Clinical Parkinsonism & Related Disorders 3 (2020) 100073

Contents lists available at ScienceDirect

Clinical Parkinsonism & Related Disorders

journal homepage: www.elsevier.com/locate/prdoa

Apraxia of eyelid opening might be critical for levodopa-carbidopa intestinal gel treatment

Hiroshi Kataoka [a,*], Yasuhiko Sawada [b], Naotaka Shimozato [b], Shinichiro Inatomi [a], Naohiko Iguchi [a], Hitoshi Yoshiji [b], Kazuma Sugie [a]

[a] Department of Neurology, Nara Medical University, Kashihara, Nara, Japan
[b] Third Department of Internal Medicine, Nara Medical University, Kashihara, Nara, Japan

ARTICLE INFO

Article history:
Received 24 June 2020
Received in revised form 7 September 2020
Accepted 12 September 2020
Available online 25 September 2020

Keywords:
Parkinson
Apraxia of eyelid opening
Apraxia. LCIG
Levodopa

ABSTRACT

Apraxia of eyelid opening (AEO) has been associated with levodopa. It has also been linked to impaired function of the frontal lobe, with the dopaminergic neuron projected to the frontal lobe. However, dopaminergic treatment for AEO is still controversial. Here we describe two patients with both Parkinson's disease (PD) and AEO, who responded differently to a continuous intrajejunal levodopa-carbidopa intestinal gel (LCIG) infusion. One of the patients manifested a deterioration of AEO after LCIG infusion, and off-periods were shortened by the decrease in the severity of dyskinesia. After discontinuing the use of LCIG, there was an improvement in the patient's ability to open her eyelids. The other patient had AEO prior to LCIG treatment, and this treatment spontaneously elevated her eyelids. These two PD patients raised the concern as to whether AEO may be a critical symptom for the indication of LCIG treatment. The different responses to LCIG might have been due to the fluctuation in brain dopamine levels during LCIG treatment.

Apraxia of eyelid opening (AEO) is defined as the intermittent non-paralytic bilateral loss of the volitional ability to open the eyes or sustained eyelid elevation at certain times which cannot be explained by focal muscle weakness or dysfunction of neither the third nor the seventh cranial nerve [1,2]. The presence of AEO in association with diseases affecting extrapyramidal system, the rostral brainstem or the right hemisphere [3,4] suggests the basal ganglia structure and the associated neuronal networks involves in the pathogenesis of AEO. Patients with Parkinson's disease (PD) sometimes exhibit AEO. Different eyelid manifestations can occur in patients with PD and dopaminergic treatment for AEO is still controversial [5–8]. Here, we describe two patients with PD and AEO who responded differently to continuous intrajejunal infusion of levodopa-carbidopa intestinal gel (LCIG).

1. Case 1

With the present case, we describe a 66-year-old right-handed woman with a disease history started 20 years before with decelerated walking. She was diagnosed with PD diagnosis based on Parkinson's features, and she was given antiparkinsonian medications. Cardiac iodine 123 (^{123}I)-metaiodobenzylguanidine (MIBG) scintigraphy uptake was reduced. Medication-related information, such as dosage or kind, was undetermined because the clinical chart had already been destroyed. Nine years after the disease onset, her off-periods were prolonged, and levodopa-induced peak-dose dyskinesia developed. For prolonging on-periods, the treatment was modified either by increasing levodopa dosage (500 mg/day, four times) or by adding catechol-*O*-methyltransferase (COMT) inhibitors (600 mg/day, four times) or ropinirole (16 mg/day). Long-acting rotigotine (9 mg/day) for nocturnal symptoms was initiated, although it was later discontinued due to cutaneous reactions. Fourteen years after the disease onset, the patient received subcutaneous apomorphine (2 to 3 mg/day) to prevent severe off-periods, and infusions were increased to four times a day. However, the on-periods did not persist for more than 2 h, and she sometimes experienced difficulties in elevating her eyelids. This occurred at rest without any trigger and related to her volitional opening. Moreover, she was transferred to our hospital for LCIG treatment. During this time, she was given levodopa (650 mg/day, eight times), ropinirole (12 mg/day), and zonisamide (50 mg/day). She had dyskinesia and nightmare-enacting behaviors. Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB) scores were 28/30 and 15/18, respectively. She had no history of psychosis or hallucinations. Her body mass index was low, probably due to dyskinesia. We used levodopa infusion on the patient to confirm its effect on motor symptoms. Levodopa (25 mg) in saline solution (100 mL) was intravenously infused over 30 min in the evenings, during the patient's off-periods. Twenty min after the levodopa infusion (60 mg), the unified PD rating scale (UPDRS)-III score decreased from 45 to 11. Dyskinesia was observed a few minutes after the infusion (10 mg), and this examination was discontinued due to the development of prominent and intolerable dyskinesia with the dyskinesia subitem 2 score on Movement Disorder Society (MDS)-UPDRS part IV was 4 [9]. Since her incessant motor fluctuation was not

