Anticholinergic Agents Can Induce Oromandibular Dyskinesia

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Background and Purpose: Oromandibular dyskinesia (OMD) can occur spontaneously or they can be induced by the conventional dopamine receptor antagonists. Anticholinergic medications have rarely been reported to cause OMD in parkinsonian or non-parkinsonian patients. Methods: We analyzed the clinical features of two parkinsonian and one non-parkinsonian patients who experienced OMD after anticholinergic medication. Results: Each patient of our cases developed oromandibular symptoms in the temporal regions that were related to the addition of anticholinergic agents, and the symptoms were relieved following the discontinuation of the causative anticholinergic drugs. In one of our case, levodopa alone did not cause dyskinesia but augmented dyskinesia associated with anticholinergics. Conclusions: Here we report two parkinsonian and one non-parkinsonian patients with OMD induced by the use of anticholinergic agents. In our cases, we could not find any other precipitating or actual secondary causes for the OMD symptoms in our patients. Furthermore, the fact that the OMD in our cases were ameliorated with cessation of anticholinergics suggests that it may be anticholinergic-induced. Key Words: Oromandibular dyskinesia, Anticholinergic agents, Drug-induced.

Introduction

Oromandibular dyskinesia (OMD) occurs as involuntary, repetitive, stereotypical movements of the lips, tongue, and sometimes the jaw during the day. It occurs spontaneously or can be induced by medication. Most of the conventional dopamine receptor antagonists can cause OMD, and co-administration of anticholinergic agents is a recognized risk factor for tardive dyskinesia. Several authors described previously a few cases of orobuccal dyskinesias caused by administration of anticholinergic medications in patients with parkinsonism, and non-parkinsonian patients.

Here we report the experience of patients with dyskinesia that was limited to the oromandibular area and was induced by the use of anticholinergic drugs and relieved by withdrawal of causative drugs.

Case Report

Case 1

A 6-year-old boy was referred to our clinic due to episodes of tremor and rigidity a few days prior to his visit to our clinic. He was diagnosed with acute lymphocytic leukemia (ALL), and treated with bone marrow transplantation and chemotherapeutic agents, including cyclosporine, azathioprine, and prednisolone. On examination, he showed resting tremor, rigidity and bradykinesia in both extremities, cervical dystonia and choreiform movements of the upper extremities, but no dyskinesias in his facial area. His parkinsonism and choreic limb movements were thought to be caused by cyclosporine-induced leukoen cephalopathy with hemorrhage involving the bilateral basal ganglia. We medicated with biperiden at a dose of 6 mg per day to manage his parkinsonism. Levodopa was not administered to him for his parkinsonism. Three months after beginning treatment with biperiden,
he began to experience abnormal involuntary movement in his oromandibular area. We discontinued the causative anticholinergic drug, biperiden but kept the other drug at the same dose. OMD markedly improved four months after the discontinuation of anticholinergics.

Case 2
A 76-year-old woman visited our clinic due to involuntary movements in her orofacial area. She was diagnosed with Parkinson’s disease 2 years prior and treated with levodopa at a dose of 600 mg per day. Trihexyphenidyl (4 mg per day) was added to her treatment regimen due to aggravated hand tremor. Three months after starting trihexyphenidyl, she experiences orofacial dyskinesia. On examination, she showed OMD and parkinsonian symptoms (Hoehn and Yahr stage 2) without any other drug-related complications. We could not find other causes for the OMD symptoms including history of head or facial trauma or denture. In addition, she had not received any other drugs, commonly used and known to cause tardive dyskinesia. We discontinued the trihexyphenidyl but continued the other medication for the treatment of her parkinsonism. The OMD disappeared within 2 months and did not recur for 2 years.

Case 3
A 62-year-old man was referred to us due to involuntary movement of the oromandibular area. He suffered from forceful involuntary eye closing without orofacial movements, and was diagnosed with blepharospasm 2 years prior. He was treated with procyclidine at a dose of 10 mg per day. One year after administration of procyclidine, he complained of abnormal movements in his oromandibular area and occasionally crushed his lips. Because his abnormal movement was suggested to be a drug-induced OMD, we discontinued treatment with procyclidine. His OMD was markedly relieved 4 weeks after the discontinuation of procyclidine. His blepharospasm also improved following periorbital injection of botulinum toxin type A.

Discussion
Each patient of our cases developed oromandibular symptoms in the temporal regions that were related to the addition of anticholinergic agents, and the symptoms were relieved following the discontinuation of the causative anticholinergic drugs.

