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Reevaluation of levodopa therapy for the treatment of advanced Parkinson's disease

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Abstract

Levodopa is the most appropriate drug in theory for supplementing dopamine deficiency in the brain of Parkinson's disease (PD) patients. In consideration of the pharmacological properties of levodopa, measurement of 3,4-dihydroxyphenylalanine (DOPA) plasma concentration is significant and important in daily medical care. Akinesia of advanced PD patients comprises a combination of two distinct symptoms, hypokinesia and bradykinesia. It is probable that hypokinesia in PD does not originate from failure of neural pathways from the substantia nigra to motor striatum but is associated with dysfunction of the limbic striatum. Herein the pathophysiologic condition of the limbic striatum in PD patients is discussed and reasons suggested why drug efficacy of dopamine replenishment in this system is meager.

Keywords: Parkinson's disease; Levodopa; DOPA plasma concentration; Dopamine deficiency; Akinesia; Hypokinesia; Bradykinesia; Motor striatum; Limbic striatum; Meso-limbic-cortical system

1. Introduction

1.1. Classification and definition of advanced-stage PD

Advanced PD is defined as phases 3 and 4 in the schema proposed by Fahn [1] (Table 1). At this stage, usually beginning about 5 years after the initial onset of the disease symptoms, clinical manifestations progress markedly and the decline in the effectiveness of drug therapy becomes prominent, with the net result that the patient's functional status returns to pretreatment levels.

Table 1
Clinical phases of levodopa therapy

Phase 1: Honeymoon period	Usually lasts 2–3 years.
Phase 2: Motor complication period	After 5 years of levodopa therapy, 75% of patients develop response fluctuations (wearing-off and on-off phenomena) or dyskinesia [12].
Phase 3: Period of progression and drug-resistant parkinsonism	By 5 years of levodopa therapy, clinical severity returns to the level prior to initiating levodopa therapy [13,14].
Phase 4: Dementia period	Development of dementia, confusion, hallucination

1.2. Japanese Society of Neurology guidelines for treatment of PD [2]

1.2.1. General concepts

The general concepts of anti-PD treatment are outlined in Table 2. Levodopa and dopamine agonists are the key drugs for the treatment of PD, and levodopa appears most suitable for physiological treatment. However, because the frequency of adverse effects is high when levodopa is used, dopamine agonists are used together with levodopa to reduce their occurrence. In particular, levodopa-induced dyskinesia is believed related to the age of onset of PD.

1.2.2. Guidelines for treatment of advanced-stage PD

Several issues concerning the use of levodopa in the treatment guidelines for patients with advanced-stage PD,

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Table 2
Guidelines for treatment of PD (general remarks) [12]

- Main drugs: Levodopa and dopamine agonist.
  Others are supplemental drugs [15]
- Levodopa appears optimal for physiological treatment. However, its use is associated with a high frequency of occurrence of motor complications; wearing-off, on-off, and no-on/delayed-on phenomena and dyskinesia.
- (1) Prolongation of DOPA-induced motor complications by dopamine agonist-combination therapy (Level Ib).
- (2) Relation between age of onset and DOPA-induced motor complication (Level III)
  (3) Appropriate retaining dose of levodopa and dopamine agonist
  (4) The levodopa dose does not promote nigral degeneration (Level III, IV)
  (5) Is there neuro-protective action of antiparkinson drugs?

established by the Japanese Society of Neurology, are described below.

Measures for wearing-off and on-off phenomena. If wearing-off and on-off phenomena are accompanied by dyskinesia in a patient, monoamine oxidase (MAO)-B inhibitors or catechol-*O*-methyl transferase (COMT) inhibitors should be used in combination with levodopa. The hierarchical measures taken after their use are as follows: levodopa is administered in divided doses and, at the same time, the combined use of a dopamine agonist is initiated or the dose of the dopamine agonist is increased; thereafter, the combined use of amantadine may be considered, and stereotaxic brain surgery (deep brain stimulation) may be considered as the last resort.

Measures for no-on and delayed-on phenomena. Patients experiencing no-on and delayed-on phenomena are instructed to take their medications on an empty stomach before meals. Efforts are made to maintain gastric acidity. The dose of levodopa is increased. A COMT inhibitor is used in combination with levodopa. Patients are instructed to eat the daily-required amount of protein at supper and limit the amount of protein in meals during the daytime.

