estingly, ZNS administration increased both intracellular and extracellular S100β-positive signals in and around astrocytes. S100β is secreted primarily by astrocytes, and extracellular S100β exerts autocrine effects to promote astrocyte proliferation.[19,20] In the C6 cells, anti-S100β antibody completely neutralized the astrocyte-proliferating effects of ZNS, indicating that ZNS might promote proliferation via its enhancing effect on S100β production or secretion in/from astrocytes. Taken together with the effects of ZNS on xCT expression in activated astrocytes, these data suggest that ZNS-induced increase in GSH is mediated through enhancing effects on astroglial cyst(e)ine transport system and/or on astroglial proliferation via S100β production or secretion. Especially in the lesioned side of the striatum of hemi-PD mice, ZNS enhanced xCT expression in activated astrocytes but not further astroglial proliferation. Thus, the former enhancing effects on astroglial cyct(e)ine transport system appear to mainly contribute to the GSH-increasing effects of ZNS in the dopaminergic neurodegenerative state in PD models.

The reduction of nigrostriatal DA neurons in the lesioned side of hemiparkinsonian mice was significantly prevented by repeated 1-week injections of ZNS, starting at 3 weeks after the 6-OHDA lesioning. This neuroprotective effect might reflect the strong antioxidative properties of ZNS via GSH, whereby it protects against sustained oxidative stress caused by mitochondrial dysfunction, among other causes, but not against free radical or quinone generation from 6-OHDA itself in the short term. It is therefore possible that the GSH-increasing effect of ZNS contributes to the neuroprotective effect of the drug against dopaminergic neurodegeneration.

The large amount of free cytosolic DA outside the synaptic vesicle is spontaneously oxidized to produce reactive quinones such as DA quinones or DOPA quinones.[23–28] The generated DA quinones covalently conjugate with the sulfhydryl group of cysteine on various functional proteins[24,29] including several key molecules, for example, TH, DAT, and parkin, which are involved

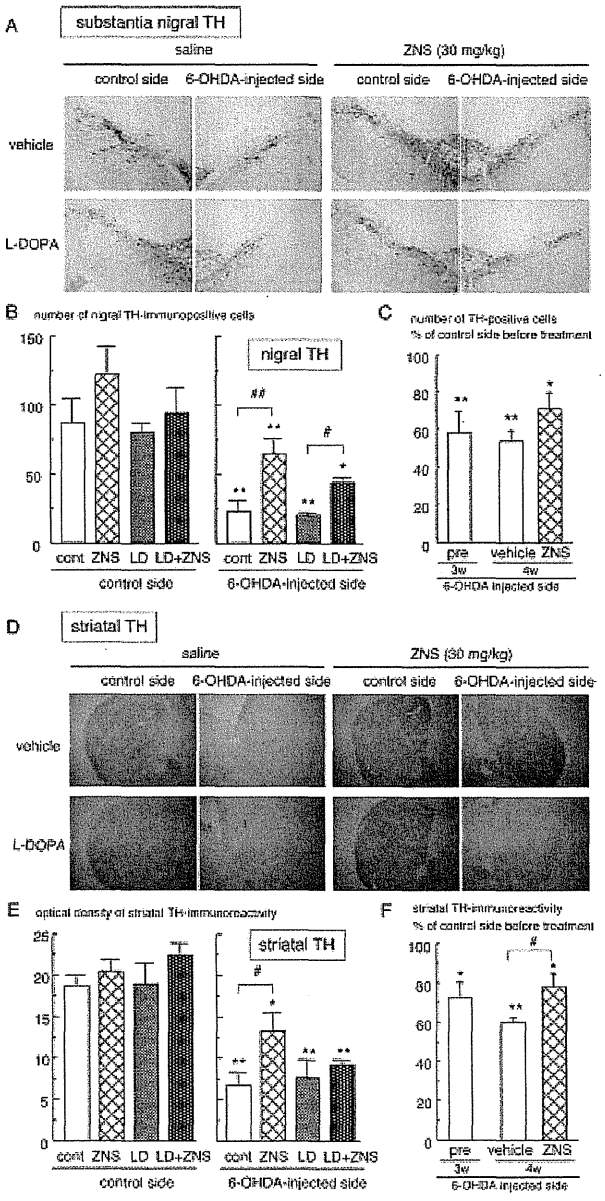

FIGURE 5: Effects of in vivo zonisamide (ZNS) administration on reduction of dopaminergic neuronal damage in the basal ganglia of hemi-Parkinson's disease (PD) mice. Representative photomicrographs of immunohistochemistry for tyrosine hydroxylase (TH) in the substantia nigra (A) and in the midstriatum (D) of hemi-PD mice after the 1-week administration with L-dopa and/or ZNS (at 4 weeks after the 6-hydroxydopamine [6-OHDA] lesioning). Changes in the number of nigral TH-positive dopaminergic neurons (B) and the striatal immunoreactivity of TH (E) of hemi-PD mice at 4 weeks after the 6-OHDA lesioning, and effects of administration with L-dopa/carbidopa (50/5mg/kg/day) and/or ZNS (30mg/kg/day) for 7 days starting at 3 weeks after the lesioning. LD = L-dopa–treated group; LD+ZNS = L-dopa+ZNS-treated group. Data are means ± standard error of the mean (SEM) (n = 5–6). *$p < 0.05$, **$p < 0.01$ compared with the control side of each drug-treated group; #$p < 0.05$, ##$p < 0.01$ compared with the two groups indicated. Time-dependent changes in the number of TH-positive neurons in the substantia nigra (C) and signal intensity of striatal TH immunoreactivity (F) in the lesioned side at 3 weeks (pre) and 4 weeks after 6-OHDA lesioning, and effects of the repeated 1-week administration of ZNS starting 3 weeks after the lesioning. Data are means ± SEM presented as percentage of mean value on the control side in the pretreatment group (n = 6). *$p < 0.05$, **$p < 0.01$ compared with the control side in the pretreatment group at 3 weeks after 6-OHDA lesioning; #$p < 0.05$ compared with the two groups indicated.

