Clinical Case Report

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Pramipexole-induced limb dystonia and its associated complex regional pain syndrome in idiopathic Parkinson's disease

A case report

Donghwi Park, MD*

Abstract

Rationale: This case may be due to basal ganglia dysfunction, which was probably caused by abnormal activation of dopamine 1-like receptor (D1R) boosted by pramipexole binding on dopamine 3-like receptor (D3R) in a situation where D3R was overexpressed by the chronic treatment of L-dopa.

Patient concerns: Striatal hand and foot deformities.

Diagnoses: Striatal hand and foot deformities with CRPS.

Interventions: Steroid treatemnt and withdrawal of the pramipexole.

Outcomes: Recovered significantly.

Lessons: Since the degree of overexpression of D3R is increased in a high dose of pramipexole, for patients with PD who are treated with L-dopa chronically, a new use of pramipexole and an increase in dose to alleviate the symptoms of PD should be implemented with caution while closely observing the occurrence of drug-induced complications such as dystonia and CRPS.

Abbreviations: CRPS = complexion regional pain syndrome, D1R = dopamine 1-like receptor, D3R = dopamine 3-like receptor, MCP = metacarpal phalangeal, MDs = movement disorders, MRI = magnetic resonance image, PD = Parkinson's disease, PET = positron emission tomography.

Keywords: CRPS, dystonia, Parkinson's disease, pramipexole

1. Introduction

Striatal hand and foot deformities are disabling symptoms in Parkinson's disease (PD) patients and might be present in up to 10 percent of untreated cases of advanced PD.[1,2] These deformities may be responsive to levodopa and may occur as part of the process of the wearing off of dystonia.[3] However, the pathogenesis of these deformities is not well understood, although limb dystonia contractures and rigidity play an important role.[4] There are a few reports indicating that pramipexole can induce these deformities or antecollis (a dystonia characterized by severe neck flexion due to disproportionate tonus of the neck muscles), which is reversed on stopping the pramipexole.[4,5] However, to the best of our knowledge, no previous study has reported on a PD patient who was taking pramipexole and developed both limb dystonia and its associated CRPS, and who recovered significantly after steroid pulse treatment and withdrawal of the pramipexole.

2. Case report

The family of patient was informed that data concerning the case would be submitted for publication, and they provided consent. This case report was approved by ethics committee of our hospital (Institutional Review Board of Daegu Fatima Hospital). The patient was a 71-year-old woman who had suffered idiopathic PD since the age of 66 years, who presented in 2011 with both hand resting tremor, cogwheel type rigidity, and bradykinesia.

Before transferring to our department, she was treated with 300 mg/day/30 mg/day of levodopa/carbidopa; however, bradykinesia and cogwheel type rigidity were sustained. To improve the remaining bradykinesia and cogwheel type rigidity despite levodopa/carbidopa treatment, pramipexole (dopamine agonist) was initiated at a dose of 0.125 mg twice a day for 1 week and then the dose was increased gradually and carefully over a 3-week period to 1.0 mg 2 times a day (total 2.0 mg). The dose of levodopa/carbidopa was not changed throughout the clinical

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Department of Rehabilitation Medicine, Daegu Fatima Hospital, Daegu, South Korea.

* Correspondence: Donghwi Park, Department of Rehabilitation Medicine, Daegu Fatima Hospital, Dong-gu, Korea (e-mail: bdome@hanmail.net).

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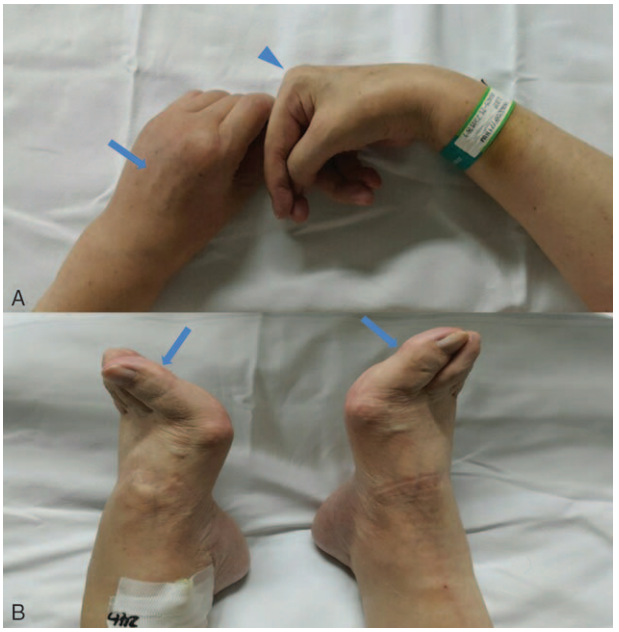

Figure 1. Pramipexole-associated limb dystonia. (A) Both hands. Arrow: swelling and redness of left hands. Arrowhead: striatal hand deformity with flexion of metacarpal, proximal interphalangeal, and distal interphalageal joints. (B) Both feet. Arrow: extension of great toe with flexion of other toe.

course. Within 2 weeks of taking pramipexole at 2.0 mg/day (5 weeks from initiation of pramipexole), she complained of both hand pain (left more involved) with stiffness and difficulty of using the hands.