Measures for levodopa-induced dyskinesia. In patients with levodopa-induced dyskinesia, the use of MAO-B inhibitors or COMT inhibitors in combination with levodopa should be stopped. The daily dose of levodopa is divided into more frequent, lower doses and the total dose is also reduced. Minor adjustments, such as adding a dopamine agonist or increasing the dose of the dopamine agonist, are made. Amantadine is used in combination with levodopa. Tiapride or risperidone is used concomitantly to reduce dyskinesia. In this author's practical experience, sulpiride has shown clear effectiveness against buccolingual dyskinesia. If the effectiveness of adjusting the drug dose is limited, stereotaxic brain surgery may be considered.

Measures for hallucination and delusion. In patients who develop hallucinations or delusions, any medications that have been added to levodopa immediately prior to the occurrence of these symptoms should be stopped. If the hallucinations or delusions continue, other drugs that are being used in combination with levodopa are stopped one at a time, if necessary until only levodopa is still being administered. If symptoms still persist, levodopa dose is decreased. However, if deterioration in motor function then precludes further levodopa dosage reduction, atypical antipsychotics or tiapride are used in combination with levodopa to control the symptoms. Donepezil is effective for treating visual hallucinations. Typical antipsychotics may be necessary if it becomes difficult to control symptoms such as restlessness and agitation. Careful attention is especially necessary when typical antipsychotics are used for elderly patients, because sometimes the use of typical antipsychotics leads to exacerbation of motor symptoms – even one or two doses may do irreparable damage. Modified electroconvulsive therapy should be considered by an experienced specialist (psychiatrist) who attends the patient; this therapy should not be used without careful consideration.

1.2.3. Current understanding of levodopa pharmacokinetics

A schema of the pharmacokinetics of levodopa treatment is shown in Fig. 1. During the combined use of levodopa with a decarboxylase inhibitor, when the bioavailability of levodopa is increased, the levodopa dose should be decreased to one fifth of that in the case of levodopa monotherapy. However, 3-*O*-methyldopa (3-OMD), which exists in trace amounts in the blood, reaches high concentrations in plasma during long-term administration of levodopa and a decarboxylase inhibitor. The existence of 3-OMD in the plasma is not viewed as a problem when combined administration of levodopa and a decarboxylase inhibitor is established as a treatment strategy because 3-OMD itself is recognized as having no physiological activity; however, recently it has been pointed out that a high concentration of plasma 3-OMD may destabilize the pharmacokinetics and pharmacodynamics of levodopa. The regimen for replenishing brain dopamine deficiency – normalizing the concentration of plasma 3-OMD by administering a COMT inhibitor and further increasing the bioavailability of levodopa – was established from the viewpoint of pharmacokinetics and pharmacodynamics.

1.2.4. Significance of monitoring plasma concentration of DOPA

The mysteries and problems associated with the clinical pharmacodynamics of levodopa remain unsolved. During the early stages of therapy, patients usually experience a "honeymoon period" in which a stable effect of levodopa is attained. With time, however, phenomena such as motor fluctuations and dyskinesia develop and measures are required to deal with these adverse effects. The large individual variation in the correlation between the dose of levodopa and the plasma concentration of DOPA (Fig. 2) is remarkable compared with other drugs. The large individual variation depending on the treatment strategy (Fig. 3) is yet another mystery [3]. A normal pattern of pharmacokinetics has been observed