in the pathogenesis of PD, to form protein-bound quinones (quinoproteins), and cause the dysfunction of these proteins.[30–34] We reported previously that repeated administration of L-dopa increased striatal DA turnover and formation of quinoproteins specifically in the parkinsonian side, but not in the control side, of hemiparkinsonian animal models.[16,35] The sulfhydryl group of free cysteine in GSH and thiol reagents compete with the sulfhydryl group on cysteine in functional proteins bound by DA quinones.[15,23,30,36,37] Therefore, GSH acts as an antioxidant through its quenching properties not only for general reactive oxygen species but also DA quinones.[38] That ZNS dramatically increased GSH levels in the striatum suggests ZNS treatment can suppress in vivo quinone formation by increasing GSH. Therefore, we also examined effects of ZNS in 6-OHDA–lesioned hemi-PD mice that received adjunct L-dopa treatment. As expected, repeated ZNS injections resulted in complete suppression of striatal quinone formation in L-dopa–treated PD models. With regard to the effects of L-dopa treatment on neurodegeneration, repeated L-dopa injections did not aggravate neurodegeneration of nigrostriatal DA neurons in the lesioned side of parkinsonian models, in agreement with the results of a clinical Earlier vs. Later Levodopa (ELLDOPA) study that showed no aggravation of clinical PD symptoms and less deterioration of neurodegeneration after long-term L-dopa treatment.[39] The protective effects of ZNS treatment against reduction of nigral DA neurons were observed in both the ZNS alone–treated group and the L-dopa+ZNS–treated group. These findings suggest that the neuroprotective effects of ZNS against progressive nigral neuronal loss are mediated through its antioxidative properties via GSH against predominantly general reactive oxygen species rather than quinone formation.

Furthermore, recent studies emphasized the involvement of GSH or astroglial dysfunction in the pathogenesis of PD. Chinta and colleagues[12,13] showed that depletion of GSH levels in dopaminergic neurons of GCL-knockdown transgenic mice caused impairment of mitochondrial complex I activity and consequent age-dependent nigrostriatal neurodegeneration. Furthermore, Solano and colleagues[14] demonstrated astroglial dysfunction in parkin null mice; glia-conditioned medium of midbrain astrocytes from aged parkin knock-out mice contained low levels of GSH, rendered DA neurons less susceptible to oxidative stress, and the vulnerability was corrected by supplementation with GSH. These findings suggested that GSH or its synthesis-related molecules in astrocytes, or both, play an important role in protecting against age-dependent nigrostriatal dopaminergic neurodegeneration.

The clinical use of GSH in PD was reported in a small pilot study.[40] In that case, intravenous administration of 600mg GSH twice daily for 30 days significantly improved disability in PD patients. More recently, a small, double-blind, clinical trial also showed mild but not significant improvements in the Unified Parkinson's Disease Rating Scale activities of daily living plus motor score of PD patients treated with 1,400mg GSH intravenously three times a week over 4 weeks.[41] However, large amounts of these molecules were required to achieve efficacy because of their low transport capacity across the blood–brain barrier and their peripheral metabolism.[42] Furthermore, the clinical nosotropic effects of GSH on motor symptoms of PD remain difficult to explain biologically to date because there is no evidence to show how GSH modulates PD motor symptoms. Therefore, the increasing GSH levels in the brain by ZNS treatment might prove clinically useful through its antioxidant effects to diminish oxidative stress, and hence potentially prevent further pathological progression and enhancement of intrinsic neuroprotective mechanisms in PD patients rather than through improvement of motor symptoms.

About the concentration of ZNS, the peak of ZNS concentration in mouse plasma was seen several hours after single or repeated daily administration. The plasma concentration of ZNS was 3.5 to 5.0μg/ml or 13.5 to 14.9μg/ml at 2 hours after the cessation of repeated ZNS administration (10 or 30mg/kg/day) for 7 or 14 days (see Supplementary Table 1). The previous study also showed similar peak plasma concentration of ZNS in rats.[43] The maximum concentration (C_{max}) in rat plasma at 3 hours after the single ZNS treatment (20mg/kg orally) is 14.1μg/ml (prescribing information, Dainippon Sumitomo Pharma). In humans, the average plasma concentration of ZNS at steady state is 3.5μg/ml after daily ZNS treatment at a dose of 50mg/day orally (prescribing information). The dosage of ZNS (30mg/kg/day), which increased GSH levels in this study, appears to be greater than the clinically effective dosage against PD symptoms (25–50mg/day). Therefore, a relatively higher dosage of ZNS, compared with the clinical dosage used for PD motor symptoms, might be required to induce the neuroprotective GSH-increasing effects in PD patients. However, plasma concentration of ZNS rapidly declines to less than 1μg/ml at 24 hours after single or repeated ZNS treatment (10 or 30mg/kg/day) for 7 or 14 days in mice (see Supplementary Table 1) because of its quite shorter half-life time in rodents ($T_{1/2}$ = 8 hours) than in humans ($T_{1/2}$ = 62 hours). In the repeated treatment of ZNS (20mg/kg/day orally) for 14 days in rats, plasma concentration of ZNS settles down at 24 hours after every treat-

ment to approximate 2 to 2.4μg/ml (prescribing information, Dainippon Sumitomo Pharma). The level of plasma ZNS 24 hours after ZNS treatment in rodents is close to or rather lower than the average plasma concentration of 3.5μg/ml at steady state after repeated ZNS treatment (50mg/day) in PD patients. Furthermore, the increase of DA and DOPA contents and TH activity in rat striatum after repeated treatment of ZNS for 2 or 3 weeks was most prominent at a dose of 50mg/kg.[2,7] The marked increases in striatal GSH levels were detected at 24 hours after the cessation of the repeated administration of ZNS (10, 30mg/kg) for 14 days. Taken together with these findings, it is possible that the clinically effective dosage against PD symptoms might exert similar neuroprotective GSH-increasing effects in PD patients. Because the pharmacokinetics of ZNS in humans is different from that in rodents, further clinical studies will be needed to clarify the potentially neuroprotective dosage of the drug to increase GSH levels in PD patients.

In conclusion, the novel antiparkinsonian agent ZNS has unique astrocyte-targeted pharmacological properties that result in a marked increase in GSH levels in the basal ganglia. ZNS might elicit this effect by enhancing astroglial cyst(e)ine transport and/or astroglial proliferation via S100β production or secretion. Furthermore, ZNS appears to act as a neuroprotectant against oxidative stress and dopaminergic neurodegeneration. Further examination of this unique astrocyte-targeting agent may ultimately provide neuroprotection in PD.

This work was supported in part by Health and Labour Sciences Research Grants for Research on Measures for Intractable Diseases (H15-Intractable-01 and H18-Intractable-005, M.A. and M.M.), for Research on Psychiatric and Neurological Diseases and Mental Health, and for Comprehensive Research on Aging and Health (M.A.) from the Japanese Ministry of Health, Labour and Welfare, and by Grants-in-Aid for Scientific Research (C) (17590878, M.A.) and for Young Scientists (B) (18700364, I.M.) from the Japanese Ministry of Education, Culture, Sports, Science and Technology.

We thank Dr Y. Urakubo, Y. Tsutsui, M. Yoshimoto, T. Sakura, T. Masuda, and R. Takahashi for excellent technical assistance.

