting drugs were not administered in these patients (6, 7, 16, 17). The present patient developed cervical dystonia at 10 months after a single administration of donepezil. Therefore, slowly progressive cholinergic overfunction could result in the delayed onset of dystonia when patients received single treatment with ChEI.

### Table

**Clinical Features of ChEI-associated Dystonia in AD Patients Treated without Other CNS-acting Drugs**

<table>
<thead>
<tr>
<th>Age/gender</th>
<th>Country</th>
<th>ChEI</th>
<th>Duration of ChEI treatment</th>
<th>Prognosis of dystonia after ChEI withdrawal</th>
<th>Recurrence of dystonia after ChEI re-administration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>57 years/male</td>
<td>Japan</td>
<td>Donepezil</td>
<td>1 month</td>
<td>Improvement at 1 week</td>
<td>Donepezil</td>
<td>13</td>
</tr>
<tr>
<td>72 years/female</td>
<td>Spain</td>
<td>Donepezil</td>
<td>2 months</td>
<td>Improvement at 16 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 years/female</td>
<td>Sardinia</td>
<td>Galantamine</td>
<td>1 month</td>
<td>Improvement after injections of botulinum toxin</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>83 years/female</td>
<td>Italy</td>
<td>Rivastigmine</td>
<td>5 months</td>
<td>Improvement at 16 days</td>
<td>Donepezil</td>
<td>16</td>
</tr>
<tr>
<td>84 years/female</td>
<td>Italy</td>
<td>Donepezil</td>
<td>4 months</td>
<td>Improvement at 1 week</td>
<td>Rivastigmine</td>
<td></td>
</tr>
<tr>
<td>75 years/female</td>
<td>Italy</td>
<td>Donepezil</td>
<td>2.5 years</td>
<td>Improvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>79 years/male</td>
<td>France</td>
<td>Rivastigmine</td>
<td>2 years</td>
<td>ChEI was continued and death</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>82 years/male</td>
<td>Brazil</td>
<td>Donepezil</td>
<td>3 years</td>
<td>Improvement</td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>98 years/male</td>
<td>France</td>
<td>Donepezil</td>
<td>3 months</td>
<td>Improvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 years/male</td>
<td>France</td>
<td>Donepezil</td>
<td>18 months</td>
<td>Improvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>79 years/female</td>
<td>Japan</td>
<td>Donepezil</td>
<td>A few weeks</td>
<td>Improvement at 2 weeks</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>74 years/female</td>
<td>Greece</td>
<td>Donepezil</td>
<td>A few hours</td>
<td>Improvement at 8 days</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>70s late/female</td>
<td>Japan</td>
<td>Donepezil</td>
<td>&lt; 1 month</td>
<td>Improvement at several weeks</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>81 years/female</td>
<td>Japan</td>
<td>Donepezil</td>
<td>10 months</td>
<td>Improvement at 6 weeks</td>
<td></td>
<td>Present case</td>
</tr>
</tbody>
</table>

AD: Alzheimer’s disease, ChEI: cholinesterase inhibitor, CNS: central nervous system

*Reference number
† Cervical dystonia
As a therapeutic strategy for drug-induced Pisa syndrome, withdrawing or reducing the dose of the causative drug is recommended. Anticholinergic drugs are effective in some patients treated with neuroleptics (9). However, anticholinergic medication is unfavorable in AD patients. A previous study mentioned that amantadine, a dopamine agonist, improved Pisa syndrome slightly in AD patients (26) whereas other studies reported no benefits of this drug (27). ChEI withdrawal markedly ameliorated dystonia in most patients (6, 7, 12-16, 18-22). One patient died to continue administration of rivastigmine (6). Compared to the first episode, dystonia reappeared at shorter periods after the same or a different ChEI was administered again (12, 13, 16, 21). Instead of ChEIs, memantine hydrochloride, a N-methyl-D-aspartate receptor antagonist, was administered in two patients with AD. One patient exhibited galantamine-induced Pisa syndrome (18) and another patient developed cervical dystonia after donepezil treatment (22). Dystonia did not recur in both patients after administration of memantine hydrochloride (18, 22). The present patient was also treated with memantine hydrochloride. Further follow-up studies are needed to determine whether this drug is a useful and safe medication in AD patients with ChEI-associated dystonia.

In conclusion, we highlighted an AD patient with donepezil-induced cervical dystonia. Donepezil caused cervical dystonia without truncal dystonia in the present and two previous patients (19, 22). The similar pathogenesis to Pisa syndrome was suspected in these patients. There are no reports of cervical dystonia related to other ChEIs. In addition to Pisa syndrome, focal dystonia should be investigated cautiously in galantamine- or rivastigmine-treated patients. Dystonia occurs at various durations of ChEI treatment, from a few hours to four years. The rapid cessation of ChEI is the best management for improving dystonia. Thus, physicians should pay more attention to the presence of acute or tardive dystonia in ChEI-treated AD patients.

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

References