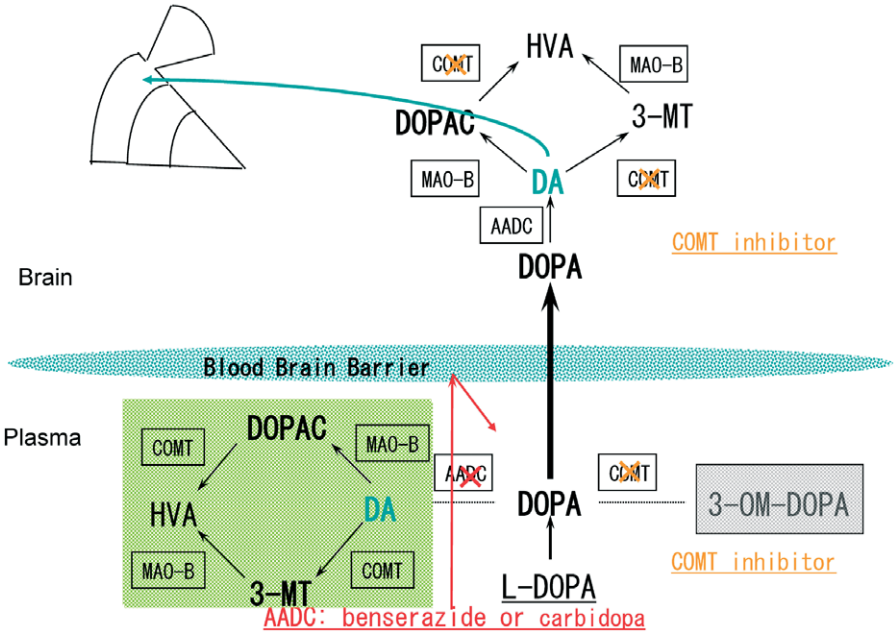

Fig. 1. Dopamine metabolism in plasma and brain – enzymes and metabolites. Abbreviations: DOPA, 3,4-dihydroxyphenylalanine; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; 3-MT, 3-metoxytylamine; HVA, homovanillic acid; AADC, aromatic aminoacid decarboxylase; MAO-B, monoamine oxidase B; COMT, catechol-*O*-methyltransferase; 3-OM-DOPA, 3-*O*-methylated dihydroxyphenylalanine.

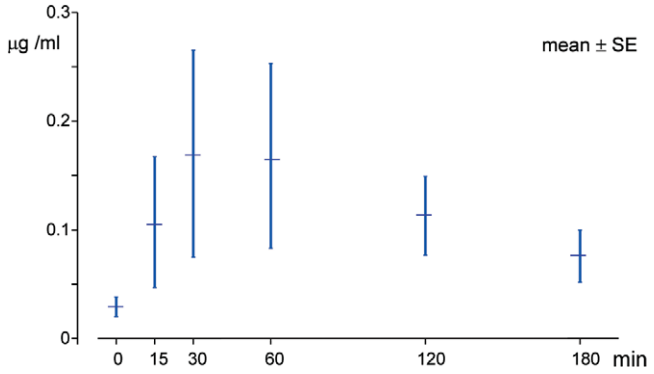

Fig. 2. Plasma dopamine concentration after oral administration of levodopa 500 mg in PD patients.

in younger PD patients, whereas in elderly PD patients an abnormal pattern of pharmacokinetics was observed and the bioavailability of levodopa was poor (Fig. 4) [4]. Although the cause of this abnormal pattern has not been clarified, it is possible that the impaired metabolic absorption of levodopa observed in elderly PD patients is related to the root cause of the disease. Levodopa therapy should be administered by paying attention to the large individual variation in levodopa kinetics caused by various factors. Because the plasma DOPA concentration is closely related to changes of symptoms and to the brain concentration of dopamine in typical cases, the monitoring of plasma DOPA concentration is important for understanding the physiological kinetics of levodopa. From this viewpoint, plasma DOPA concentration is monitored as necessary during daily treatment at our hospital. We previously determined the optimum plasma DOPA concentration from the results of blood tests carried out during consultations. As a result, it was found that the optimum plasma DOPA concentration is approximately 500 ng/ml 1.5 hours after administration, as shown in Fig. 5. In a study performed independently but using the same method, Copeland et al. [5] suggested the same optimum plasma concentration. Unlike antiepileptic drugs, which are covered by the health insurance system in Japan, DOPA is not included in the list of drugs that require routine monitoring of plasma concentrations. The results of these studies favor the inclusion of DOPA on this list.

1.2.5. Definition of akinesia

Among the symptoms ameliorated by brain dopamine replacement, akinesia is of particular interest. Akinesia actually includes two distinct motor disorders (Table 3).

One motor disorder of akinesia is bradykinesia (slowness of movement) which is studied by evaluation of manifested movement. Bradykinesia occurs in parallel with rigidity and impaired skilled motor performance in PD patients and is considered as secondary akinesia. The other presenting feature of akinesia is hypokinesia (absence of movement). This is a condition in which any movements or actions which are unconscious movements, including accessory movements such as gestures and swallowing actions, are scarce, although the elemental motor function is maintained. Hypokinesia may be the essential feature of PD and might be labeled primary akinesia.