References

1. Murata M, Horiuchi E, Kanazawa I. Zonisamide has beneficial effects on Parkinson's disease patients. Neurosci Res 2001;41: 397–399.
2. Murata M. Novel therapeutic effects of the anti-convulsant, zonisamide, on Parkinson's disease. Curr Pharm Des 2004;10: 687–693.
3. Murata M, Hasegawa K, Kanazawa I, et al. Zonisamide improves motor function in Parkinson disease: a randomized, double-blind study. Neurology 2007;68:45–50.
4. Kito M, Maehara M, Watanabe K. Mechanisms of T-type calcium channel blockade by zonisamide. Seizure 1996;5:115–119.
5. Suzuki S, Kawakami K, Nishimura S, et al. Zonisamide blocks T-type calcium channel in cultured neurons of rat cerebral cortex. Epilepsy Res 1992;12:21–27.
6. Okada M, Kaneko S, Hirano T, et al. Effects of zonisamide on extracellular levels of monoamine and its metabolite, and on Ca2+ dependent dopamine release. Epilepsy Res 1992;13: 113–119.
7. Okada M, Kaneko S, Hirano T, et al. Effects of zonisamide on dopaminergic system. Epilepsy Res 1995;22:193–205.
8. Gluck MR, Santana LA, Granson H, Yahr MD. Novel dopamine releasing response of an anti-convulsant agent with possible anti-Parkinson's activity. J Neural Transm 2004;111:713–724.
9. Ichikawa J, Dai J, Meltzer HY. Lithium differs from anticonvulsant mood stabilizers in prefrontal cortical and accumbal dopamine release: role of 5-HT1A receptor agonism. Brain Res 2005;1049: 182–190.
10. Shih AY, Erb H, Sun X, et al. Cystine/glutamate exchange modulates glutathione supply for neuroprotection from oxidative stress and cell proliferation. J Neurosci 2006;26:10514–10523.
11. Wang XF, Cynader MS. Astrocytes provide cysteine to neurons by releasing glutathione. J Neurochem 2000;74:1434–1442.
12. Chinta SJ, Andersen JK. Reversible inhibition of mitochondrial complex I activity following chronic dopaminergic glutathione depletion in vitro: implications for Parkinson's disease. Free Radic Biol Med 2006;41:1442–1448.
13. Chinta SJ, Kumar MJ, Hsu M, et al. Inducible alterations of glutathione levels in adult dopaminergic midbrain neurons result in nigrostriatal degeneration. J Neurosci 2007;27:13997–14006.
14. Solano RM, Casarejos MJ, Menendez-Cuervo J, et al. Glial dysfunction in parkin null mice: effects of aging. J Neurosci 2008; 28:598–611.
15. Haque ME, Asanuma M, Higashi Y, et al. Apoptosis-inducing neurotoxicity of dopamine and its metabolites via reactive quinone generation in neuroblastoma cells. Biochim Biophys Acta 2003;1619:39–52.
16. Miyazaki I, Asanuma M, Diaz-Corrales FJ, et al. Dopamine agonist pergolide prevents levodopa-induced quinoprotein formation in parkinsonian striatum and shows quenching effects on dopamine-semiquinone generated *in vitro*. Clin Neuropharmacol 2005;28:155–160.
17. Diaz-Corrales FJ, Asanuma M, Miyazaki I, et al. Rotenone induces aggregation of gamma-tubulin protein and subsequent disorganization of the centrosome: relevance to formation of inclusion bodies and neurodegeneration. Neuroscience 2005;133: 117–135.
18. Lee JM, Calkins MJ, Chan K, et al. Identification of the NF-E2-related factor-2-dependent genes conferring protection against oxidative stress in primary cortical astrocytes using oligonucleotide microarray analysis. J Biol Chem 2003;278:12029–12038.
19. Donato R. Intracellular and extracellular roles of S100 proteins. Microsc Res Tech 2003;60:540–551.
20. Selinfreund RH, Barger SW, Pledger WJ, Van Eldik LJ. Neurotrophic protein S100 beta stimulates glial cell proliferation. Proc Natl Acad Sci USA 1991;88:3554–3558.
21. Tokinaga N, Mizono K, Okada M, et al. Effects of antiepileptic drugs on epoxide hydrolase and glutathione-S-transferase activities. Epilepsia 1996;37(suppl 3):101–102.

22. Shih AY, Johnson DA, Wong G, et al. Coordinate regulation of glutathione biosynthesis and release by Nrf2-expressing glia potently protects neurons from oxidative stress. J Neurosci 2003; 23:3394–3406.

23. Asanuma M, Miyazaki I, Ogawa N. Dopamine- or L-dopa-induced neurotoxicity: the role of dopamine quinone formation and tyrosinase in a model of Parkinson's disease. Neurotox Res 2003; 5:165–176.

24. Graham DG. Oxidative pathways for catecholamines in the genesis of neuromelanin and cytotoxic quinones. Mol Pharmacol 1978;14:633–643.

25. Ogawa N, Asanuma M, Miyazaki I, et al. L-dopa treatment from the viewpoint of neuroprotection: possible mechanism of specific and progressive dopaminergic neuronal death in Parkinson's disease. J Neurol 2005;252(suppl 4):iv23–iv31.

26. Sulzer D, Zecca L. Intraneuronal dopamine-quinone synthesis: a review. Neurotox Res 2000;1:181–195.

27. Sulzer D, Bogulavsky J, Larsen KE, et al. Neuromelanin biosynthesis is driven by excess cytosolic catecholamines not accumulated by synaptic vesicles. Proc Natl Acad Sci USA 2000;97: 11869–11874.

28. Tse DC, McCreery RL, Adams RN. Potential oxidative pathways of brain catecholamines. J Med Chem 1976;19:37–40.

29. Fornstedt B, Rosengren E, Carlsson A. Occurrence and distribution of 5-S-cysteinyl derivatives of dopamine, dopa and dopac in the brains of eight mammalian species. Neuropharmacology 1986;25:451–454.

30. Kuhn DM, Arthur RE Jr, Thomas DM, Elferink LA. Tyrosine hydroxylase is inactivated by catechol-quinones and converted to a redox-cycling quinoprotein: possible relevance to Parkinson's disease. J Neurochem 1999;73:1309–1317.

31. LaVoie MJ, Ostaszewski BL, Weihofen A, et al. Dopamine covalently modifies and functionally inactivates parkin. Nat Med 2005;11:1214–1221.

32. Machida Y, Chiba T, Takayanagi A, et al. Common anti-apoptotic roles of parkin and alpha-synuclein in human dopaminergic cells. Biochem Biophys Res Commun 2005;332:233–240.

