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Letter to the Editor: New Observation

Propofol Withdrawal Dyskinesia in a Parkinson's Disease Patient with Levodopa-Induced Dyskinesia

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The precise mechanism of dyskinesia in Parkinson's disease (PD) remains unclear. Herein, we report a case of a patient with PD who experienced dyskinesia and received propofol as premedication before deep brain stimulation (DBS) surgery. We also discuss the mechanisms underlying PD dyskinesia.

A 67-year-old man with a 30-year history of PD was admitted to our hospital as a possible candidate for subthalamic DBS. He had severe motor fluctuations and end-of-dose dyskinesia that were refractory to medical therapy. His daily medications included 500 mg levodopa/carbidopa, 500 mg entacapone, 0.75 mg pramipexole, 300 mg amantadine, and 4 mg biperiden hydrochloride. He showed neither cognitive decline, based on the Japanese version of the Montreal Cognitive Assessment (29 points) and Frontal Assessment Battery (17 points), nor psychiatric problems. His Unified Parkinson's Rating Scale motor score (Movement Disorder Society revision) was 76 in an "off" state (withdrawal of anti-Parkinsonian drugs for >12 h) and 17 in an "on" state (60 min after taking 1.5 times higher than the usual morning levodopa dose after the drug-off phase). After the evaluation for surgery, he was admitted for the procedure. All antiparkinsonian drugs were discontinued >14 h before surgery. On the morning of the surgery, intravenous propofol infusion, whose sedative effect lasts for approximately 3–8 min,[1] at a total of 32 mg was administered over 2 min for placement of the stereotactic frame. Twenty minutes after the propofol infusion was stopped, he experienced severe dyskinesia similar to propofol-induced end-of-dose dyskinesia, which lasted for approximately 10 minutes (Online Resource 1). After the disappearance of dyskinesia, resting tremor, which indicate an "off" state of Parkinson's disease, appeared (Online Resource 2: Figure 1).

This present case may have several implications on the pathophysiology of PD dyskinesia. There have been several cases that showed involuntary movements with propofol use, but there have only been two reports of propofol-induced dyskinesia in patients with PD.[2,3] Kraus et al. reported on patients who experienced dyskinesia after a bolus injection of propofol, and increasing the dose worsened the dyskinesia. Another patient also developed dyskinesia after starting continuous intravenous infusion of propofol, which did not resolve even after stopping the propofol infusion. In these cases, dyskinesia occurred at high concentrations of propofol in the plasma. This phenomenon is similar to levodopa-induced peak-dose dyskinesia, which occurs when the levodopa plasma levels are the highest. However, in our case, dyskinesia appeared not during propofol infusion but several minutes after cessation of propofol infusion; it was followed by the appearance of a PD symptom typically observed in the "off" state, i.e., resting tremor. Phenomenologically, the dyskinesia of our patient was very similar (i.e., predominant in lower legs, ballistic movement) to levodopa-induced end-of-dose dyskinesia. Although the blood levels of propofol were not measured in this case, we speculated that little amount of propofol remained in the patient's system when the dyskinesia appeared, since the half-life of the blood concentration of propofol is 2–4 min.[1] Therefore, we surmised the patient had propofol-induced end-of-dose dyskinesia. Previous patients with propofol-induced dyskinesia had a history of preoperative levodopa-induced peak-dose dyskinesia, whereas our patient had preoperative levodopa-induced end-of-dose dyskinesia. The degree of functional changes in direct and indirect pathways in the cortico-basal ganglia circuit was theorized to differ between peak and diphasic (levodopa-induced end-of-dose and/or initial-dose) dyskinesia.[4] Considering the literature and our observations, once functional changes of cortico-basal ganglia circuits, which depend on the type of dyskinesia in each case, are established, dyskinesia can be triggered by either dopamine or propofol. One study showed that intravenous injection of propofol increases dopamine concentration in the sensory cortex of rats.[5] This phenomenon may explain the mechanisms of both propofol-induced peak-dose and end-of-dose dyskinesia in patients with advanced PD. However, considering that not all patients with dyskinetic PD show propofol-induced dyskinesia, and propofol's effect on dopamine

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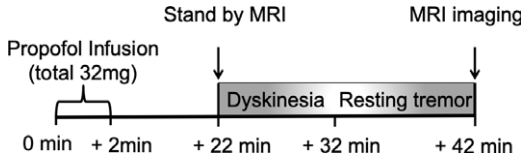

Figure 1: Timeline of the patient course.

release is controversial,[6] mechanisms of dyskinesia appearance seem to differ between dopamine and propofol induction.

There are two main neurotransmitters in the cortico-basal ganglia circuits: gamma-aminobutyric acid (GABA) and glutamate. Several reports have shown how propofol enhanced GABAergic synaptic transmission[7] and its inhibitory effect on glutamate release. Further, altered amounts of both GABA[8] and glutamate receptors in advanced PD have been reported. Previous reports suggest that the functional changes of the GABAergic-glutamatergic system may play an important role in peak dose propofol-induced dyskinesia in PD.[3] Therefore, these neurotransmitters may also be implicated in the pathophysiology of propofol-induced end-of-dose dyskinesia in PD. Altered cholinergic signaling has been shown to be another important factor in the development of dyskinesia. Drugs targeting various types of nicotine acetylcholine receptors as well as muscarine acetylcholine receptors are thought to be effective interventions to alleviate dyskinesia.[9] Some of these receptors are expressed in GABA interneurons and glutamatergic terminals. Therefore, considering the effects of propofol on the GABAergic-glutamatergic system, withdrawal of anticholinergic medication may play a role in propofol-induced dyskinesia. These speculations may help to elucidate the mechanisms of both levodopa-induced peak-dose and end-of-dose dyskinesia in PD. Further research is warranted to pursue this hypothesis.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2022.4.

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Availability of Data and Material. All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Ethics Approval. All procedures performed in this study were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration.

Consent for Participate. Informed consent was obtained from the patient included in the case report.

Consent for Publication. The patient gave written informed consent for the publication of any potentially identifiable images or data included in this article.

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