Table 3
Definition of akinesia – two essentially distinct phenomena

A:	Bradykinesia (slowness of movement): = secondary akinesia
B:	Hypokinesia (poverty of movement, lack of accessory movement, idle state): Scarcity of movements = primary akinesia

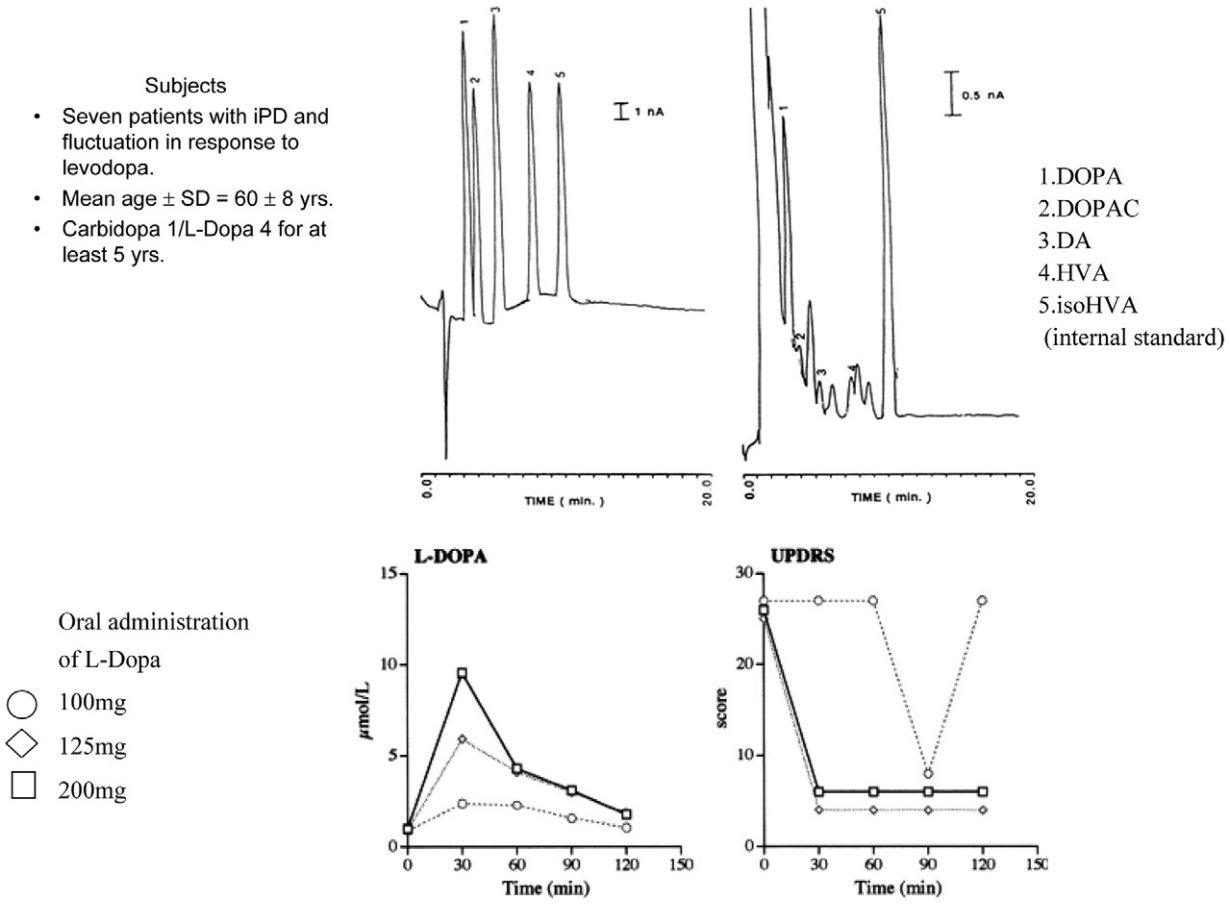

Fig. 3. Microdialysis–HPLC for plasma levodopa and metabolites monitoring in PD patients (adapted from Dethy et al. [3]). Abbreviations: DOPA, 3,4-dihydroxyphenylalanine; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; UPDRS, Unified Parkinson Disease Rating Scale.