33. Whitehead RE, Ferrer JV, Javitch JA, Justice JB. Reaction of oxidized dopamine with endogenous cysteine residues in the human dopamine transporter. J Neurochem 2001;76:1242–1251.

34. Xu Y, Stokes AH, Roskoski R Jr, Vrana KE. Dopamine, in the presence of tyrosinase, covalently modifies and inactivates tyrosine hydroxylase. J Neurosci Res 1998;54:691–697.

35. Ogawa N, Tanaka K, Asanuma M. Bromocriptine markedly suppresses levodopa-induced abnormal increase of dopamine turnover in the parkinsonian striatum. Neurochem Res 2000;25: 755–758.

36. Hastings TG. Enzymatic oxidation of dopamine: the role of prostaglandin H synthase. J Neurochem 1995;64:919–924.

37. Lai CT, Yu PH. Dopamine- and L-β-3,4-dihydroxyphenylalanine hydrochloride (L-dopa)-induced cytotoxicity towards catecholaminergic neuroblastoma SH-SY5Y cells. Effects of oxidative stress and antioxidative factors. Biochem Pharmacol 1997;53: 363–372.

38. Miyazaki I, Asanuma M. Approaches to prevent dopamine quinone-induced neurotoxicity. Neurochem Res 2009;34:698–706.

39. Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's disease. N Engl J Med 2004;351:2498–2508.

40. Sechi G, Deledda MG, Bua G, et al. Reduced intravenous glutathione in the treatment of early Parkinson's disease. Prog Neuropsychopharmacol Biol Psychiatry 1996;20:1159–1170.

41. Hauser RA, Lyons KE, McClain T, et al. Randomized, double-blind, pilot evaluation of intravenous glutathione in Parkinson's disease. Mov Disord 2009;19:19.

42. Zeevalk GD, Razmpour R, Bernard LP. Glutathione and Parkinson's disease: is this the elephant in the room? Biomed Pharmacother 2008;62:236–249.

43. Masuda Y, Utsui Y, Shiraishi Y, et al. Relationships between plasma concentrations of diphenylhydantoin, phenobarbital, carbamazepine, and 3-sulfamoylmethyl-1,2-benzisoxazole (AD-810), a new anticonvulsant agent, and their anticonvulsant or neurotoxic effects in experimental animals. Epilepsia 1979;20: 623–633.

Parkinsonism and Related Disorders 16 (2010) 503–506

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Risk of pneumonia onset and discontinuation of oral intake following videofluorography in patients with Lewy body disease☆

Toshiyuki Yamamoto [a,b,*], Yoko Kobayashi [a], Miho Murata [b]

[a] Departments of Rehabilitation, National Center Hospital of Neurology and Psychiatry, 4-1-1 Ogawahigashi-cho, Kodaira City, Tokyo 187-8551, Japan
[b] Neurology, National Center Hospital of Neurology and Psychiatry, 4-1-1 Ogawahigashi-cho, Kodaira City, Tokyo 187-8551, Japan

ARTICLE INFO

Article history:
Received 2 March 2010
Received in revised form
31 May 2010
Accepted 1 June 2010

Keywords:
Pneumonia onset
Discontinuation of oral intake
Videofluorography
Parkinson's disease
Dementia with Lewy bodies

ABSTRACT

Objective: We investigated the time course of pneumonia onset and duration of continued oral intake following videofluorography (VFG) in patients with Lewy body disease.
Patients and Methods: Subjects were 90 patients with idiopathic Parkinson's disease (IPD) and 45 with Lewy body dementia (LBD). We performed a follow-up study of the time from VFG until onset of pneumonia or discontinuation of oral intake, up to a maximum of 24 months, and determined the associated risk factors. We evaluated the cumulative rates of pneumonia onset and continued oral intake over 24 months for each disease.
Results: Among patients with Lewy body disease, 53 developed pneumonia and 21 discontinued oral intake; patients with aspiration fared significantly worse [hazard ratio (HR) = 26.62, 3.21, $p < 0.01$, $= 0.05$]. Hoehn–Yahr (HY) stage during VFG was also a risk factor for discontinuation of oral intake. The cumulative rate of pneumonia onset was significantly higher in the aspiration group for both IPD and LBD ($p < 0.01$, <0.01). The cumulative rate of continued oral intake tended to be lower in the aspiration group for IPD, and was significantly lower for LBD ($p = 0.07$, <0.01).
Conclusion: Aspiration during VFG was a risk factor for pneumonia onset in patients with Lewy body disease. Aspiration and HY stage during VFG were risk factors for discontinuing oral intake. The cumulative rate of continued oral intake up to 24 months after VFG was poorest for LBD patients with aspiration.

1. Introduction

Many patients with idiopathic Parkinson's disease (IPD) and Lewy body dementia (LBD), including both dementia with Lewy bodies and Parkinson's disease with dementia, die from pneumonia regarded as stemming from dysphagia [1].

Aspiration during videofluorography (VFG), whatever the underlying disease, is important as a risk factor for pneumonia, with this risk being 3.86 times higher for patients with laryngeal penetration, 10.25 times higher for patients with aspiration, and 12.65 times higher for patients with asymptomatic aspiration compared with patients with no laryngeal penetration or aspiration [2]. The risk factors for pneumonia in elderly people are old age, male sex, and difficulty swallowing [3,4]. This means that patients with advanced Lewy body disease are likely to have multiple risk factors. We performed VFG on patients with Lewy body disease and investigated the time from scanning until pneumonia onset or discontinuation of oral intake.

2. Patients and methods

A total of 135 patients with Lewy body disease (mean age 70.3 ± 7.8 years; 76 men, 59 women; average disease duration 9.2 ± 6.4 years; Hoehn–Yahr stage I (HY-I), $n = 4$; HY-II, $n = 20$; HY-III, $n = 46$; HY-IV, $n = 46$; HY-V, $n = 19$) who were feeding orally were enrolled in this study and gave consent. These subjects were selected for inclusion in the study irrespective of subjective symptoms of dysphagia from among 218 patients with Lewy body disease (mean age, 69.1 ± 8.6 years; 91 men, 127 women; Hoehn–Yahr stage I (HY-I), $n = 6$; HY-II, $n = 25$; HY-III, $n = 61$; HY-IV, $n = 68$; HY-V, $n = 58$) who were admitted to our hospital between March 2004 and June 2007. All patients were undergoing treatment with L-dopa, which was determined to be effective. All patients underwent cranial magnetic resonance imaging (MRI), and cerebral infarction, arteriosclerotic Parkinsonism, progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration were excluded. ^{123}I-meta-iodobenzylguanidine (MIBG) scanning was also performed, and it was confirmed that the heart/mediastinum ratio of MIBG uptake declined to ≤1.6 in the delayed phase [5,6]. Patients ($n = 83$) who were being fed by tube or undergoing treatment for complications such as respiratory disorders, dehydration, pneumonia, delirium, depression, a fracture, or dystonia were excluded.