* Corresponding author at: Department of Neurology, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan.
E-mail address: hk55@naramed-u.ac.jp. (H. Kataoka).

http://dx.doi.org/10.1016/j.prdoa.2020.100073

controlled by the antiparkinsonian medication or infusion, and the motor severity responded to levodopa, she was administered LCIG through a nasoduodenal tube. The dosage of ropinirole was gradually reduced to avoid dopamine agonist withdrawal syndrome. She was satisfied with daily living since her off-periods were shortened, and the severity of dyskinesia was decreased. The dyskinesia subitem 1 and 2 scores on MDS-UPDRS part IV were decreased from 4 to 2 and from 4 to 2, respectively. Two days after the start of the LCIG infusion (carbidopa-levodopa, 42/9.7 mg/h), she had difficulties opening her eyelids. The LCIG dosage (carbidopa-levodopa, 60/12.8 mg/h) or the frequency of additional rescue infusion was increased. However, both the frequency and duration of the difficulty of eyelid opening were also increased. Neither duloxetine (20 mg/day) nor amantadine (200 mg/day) was effective for this eyelid manifestation. Eighteen days after LCIG initiation, she could not open her eyelids all day, and dyskinesia was significant. Hence, treatment was discontinued 21 days after initiating LCIG, and we restarted levodopa (650 mg/day, eight times), ropinirole (4 mg/day), and zonisamide (50 mg/day), which were the same kind of medication as those she took prior to LCIG treatment, in addition to amantadine (200 mg/day) for dyskinesia. The ability to open her eyelids improved two days later, and her daily activities were no longer affected. The severity of dyskinesia reduced, and levodopa and ropinirole dosages were increased to 700 mg/day and 12 mg/day, respectively. She had some trouble elevating her eyelids, but this did not last for more than 30 min, and the frequency was one or two times per day.

2. Case 2

A 66-year-old right-handed woman presented with left-hand tremor started eight years before. PD was diagnosed based on Parkinsonian features and she received selegiline (7.5 mg/day). The uptake on cardiac MIBG scintigraphy was reduced. She had a clinically-probable rapid eye movement sleep behavioral disorder, a decline in smelling ability, and restless leg syndrome. The disease gradually progressed, and antiparkinsonian treatment was modified. However, off-periods were prolonged, so she was transferred to our hospital for LCIG treatment.

During that time, she was given levodopa (700 mg/day, seven times), COMT inhibitors (600 mg/day, six times), rasagiline (1 mg), istradefylline (40 mg), and rotigotine (18 mg/day). During her on-periods, the UPDRS-III score was 34, and MMSE and FAB scores were 27/30 and 16/18, respectively. Also, she could not open her eyelids spontaneously, and her eyes were closed throughout all consultations. This persisted for at least one year, and her condition impaired her daily activity. Due to the prominent alternating phenomenon of on-state and off-related disability, she was administered intrajejunal LCIG infusion four years later. The UPDRS-III score decreased to 17, and this on-state persisted after LCIG treatment (carbidopa-levodopa, 68/15.7 mg/h) in addition to rotigotine (18 mg/day) due to morning and night akinesia. Her eyelids elevated spontaneously, and after leaving the hospital, she could already open her eyes on every visit to our hospital, although she sometimes complained of difficulty. Two years after initiating LCIG treatment, the difficulty in opening her eyelids increased, which interfered with her daily living.

AEO did not show visible contraction of orbicularis oculi muscle or facial muscles. Before opting for LCIG treatment on the two patients, each outpatient doctor informed the patients and their families about the LCIG treatment. Moreover, the patients agreed to receive this treatment. Levodopa dosage of LCIG or medications was determined based on both daily Parkinson's symptoms and repeated medical observations within a day under hospitalization. MMSE and FAB testing were performed to determine whether LCIG pump and gastrostomy tube management were possible.

Written informed consent was obtained from these patients for the publication of this case report.

3. Discussion

We have described two patients with both Parkinson's disease (PD) and AEO, who responded differently to a continuous intrajejunal LCIG infusion. The frequency of AEO diminished in the second patient for a certain period. Other patients with PD have been described, and in these patients, AEO was considered as an off-phase dystonic symptom, since it was alleviated by sensory tricks, such as touching the temporal region [4,10]. AEO often develops after the onset of parkinsonian syndromes. Moreover, AEO in a patient with parkinsonian syndrome responded to carbidopa-levodopa drug therapy [8]. Meanwhile, the conditions of other patients that manifested AEO were deteriorated by the infusion of LCIG, and the severity of AEO was markedly decreased by discontinuing the use of LCIG. This was also evident in previous patients with PD [6,7]. Therefore, the role of levodopa therapy remains controversial. Subthalamic nucleus deep brain stimulation (STN-DBS) produces the time elapsing between the end of the eye-closing phase and the beginning of the eye-opening phase [11]. One study of STN-DBS demonstrated two subtypes, in which AEO either proved to be a side effect or was improved by STN stimulation, and AEO was not a specific side effect of target stimulation but occurred at higher voltage thresholds [4]. Patient 1 with deteriorated AEO had dyskinesia, but dyskinesia was not observed during the disease course of patient 2. Dyskinesia is considered to be caused by pulsatile dopaminergic stimulations and is commonly accompanied by dopamine activity fluctuations in the brain. In one PD patient, it was reported that AEO dose-dependently responded to levodopa [5]. The different responses to LCIG might be due to the fluctuation in dopamine brain levels during LCIG treatment.