Several parkinsonian patients including our two cases have been reported to develop OMD following the introduction of anticholinergic therapy regardless of co-administration of levodopa (Table 1).4,5,7 In the previous report, levodopa alone did not cause dyskinesia but augmented dyskinesia associated with anticholinergics.7 This finding was also observed in one of our cases. Relatively high frequency of anticholinergic-induced OMD in parkinsonian patients may be caused by the pre-existing imbalance between the activity of dopaminergic and cholinergic systems in the basal ganglia as well as alterations in striatal cholinergic neurons.9,10 Anticholinergic agents might diminish gamma-aminobutyric acid-ergic inhibition of dopaminergic nigral neurons and increase in endogenous striatal dopaminergic activity.6

OMD has also been observed following introduction of anticholinergic agents to non-parkinsonian patients including

Table 1. Reported cases of oromandibular dyskinesia induced by anticholinergic drugs in parkinsonian patients

| Reference author | Age/gender | Diagnosis       | Anticholinergics (dose/day) | Co-administered drug (dose/day) | Onset of dyskinesia | Time to improvement |
|------------------|------------|-----------------|-----------------------------|--------------------------------|---------------------|---------------------|
| Fahn and David4  | 76/M       | PD              | Trihexyphenidyl (NA)        | Ethopropazine (NA)             | NA                  | 3 days              | 2 days              |
|                  | 76/F       | PD              | Trihexyphenidyl (NA)        | Ethopropazine (NA)             | NA                  | NA                  | NA                  |
| Birket-Smith5    | 65/F       | PD              | Procyclidine (15-30 mg/d)   | None                           | 7 days              | 6 days              |
|                  | 72/F       | PD              | Biperiden (12 mg/d)         | None                           | 42 days             | 42 days             |
|                  | 71/F       | PD              | Biperiden (15 mg/d)         | Orphenadrine (150 mg/d)        | 7 days              | 56 days             |
|                  | 74/F       | PD              | Biperiden (12 mg/d)         | Orphenadrine (150 mg/d)        | 93 days             | 28 days             |
| Warne, et al.6   | 73/M       | DIP             | Benzhexol (15 mg/d)         | None                           | 14 days             | NA                  |
|                  |            |                 | Benzhexol (15 mg/d) with ethopropazine (150 mg/d) | NA | 7 days | 14 days |
| Hauser and Olanow7| 60/M     | PD              | Trihexyphenidyl (4 mg/d)    | Levodopa (400 mg/d)            | 3 days              | 5 days              |
| Our case 1       | 6/M        | Parkinsonism    | Biperiden (6 mg/d)          | None                           | 3 months            | 4 months            |
| Our case 2       | 76/F       | PD              | Trihexyphenidyl (4 mg/d)    | Levodopa (600 mg/d)            | 3 months            | 2 months            |

PD: Parkinson’s disease, DIP: drug-induced parkinsonism, NA: not available.
one of our cases (Table 2).4,5,8 It was recently suggested that anticholinergic agents increase the risk of tardive dyskinesia (TD) in patients treated with neuroleptic drugs.5 Unlike the patients in the previous report, the patients in the present study had never taken any neuroleptic drugs, which are known to affect the dopaminergic system.

Because of the relatively delayed onset (for patient 1 and 2, 3 months and for patient 3, 12 months after medication) of OMD in our cases, their OMD might be diagnosed as a TD. Because TD is traditionally used to describe abnormal movements developing after chronic exposure to dopamine receptor blocking agents, rather than drug-induced OMD, which are known to affect the dopaminergic system.

Table 2. Reported cases of oromandibular dyskinesia induced by anticholinergic drugs in non-parkinsonian patients

| Reference author | Age/gender | Diagnosis | Anticholinergics (dose/day) | Co-administered drug (dose/day) | Onset of dyskinesia | Time to improvement |
|------------------|------------|-----------|-----------------------------|---------------------------------|---------------------|-------------------|
| Fahn and David*  | 78/F ET    | Trihexyphenidyl (NA) | NA | NA | NA |
|                  | 66/M ET    | Procyclidine (NA) | NA | 2 days | NA |
| Birket-Smith5    | 63/F ET    | Benzhexol (4 mg/d) | None | 30 days | 15 days |
|                  | 66/F ET    | Procyclidine (15 mg/d) | None | 42 days | 30 days |
| Suzuki, et al.8  | 40/M TD    | Biperiden (3 mg/d) | Risperidone (3-6 mg/d) | 14 days | 23 days |
|                  | 28/F TD    | Biperiden (6 mg/d) | Risperidone (9 mg/d) | 2 months | 6 weeks |
|                  | TD         | Biperiden (2-4 mg/d) | Risperidone (2 mg/d) | 2 months | 6 weeks |
| Our case 3       | 62/M ET    | Procyclidine (10 mg/d) | None | 12 months | 4 weeks |

ET: essential tremor, TD: tardive dyskinesia, NA: not available.

The main concerns of our cases are that complete resolution had not been observed in all the cases and there was no re-challenge with the anti-cholinergic medications. However, we could not find any other precipitating or actual secondary causes for the OMD symptoms in our patients. Furthermore, the fact that the OMD in our cases were ameliorated with cessation of anticholinergics suggests that it may be anticholinergic-induced.

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