IPD patients consisted of 90 patients who were clinically diagnosed with probable PD [7] (47 men, 43 women; average age 68.4 ± 7.3 years), with no dementia or delirium. LBD patients consisted of 45 patients who were clinically diagnosed with

☆ The review of this paper was entirely handled by an Associate Editor, Eng-King Tan.

* Corresponding author at: Departments of Rehabilitation, National Center Hospital of Neurology and Psychiatry, 4-1-1 Ogawahigashi-cho, Kodaira City, Tokyo 187-8551, Japan. Tel.: +81 42 341 2711.

1353-8020/$ – see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.parkreldis.2010.06.002

Table 1
Patient information.

Disease	n (M:F)	Age	Disease duration	HY-I	HY-II	HY-III	HY-IV	HY-V
IPD	90 (47:43)	68.4 ± 7.3 years	9.9 ± 6.4 years	3	16	36	28	7
LBD	45 (29:16)	74.2 ± 7.2 years	7.9 ± 6.1 years	1	4	10	18	12

IPD, Idiopathic Parkinson's disease; LBD, Lewy body dementia; M, male; F, female; HY, Hoehn–Yahr stage.

probable dementia with Lewy bodies (DLB) or Parkinson's disease with dementia [8] (29 men, 16 women; average age 74.2 ± 7.2 years), including some who were unable to complete L-dopa treatment because of hallucinations or delusions (Table 1).

This study was approved by our institution's ethics committee. Patients or their families were provided with a written explanation of the VFG procedure and of the use of the results for the purpose of research, and written consent was obtained from all patients who were included in the study. During VFG, patients were seated in the same posture in which they ate everyday meals, and fluoroscopy was performed from the side. The investigator used a syringe to inject a twofold dilution of 110 w/v% liquid barium (liquid) into the patient's oral cavity, and gave the patient the signal to start swallowing. The patient's swallowing movements were recorded on DVD at 30 frames/s and evaluated for aspiration by an assessor after the test. Patients who were aware of dysphagia were first tested with 5 ml of thickened liquid, and subsequently with 5 and 10 ml of thin liquid if there was no aspiration. A single VFG was recorded for each swallowing sequence, with an X-ray fluoroscopy time of less than 5 min. Patients who experienced wearing-off were tested during the "on" state. Patients in whom the liquid from the VFG penetrated past the vocal cords into the trachea were categorized as having aspiration [A(+)]. Of patients with no aspiration [A(−)], those in whom the liquid penetrated the larynx but did not reach the trachea were categorized as having laryngeal penetration [P(+)], and those with neither aspiration nor laryngeal penetration were categorized as without laryngeal penetration [P(−)]. Patients in whom the liquid penetrated the larynx during swallowing and was ejected after swallowing were also categorized as P(+), whereas those in whom the liquid penetrated the larynx during swallowing and was aspirated after swallowing were categorized as A(+). Patients who aspirated during VFG were seen by a doctor, speech therapist, and nutritionist within the next week, and received guidance on changing their eating posture and form of food. After a single assessor had evaluated all VFG results, that assessor and another each re-evaluated the results from 20 patients to confirm reproducibility. All assessors who evaluated VFG results were blinded to patient clinical status.

After VFG, we carried out a maximum 24-month follow-up study until June 2009. The primary end point was pneumonia onset, which was diagnosed according to clinical symptoms, thoracic X-ray, and blood tests. Patients who discontinued oral intake or died during the study were categorized as discontinued. The terminal end point was the time until discontinuation of oral intake, and the cause of stopping oral intake was investigated. The decision on when to discontinue oral intake was made on the basis of informed consent by the patient or family members and the attending physician, with no criteria being established. Type of disease, sex, age, disease duration, HY stage, awareness of dysphagia, and degree of penetration of the airway by liquid during VFG were used as covariates for statistical analyses, and the significant risk factors and hazard ratios (HRs) were calculated for each end point using the Cox proportional hazards model. Variables were identified by a step-up procedure to eliminate confounders. HY stage severity was categorized as no postural reflex dysfunction (HY-I+II), HY-III, HY-IV, and HY-V. Age was categorized as <70 or ≥70, and disease duration as <6 years or ≥6 years since onset. Evaluation by individual disease was regarded as clinically important, and we therefore analyzed survival for the A(+) and A(−) groups for each disease using the Kaplan–Meier method. We compared the A(+) and A(−) groups using a log-rank test, and derived the cumulative rate of pneumonia onset and cumulative rate of continued oral intake from the survival rate table after 24 months. Values of $p < 0.05$ were regarded as significant, and SPSS® (ver. 14.0) statistical software was used.

3. Results

The results of VFG showed that of the 135 patients with Lewy body disease, 31 (23.0%) were A(+) and 104 (77.0%) were A(−) [49 (36.3%) were P(+) and 55 (40.7%) were P(−)]. By disease, of the 90 IPD patients, 15 (16.7%) were A(+) and 75 (83.3%) were A(−) [37 (41.1%) were P(+) and 38 (42.2%) were P(−)], while of the 45 LBD patients, 16 (35.6%) were A(+) and 29 (64.4%) were A(−) [12 (26.7%) were P(+) and 17 (37.8%) were P(−)]. There was significant inter-rater and intra-rater agreement in evaluation of airway penetration during VFG, and as the concordance rate was high the results of the first analysis were used (κ coefficients 1.00, 0.88, $p < 0.01$, <0.01). Awareness of dysphagia was 14 (45.2%) of the A(+) group and 14 (13.5%) of A(−) group. There was no significant difference between awareness of dysphagia and aspiration during VFG (χ^2 test, $p < 0.01$) (Table 2).

1) Time until pneumonia onset.

Pneumonia was observed in 16 (11.9%) of the 135 patients with Lewy body disease during the follow-up period. By disease, pneumonia occurred in eight (8.9%) of 90 IPD patients and eight (17.8%) of 45 LBD patients; Cox proportional hazards model was significant with χ^2 test ($p < 0.01$). The depth reached by liquid in the airway was a significant covariate, with the HR for pneumonia in the A(+) group 26.62 times that of the P(−) group (95% confidence intervals (CI), 3.03–234.10; $p < 0.01$). There was no significant difference in pneumonia prevalence between P(−) and P(+) groups. Type of disease, age, sex, HY stage, disease duration and awareness of dysphagia were not significant covariates (Table 3).