AEO is a common form of blepharospasm in progressive supranuclear palsy (PSP), and the cranial dystonia is largely unaffected or aggravated by levodopa treatment [3]. In PD, cranial dystonia, including blepharospasm, was less frequently observed than PSP, and it occurred under wearing-off states and responded to levodopa, or the dystonia also observed under a “peak-dose” effect of levodopa [12]. AEO in our patients had no apparent characteristics of blepharospasm and parkinsonism responded to levodopa, and both patients did not experience early falling or eye-downward restrictions. This supports our hypothesis that AEO in our patients might have been due to PD. As a limitation, if the MDS-UPDRS-III score were used, the relation between off-periods and AEO could be found.

These two PD patients raise the concern as to whether AEO is a critical symptom for the indication of LCIG treatment.

Author responsibilities and contributions

H Kataoka was responsible for the overall study design, and wrote the manuscript.

H Kataoka, Y Sawada Y and N Shimozato contributed to organization, planning and coordination of the study.

H Kataoka, S Inaomi, and N Iguchi contributed to running the study and acquisition of data.

H Kataoka, S Inaomi, and N Iguchi contributed to analysis and interpretation of data.

H Kataoka, Y Hitoshi and K Sugie contributed to drafting and critical revision of part of the submitted materials.

Ethics statement

No investigations or interventions were performed outside of routine clinical care for this patient. As this is a case reports, without experimental intervention into routine care, no formal research ethics approval was required. Written, fully informed consent was received from the patient. This case study reports routine clinical care provided for a patient only.

Funding sources and conflict of interest

The authors report neither funding nor competing interest related to our paper.

Declaration of competing interest

The authors report no financial disclosure related to our paper.

References

[1] J.E. Goldstein, D.G. Cogan, Apraxia of lid opening, Arch. Ophthalmol. 73 (1965) 155–159.

[2] S.N. Reggie, J.J. Chen, M.S. Lee, S.M. Chung, Sleep-induced apraxia of eyelid opening, J. Neuroophthalmol. 37 (2017) 390–392.

[3] L. Marsili, M. Bologna, M. Kojovic, A. Berardelli, A.J. Espay, C. Colosimo, Dystonia in atypical parkinsonian disorders, Parkinsonism Relat. Disord. 66 (2019) 25–33.

[4] G. Tommasi, P. Krack, V. Fraix, et al., Effects of varying subthalamic nucleus stimulation on apraxia of lid opening in Parkinson's disease, J. Neurol. 259 (2012) 1944–1950.

[5] K.C. Lee, R. Finley, B. Miller, Apraxia of lid opening: dose-dependent response to carbidopa-levodopa, Pharmacotherapy 24 (3) (2004) 401–403.

[6] G. Defazio, M. De Mari, R. De Salvia, et al., "Apraxia of eyelid opening" induced by levodopa therapy and apomorphine in atypical parkinsonism (possible progressive supranuclear palsy): a case report, Clin. Neuropharmacol. 22 (1999) 292–294.

[7] P. Lamberti, M. De Mari, A. Zenzola, et al., Frequency of apraxia of eyelid opening in the general population and in patients with extrapyramidal disorders, Neurol. Sci. 23 (2002) S81–S82.

[8] S. Yamada, K. Matsuo, M. Hirayama, et al., The effects of levodopa on apraxia of lid opening: a case report, Neurology. 62 (2004) 830–831.

[9] C.G. Goetz, B.C. Tilley, S.R. Shaftman, et al., Movement disorder society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results, Mov. Disord. 23 (2008) 2129–2170.

[10] P. Krack, P. Pollak, P. Limousin, et al., From off-period dystonia to peak-dose chorea. The clinical spectrum of varying subthalamic nucleus activity, Brain 122 (1999) 1133–1146.

[11] M. Bologna, A. Fasano, N. Modugno, G. Fabbrini, A. Berardelli, Effects of subthalamic nucleus deep brain stimulation and L-DOPA on blinking in Parkinson's disease, Exp. Neurol. 235 (2012) 265–272.

[12] W.T. Yoon, E.J. Chung, S.H. Lee, B.J. Kim, W.Y. Lee, Clinical analysis of blepharospasm and apraxia of eyelid opening in patients with parkinsonism, J. Clin. Neurol. 1 (2005) 159–165.