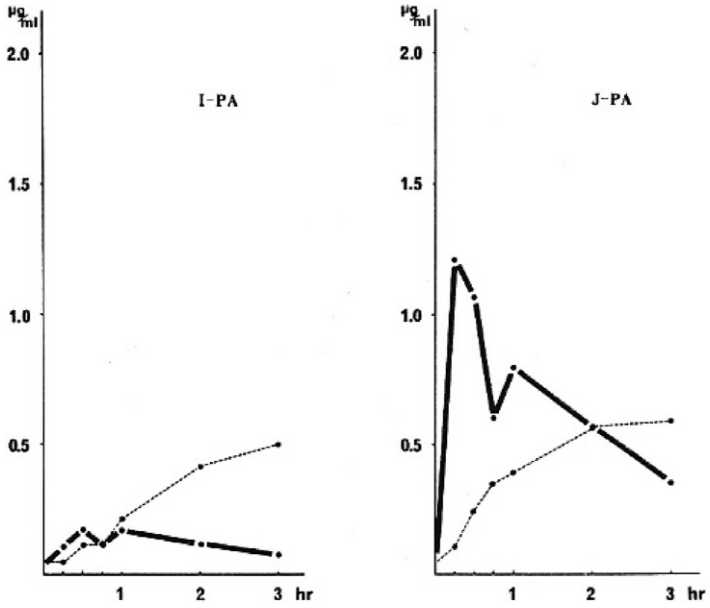

Fig. 4. Plasma concentrations of DOPA and DA after oral administration of levodopa 500 mg in younger (J-PA) and older (I-PA) PD patients (revised from Narabayashi et al. [4]). ——•——, DOPA; -----•------, DA. Abbreviations: DOPA, 3,4-dihydroxyphenylalanine; DA, dopamine; I-PA, aged PD patients; J-PA, juvenile PD patients.

We evaluated hypokinesia by performing movement analysis. For Hoehn and Yahr stage III patients, the process of accomplishing simple movement tasks was recorded using a video camera through a one-way mirror, and image analysis was performed in terms of the amount of movement per unit time. The focus of movement analysis in this experiment was

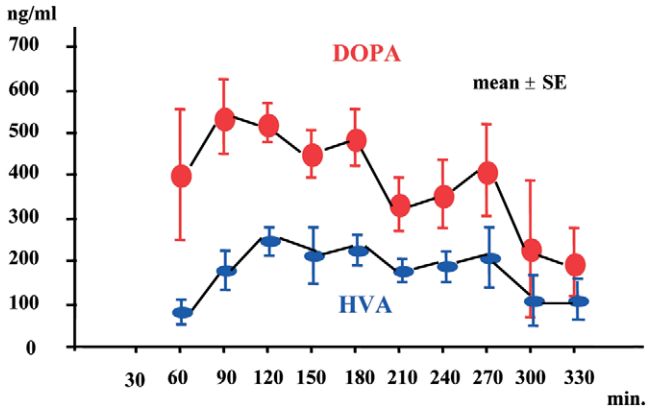

Fig. 5. Plasma DOPA and homovanillic acid (HVA) concentrations of patients with Parkinson's disease in routine outpatient monitoring. Abbreviations: DOPA, 3,4-dihydroxyphenylalanine; HVA, homovanillic acid.

not accomplishment of tasks but the movement characteristics of the patients in intervals between individual tasks. As a result, while the healthy subjects showed natural and free movements in a relaxed manner depending on the situation, the PD patients displayed an absolute scarcity of movements independent of the situation. Hypokinesia is not marked in the early stage of the disease, but becomes prominent in proportion to the disease duration. It is not directly linked to the level of rigidity, tremor, and gait dysfunction. It can be considered to be simply an idle state in which patients do not move although elemental motor functions are maintained. However, hypokinesia is not accompanied by a clear decrease in motivation or impaired cognitive function. Moreover, it is not affected by antiparkinson drugs such as levodopa; rather, it is a symptom that is not improved by brain dopamine replenishment.