The cumulative rate of pneumonia onset 24 months after VFG was 45.8% in A(+) and 3.2% in A(−) patients with IPD, and 83.4% in A(+) and 4.5% in A(−) patients with LBD (Fig. 1). In both IPD and LBD, patients with aspiration during VFG were significantly more likely to develop pneumonia ($p < 0.01$, <0.01).

2) Time until discontinuation of oral intake.

During the follow-up period, 21 (15.6%) patients discontinued oral intake. By disease, oral intake was discontinued in nine (10.0%) of 90 IPD patients and 12 (26.7%) of 45 LBD patients; Cox proportional hazards model was significant with χ^2 test ($p < 0.01$). The depth reached by liquid in the airway and HY stage were significant covariates. The risk of discontinuing oral intake in the A(+) group was 3.21 times that in the P(−) group (95%CI, 1.02–10.13; $p = 0.05$), but there was no significant difference in risk between the P(−) and P(+) groups. HY stage was a significant factor in discontinuing oral intake; when compared with the HY-I+II group, HR was 9.41 for the HY-V group (95%CI, 1.00–88.77; $p = 0.05$). Type of disease, age, sex, disease duration and awareness of dysphagia were not significant covariates (Table 3).

The cumulative continued oral intake rate was 73.4% in A(+) and 91.0% in A(−) patients with IPD, and 33.4% in A(+) and 76.2% in A(−) patients with LBD. The difference was significant for LBD but not for IPD ($p < 0.01$, = 0.07) (Fig. 2). Death was the reason for discontinuation of oral intake in three IPD patients (pneumonia in two patients and asphyxiation in one) and one LBD patient due to pneumonia. Complications of malignant syndrome due to discontinuing L-dopa treatment in two IPD patients forced the use of tube feeding (Table 4).

4. Discussion

In Lewy body disease, silent aspiration is frequent [9,10]. Our study showed that 54.8% patients had silent aspiration and 13.5%

Table 2
Differences in awareness of dysphagia and aspiration during videofluorography.

		Aspiration during videofluorography		
		+	−	Total
Awareness of dysphagia	+	14	14	28
	−	17	90	107
	Total	31	104	135

(χ^2 test, $p < 0.01$).

Table 3
Risk factors for pneumonia onset and discontinuation of oral intake after videofluorography.

Covariates		Pneumonia onset			Discontinuation of oral intake		
		HR	95%CI	*p* value	HR	95%CI	*p* value
Type of disease	LBD/IPD	2.34	0.64–9.00	0.20	2.10	0.76–5.80	0.15
Age	≥70/<70	2.91	0.78–10.87	0.11	1.34	0.50–3.57	0.56
Sex	M/F	6.60	0.78–55.40	0.08	1.59	0.56–4.51	0.39
HY stage	III/I + II	0.79	0.17–3.67	0.76	4.67	0.56–39.17	0.16
	IV/I + II	0.83	0.16–4.30	0.82	4.43	0.50–38.96	0.18
	V/I + II	0.80	0.10–6.44	0.52	9.41	1.00–88.77	0.05*
Disease duration	≥6/<6	0.52	0.13–2.01	0.35	0.47	0.17–1.28	0.14
Awareness of dysphagia	+/−	2.66	0.78–9.14	0.12	1.01	0.33–3.04	0.99
VFG	P(+)/P(−)	3.99	0.32–49.88	0.28	0.64	0.17–2.39	0.50
	A(+)/P(−)	26.62	3.03–234.10	< 0.01*	3.21	1.02–10.13	0.05*

HR, hazard ratio; CI, confidence interval; IPD, idiopathic Parkinson's disease; LBD, Lewy body dementia; M, male; F, female; HY, Hoehn–Yahr; VFG, videofluorography; P(−), neither aspiration nor laryngeal penetration; P(+), laryngeal penetration; A(+), aspiration.

patients worried about dysphagia without aspiration during VFG. Furthermore, awareness of dysphagia was not a significant risk factor for either pneumonia onset or discontinuation of oral intake in Lewy body disease. This could indicate that it is difficult to assess aspiration only from self-reported dysphagia and that some type of objective test, such as VFG, would be required not only to evaluate the present swallowing function but also to predict the course of Lewy body disease.

Our study showed that laryngeal penetration during VFG was not a risk for pneumonia onset in patients with Lewy body disease but that pneumonia incidence was 26.62 times higher in those with aspiration than in those with no laryngeal penetration. According to a report of a 1-year follow-up of 19 IPD patients following VFG, four patients in that study with laryngeal penetration or aspiration all developed airway infections within the year with a relative risk 9.75 times that in patients with no laryngeal penetration or

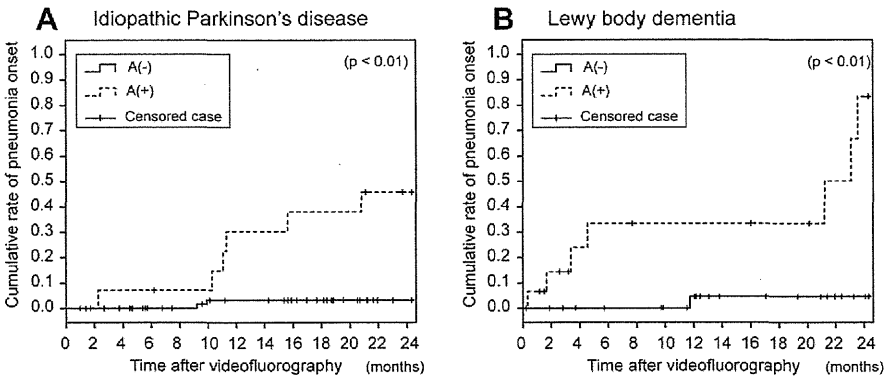

Fig. 1. Cumulative rate of pneumonia onset after videofluorography (VFG). In both diseases, patients with aspiration during VFG had a higher rate of pneumonia onset (log-rank test, $p < 0.01$, <0.01).