We determined that the pain in both hands could be a nonmotor symptom of PD, so we increased the dose of pramipexole to 3.0 mg/day (1.0 mg 3 times a day) for improvement of pain in both hands.[6] However, even 1 week after the increased dose of pramipexole, the pain in both hands had not improved at all, and she began to notice striatal deformities in her hands and feet (Fig. 1A and B). After a day, she noticed swelling and redness in her left hand and wrist (Fig. 1A). Clinical examination demonstrated severe tenderness in both wrists and hands, with left-side predominance. Three-phase bone scintigraphy showed increased uptake in the left metacarpal phalangeal (MCP) and wrist joint in the delayed phase (Fig. 2A). Then, we started steroid treatment using prednisolone for 7 days.[7] The initial dose was 60 mg (1 mg per kg of body weight), and the dose was tapered over 1 week.

After steroid treatment, the left hand and wrist joint swelling and redness were mildly improved, but the striatal hand and feet deformities were not improved. Therefore, we considered the possibility of pramipexole-induced dystonia, and tapered the dose of pramipexole to 1.5 mg (0.5 mg 3 times a day) gradually. After 1 week, however, the left hands and wrist joint swelling and tenderness recurred. Therefore, we started steroid treatment for 7 days again. With the initiation of the second steroid treatment, the pramipexole was discontinued. One week after the initiation of the second steroid treatment, the pain and swelling in her left hand and wrist joints were markedly improved. To evaluate the cause of CRPS, a brain positron emission tomography (PET) scan using F-18 FP-CIT 6.40 mCi (Fluorine-18 Fluorinated N-3-fluoropropyl-2-beta-carboxymethoxy-3-beta-(4-iodophenyl) nortropane), a brain magnetic resonance image (MRI), and electrophysiological studies of both upper extremities were performed after the second steroid treatment. The brain PET scan revealed decreased uptake of rostrocaudal gradient in the bilateral posterior putamen, which was consistent with idiopathic Parkinson's disease (Fig. 2B). However, the electrophysiological study could not reveal any abnormality of the peripheral nerve including the brachial plexus in both upper extremities, and the brain MRI study also could not reveal any evidence of acute cerebral infarction (Fig. 2C and D). After discontinuation of pramipexole without changing the dose of levodopa/carbidopa, the striatal deformity of the hands and feet showed mild improvement. Trihexyphenidyl 1.5 mg (0.5 mg tablet, 3 times a day) was added for the improvement of residual dystonia. Five days after discontinuation of pramipexole, the striatal deformity of both hands and feet disappeared, and she was able to use both hands without any assistance.

3. Discussion

This report describes the subacute onset of pramipexole-associated limb dystonia and its related CRPS in PD under treatment with levodopa/carbidopa. In previous case reports about pramipexole-associated limb dystonia in PD, the authors speculated that the cause of pramipexole-associated dystonia was probably reactive fibrosis through serotoninergic h-HT2A and 5-HT2B receptors, although pramipexole has a very low affinity for these serotoninergic receptors.[4] However, considering that the dystonia improved after discontinuation of pramipexole, the cause of dystonia cannot be explained simply by fibrotic complications. Here, we hypothesize on the pathophysiology of the dystonia by reviewing a study on levodopa-induced dyskinesia (LID), 1 on dopamine-related dystonia, and animal studies using pramipexole.

LID is a form of dyskinesia associated with levodopa used to treat Parkinson's disease. It often involves hyperkinetic movements, including chorea, dystonia, and athetosis.[8] In LID, the striatal glutamatergic dysfunction has a critical role.[9] Abnormal activation of D1-like receptors (D1Rs) is also crucial for LID.[10] In the striatum, the activation of D3Rs results in a synergistic effect on D1R-mediated transmission via direct intra-membrane inter-action. Moreover, a pramipexole shows a preferential affinity also for the D3-like receptor (D3R).[11]

In physiological conditions, however, the D1R-D3R heteromer is also not abundant, because the D3R comprise less than 1% of DA receptors in the striatum.[12] In the pathological condition, however, these fine regulations are impaired.[12]

Considering that abnormal activation of D1R is crucial for LID induction and overexpression of D3R in the experimental PD models with chronic treatment of L-dopa,[12–14] the pramipexole-associated fixed limb dystonia may be due to abnormal activation of D1R boosted by pramipexole binding on D3R in a situation where D3R is overexpressed by the chronic treatment of L-dopa.