Rigidity, slowness of movement, and impaired skilled motor performance are caused by dysfunction in the dorsal striatum (motor striatum) arising from damage in the substantia nigra pars compacta (A9). On the other hand, hypokinesia is caused by dysfunction in a different region of the central nervous system, namely the ventral striatum (limbic striatum), which receives input from the ventrotegmental

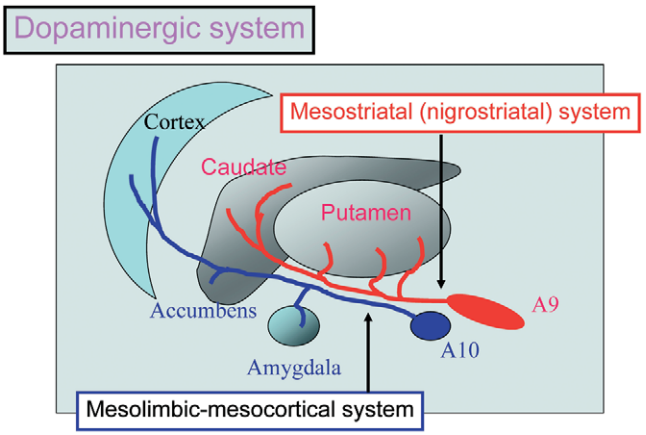

Fig. 6. Dopaminergic system of the brain. Drawing by H. Miwa.

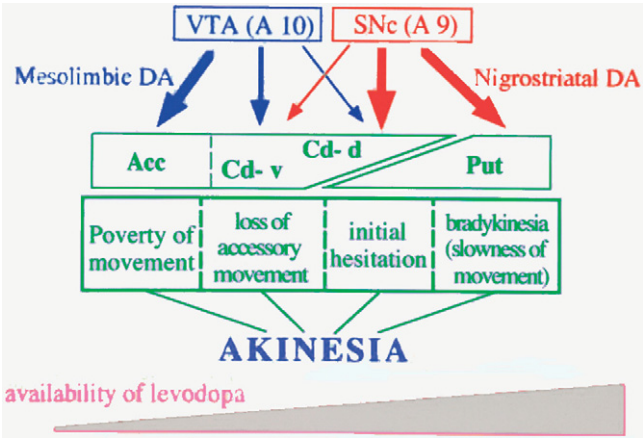

Fig. 7. Schematic representation of relation of akinesia symptoms and behavior of DA systems. See details in text. Abbreviations: Put, putamen; SNc, substantia nigra pars compacta; Cd-d, caudate nucleus pars dorsalis; Cd-v, caudate nucleus pars ventralis; VTA, ventro tegmental area; Acc, accumbens; DA, dopamine.

area (A10) (Fig. 6). We performed a series of animal experiments on the basis of this assumption. We produced an electrocoagulated lesion in the medial forebrain bundle of deeply anesthetized cats at the hypothalamic level to produce dopamine deficiency in the ventral striatum while avoiding dopamine deficiency in the dorsal striatum, thus obtaining an animal model of hypokinesia as the principal feature without disorders in elemental movements such as standing up and walking.

1.2.6. Hypokinesia in advanced-stage PD for which levodopa is ineffective

The functional linkage of hypokinesia to other PD symptoms may be considered, as shown in Fig. 7. It is probable that hypokinesia is not caused by dysfunction in the nigrostriatal dopamine projection arising from the mesencephalic substantia nigra pars compacta (A9), but by dysfunction in the mesolimbic dopamine system arising from the ventrotegmental area (A10) and projecting to the ventral striatum as well as the nucleus accumbens. Moreover, current therapy with dopamine replenishment, such as levodopa therapy, is not effective against hypokinesia, although the reason for this is unclear. As described earlier, the fact that hypokinesia worsens in advanced disease suggests that dopaminergic neurons in the ventrotegmental area are not yet impaired in early disease, and therefore can tolerate damage exposure. The number of pigmented neurons in the ventrotegmental area decreased to 37% [6,7] or 50% [8,9] of that in healthy subjects, and the levels of tyrosine hydroxylase [6,7] and homovanillic acid [10] also decreased to 50% of those seen in healthy subjects. However, these levels can be considered nearly normal compared with the decrease in the levels of these substances in the substantia nigra [11]. It is expected that the details of the clinical state of hypokinesia will be clarified in the future and that measures will be developed to deal with the symptoms and thereby improve the quality of life of advanced-stage PD patients.

Conflict of interest

The author has no conflict of interest to report. No funding applicable.

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