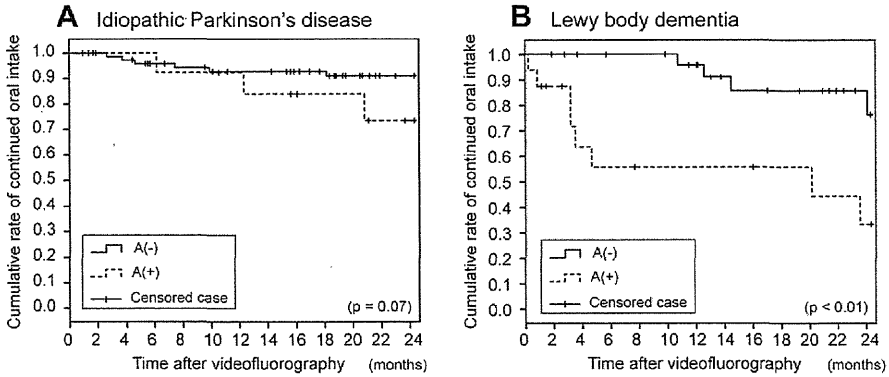

Fig. 2. Cumulative rate of continued oral intake after videofluorography (VFG). For idiopathic Parkinson's disease there was no significant difference between patients with aspiration during VFG and those with no aspiration, but for Lewy body dementia the rate of pneumonia onset was significantly higher for patients with aspiration (log-rank test, $p = 0.07$, <0.01).

Table 4
Reasons for discontinuation of oral intake after videofluorography.

Disease	Reasons for discontinuing oral intake	n
IPD	Death from pneumonia	2
	Death due to asphyxiation	1
	Malignant syndrome	2
	Sudden "off" state	2
	Nutritional deficiency	1
	Repeated asphyxiation	1
LBD	Death from pneumonia	1
	Repeated pneumonia	6
	Nutritional deficiency	5

IPD, idiopathic Parkinson's disease; LBD, Lewy body dementia.

aspiration [10]. The authors of that study evaluated laryngeal penetration and aspiration together, resulting in a lower risk of pneumonia onset than in the present study. However, the 95%CI in several of the HRs are very wide in our study. This indicates an unstable estimate, presumably because of small numbers.

In our study, HY stage was not a risk factor for pneumonia onset. L-dopa treatment improves parkinsonism in IPD, but in many cases has no effect on pharyngeal-phase dysphagia [11,12]. It is possible that among the patients whose parkinsonism had improved with L-dopa treatment there were some for whom there was no improvement of dysphagia, suggesting that aspiration during VFG is particularly important as a risk factor for pneumonia onset. Due to the ethical requirement of our treatment criteria to not perform VFG on patients who were being fed by tube or had other complications, the most severe cases were excluded from this study. Thus, these subjects may not be representative of the population of patients with Lewy body disease admitted to our hospital during the study period, and this may have affected the results.

The risk of discontinuing oral intake during the 24 months following VFG in patients with Lewy body disease with aspiration was 3.21 times higher than that for patients with no laryngeal penetration in this study. We also found that among patients with Lewy body disease, this risk was 9.41 times higher for bedridden patients (HY-V) than for patients with preserved postural reflexes (HY-I + II). Many end-stage patients with Lewy body disease have difficulty with oral intake [13]. In the present study, the reason for discontinuing oral intake was a dysphagia-related dysfunction such as pneumonia, asphyxiation, or nutritional deficiency for many patients with Lewy body disease. For IPD patients, the reason for discontinuing oral intake was difficulty in continuing oral medication for reasons such as malignant syndrome or sudden "off" state. This suggests that tube feeding may be chosen in order to continue treatment in IPD. For LBD patients, the reason for discontinuing oral intake was frequently nutritional impairment owing to reduced food intake. This suggests that tube feeding may be implemented for the purpose of nutritional management in LBD. However, as this study did not include criteria for the discontinuation of oral intake, which was carried out at the discretion of individual patients and doctors, it is possible that for patients with a high HY stage, confounders such as treatment environment may have been included.

The type of disease (IPD or LBD) was not a significant risk factor for either pneumonia onset or discontinuation of oral intake. Dysphagia occurs in Lewy body disease irrespective of dementia [14], but a retrospective study of 17 IPD and 14 DLB patients found that the average duration from disease onset to the appearance of dysphagia was 130 months for IPD and 43 months for DLB, while the average survival period after the onset of dysphagia was 24 months for IPD and 10 months for DLB [15]. In our study, LBD patients had worse outcomes than IPD patients in both cases. This suggests that LBD patients tend to have a higher risk of pneumonia than do IPD patients, and a lower rate of continuing oral intake.

Owing to ethical considerations, patients in whom aspiration was discovered during VFG in our study received therapeutic intervention. Changing the form of food or the patient's position during swallowing can compensate for dysphagia [15–18], and this may have affected these patients' courses. Intervention, however, has little effect in LBD patients [18], and it is possible that the prognosis following VFG for patients with aspiration was worse for those with LBD than for those with IPD.

The finding that the prognosis for patients with Lewy body disease can be estimated from VFG results is useful. Nonetheless, VFG scanning involves X-ray exposure, and its frequency of use needs to be reduced. Future investigation is required to establish at what stage of the appearance of clinical symptoms VFG should be performed. The effect on prognosis of post-scanning therapeutic intervention and intervention frequency may also require further study.

References

[1] Fall PA, Saleh A, Fredrickson M, Olsson JE, Granerus AK. Survival time, mortality, and cause of death in elderly patients with Parkinson's disease: a 9-year follow-up. Mov Disord 2003;18(11):1312–6.
[2] Pikus L, Levine MS, Yang YX, Rubesin SE, Katzka DA, Laufer I, et al. Videofluoroscopic studies of swallowing dysfunction and the relative risk of pneumonia. AJR Am J Roentgenol 2003;180(6):1613–6.
[3] Koivula I, Sten M, Makela PH. Risk factors for pneumonia in the elderly. Am J Med 1994;96(4):313–20.
[4] Loeb M, McGeer A, McArthur M, Walter S, Simor AE. Risk factors for pneumonia and other lower respiratory tract infections in elderly residents of long-term care facilities. Arch Intern Med 1999;159(17):2058–64.
[5] Yoshita M. Differentiation of idiopathic Parkinson's disease from striatonigral degeneration and progressive supranuclear palsy using iodine-123 meta-iodobenzylguanidine myocardial scintigraphy. J Neurol Sci 1998;155:60–7.
[6] Watanabe H, Ieda T, Katayama T, Takeda A, Aiba I, Doyu M, et al. Cardiac (123) I-meta-iodobenzylguanidine (MIBG) uptake in dementia with Lewy bodies: comparison with Alzheimer's disease. J Neurol Neurosurg Psychiatr 2001;70 (6):781–3.
[7] Gibb WR, Lees AJ. The significance of the Lewy body in the diagnosis of idiopathic Parkinson's disease. Neuropathol Appl Neurobiol 1989;15 (1):27–44.
[8] McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65(12):1863–72.
[9] Bird MR, Woodward MC, Gibson EM, Phyland DJ, Fonda D. Asymptomatic swallowing disorders in elderly patients with Parkinson's disease: a description of findings on clinical examination and videofluoroscopy in sixteen patients. Age Ageing 1994;23(3):251–4.
[10] Nobrega AC, Rodrigues B, Melo A. Is silent aspiration a risk factor for respiratory infection in Parkinson's disease patients? Parkinsonism Relat Disord 2008;14(8):646–8.
[11] Hunter PC, Crameri J, Austin S, Woodward MC, Hughes AJ. Response of parkinsonian swallowing dysfunction to dopaminergic stimulation. J Neurol Neurosurg Psychiatr 1997;63(5):579–83.
[12] Bushmann M, Dobmeyer SM, Leeker L, Perlmutter JS. Swallowing abnormalities and their response to treatment in Parkinson's disease. Neurology 1989;39(10):1309–14.
[13] Goy ER, Carter JH, Ganzini L. Parkinson disease at the end of life: caregiver perspectives. Neurology 2007;69(6):611–2.
[14] Bine JE, Frank EM, McDade HL. Dysphagia and dementia in subjects with Parkinson's disease. Dysphagia 1995;10(3):160–4.
[15] Volonte MA, Porta M, Comi G. Clinical assessment of dysphagia in early phases of Parkinson's disease. Neurol Sci 2002;23(Suppl. 2):S121–2.
[16] Muller J, Wenning GK, Verny M, McKee A, Chaudhuri KR, Jellinger K, et al. Progression of dysarthria and dysphagia in postmortem-confirmed parkinsonian disorders. Arch Neurol 2001;58(2):259–64.
[17] Troche MS, Sapienza CM, Rosenbek JC. Effects of bolus consistency on timing and safety of swallow in patients with Parkinson's disease. Dysphagia 2008;23 (1):26–32.
[18] Logemann JA, Gensler G, Robbins J, Lindblad AS, Brandt D, Hind JA, et al. A randomized study of three interventions for aspiration of thin liquids in patients with dementia or Parkinson's disease. J Speech Lang Hear Res 2008; 51(1):173–83.