To date, there have been 2 case reports about dystonia (limb dystonia and antecollis) associated with pramipexole.[4,5] In both cases, L-dopa was used before adding a pramipexole. This result also supports our speculation about the pathophysiology of pramipexole-associated dystonia. In our patient, unlike the previous 2 case reports about dystonia associated with pramipexole,[4,5] CRPS developed in her left hand a few days after dystonia occurred. There was no acute cerebral infarction lesion in a brain MRI, and no abnormal findings in an

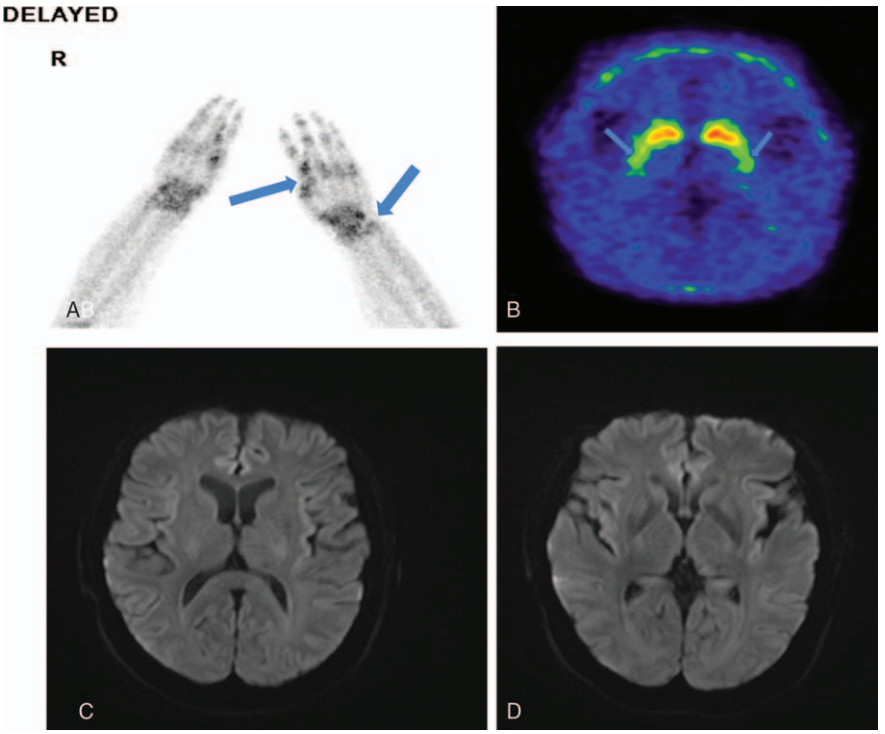

Figure 2. (A) Three phase bone scintigraphy. Increased uptake of the left wrist and MCP joint was shown in the delayed phase. (B) Brain PET scan using F-18 FP-CIT 6.40 mCi. Decreased uptake of rostrocaudal gradient in the bilateral posterior putamen, which was consistent with idiopathic Parkinson disease. (C)(D) Diffusion brain MRI. There was no acute lesion in the diffusion brain MRI. F-18 FP-CIT = Fluorine-18 Fluorinated N-3-fluoropropyl-2-beta-carboxymethoxy-3-beta-(4-iodophenyl) nortropane, MCP = metacarpal phalangeal, MRI = magnetic resonance image, MTP = metacarpal phalangeal, PET = positron emission tomography.

electrophysiological study. Therefore, we diagnosed the condition as CRPS type 1 and started steroid treatment. However, considering the fact that dystonia was not resolved and recurrence of CRPS occurred despite steroid treatment, the fact that the CRPS improved after the dystonia was resolved, and the fact that the dystonia was resolved after discontinuation of pramipexole, the cause of CRPS seemed to be dystonia induced by pramipexole.

Recently, the relationship between movement disorders (MDs) and CRPS has been reported. Several clinical case series of CRPS have described different MDs in a substantial, yet inconsistent, proportion between 10% and 90% of the patients evaluated.[15] Among the MDs, the most prominent MD in CRPS is dystonia.[15] A larger study with 692 CRPS type 1 patients found 124 (19.9%) cases of dystonia.[16] Besides MDs, the basal ganglia may be involved in several key features of central processing and modulation of nociceptive information such as the sensory-discriminative aspect of pain as well as the affective and the cognitive dimension of pain.[17] In this case report, therefore, basal ganglia dysfunction, which presented as dystonia (which may have been due to abnormal activation of D1R boosted by pramipexole binding on overexpressed D3R), may have been the cause of CRPS type 1.

Since a high dose of pramipexole increases the degree of overexpression of D3R,[12] for patients with PD who are treated with L-dopa for long periods, a new use of pramipexole and an increase in dose to alleviate the symptoms of PD should be implemented with caution while closely observing the occurrence of drug-induced complications such as dystonia and CRPS.

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