BRAIN and NERVE 63(3) : 255-265, 2011

原　著
Original Article

大規模患者調査で明らかになった 日本における Parkinson 病薬物治療の実態
―― Parkinson 病患者の服薬状況および疾患・治療に対する意識調査

藤本健一[1)]　村田美穂[2)]　服部信孝[3)]　近藤智善[4)]

Patients' Perspective on Parkinson Disease Therapies
―― Results of a Large-scale Survey in Japan

Ken-ichi Fujimoto[1)], Miho Murata[2)], Nobutaka Hattori[3)], Tomoyoshi Kondo[4)]

Abstract

Parkinson's disease (PD) affects 145,000 people in Japan. Most of these patients are treated with levodopa in combination with other anti-PD therapies. In order to maximize efficacy and patient satisfaction, this survey was conducted to investigate patients' perspective of current PD management in Japan. This survey was conducted in 2008 by questionnaire (3,935) and interview (407). The majority of responders were members of the Japan PD Association. Severity of PD, medication, impact of wearing-off, and patients' attitudes to therapy were assessed. Most patients (95%) were on levodopa, with an average dose of 370 mg/day. Although dose increased with duration of treatment, the majority of patients remained within 300-400mg/day. Patients with wearing-off were less satisfied with their therapy than those without wearing-off (36 vs 49%). Most patients are less concerned by mild dyskinesias. Hallucination is the most distressing side effect. For patients preferring mobility over dyskinesia, levodopa should be dosed sufficiently, and possibly titrated, to maximize clinical benefit and patient satisfaction.

(Received: July 12, 2010, Accepted: October 2, 2010)

Key words : patient survey, Parkinson disease, drug selection, patients' satisfaction, motor complication

はじめに

厚生労働省の患者調査[1)]によると，2005年の本邦における Parkinson 病（Parkinson disease：PD）有病者数は約145,000人，PDの有病率は人口10万人あたり約130人と考えられる。PDは中年以降の発症が多く，加齢に伴い発症率や有病率が増加[2)]するため，高齢化社会を迎える本邦では，今後有病者数の増加が予想される。近年，PDの治療法は著しい進歩を遂げ，生命予後は比較的良好となった[3)]。また近年，治療ガイドライン・アルゴリズムも編纂され[4)]，治療法の普遍化も図られている。このような状況で現在本邦で行われている治療レベルが患者にとって十分に満足いくものかどうかについては，大いに関心がある。

PD治療の主軸は，レボドパを中心とした[5)]薬物による

1) 自治医科大学内科学講座神経内科学部門〔〒329-0498　栃木県下野市薬師寺3311-1〕Department of Neurology, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan
2) 独立行政法人国立精神・神経医療研究センター神経内科診療部　Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry
3) 順天堂大学医学部脳神経内科　Department of Neurology, Juntendo University School of Medicine
4) 和歌山県立医科大学神経内科　Department of Neurology, Wakayama Medical University

1881-6096/11/¥500/論文/JCOPY

ドパミン補充療法であるが，従来から本邦でのレボドパの1日量は欧米と比べて少ないことが指摘されている[6]。われわれはこの事実を確認し，それが患者満足度にどのように影響しているかを把握する目的で，大規模患者調査を実施した。

I．調査方法

郵送による1次調査（郵送調査）と，その中で同意の得られた患者を面接員が訪問して直接聞き取りを行う2次調査（面接調査）の2段階に分けて調査を実施した。

1．郵送調査

郵送調査は2008年6～8月に実施した。「全国パーキンソン病友の会」の会員（約7,000例）および会員以外のPD患者（約1,200例）の計約8,200例に調査票を郵送し，PDの重症度（Hoehn-Yahr重症度，以下，Yahr重症度）や病歴，治療薬の服用状況，OFF時間，ジスキネジア，日常生活の活動レベルおよび介助レベル，薬物治療に対する気持ちを調査した。重症度や病歴は自己申告によるもので，重症度は(1)まったく症状なし，(2)症状は片方の手足のみで日常生活にほとんど影響なし（Yahr重症度Ⅰ度相当），(3)両方の手足に症状があるが歩行障害なし（Yahr重症度Ⅱ度相当），(4)両方の手足の症状に加えてバランス障害や歩行障害あり（Yahr重症度Ⅲ度相当），(5)起立，歩行は可能だが非常に不安定で介助が必要（Yahr重症度Ⅳ度相当），(6)ベッドまたは車椅子の生活で日常生活は全面介助（Yahr重症度Ⅴ度相当）の中から，ON時とOFF時について患者に選択させた。

本報告中のYahr重症度は自己評価によるHoehn-Yahr重症度であるため，Self-diagnosed Hoehn-Yahr重症度（以下，SHY重症度）として表記した。なお，本調査では「症状変動のない患者の重症度＋症状変動のある患者のON時の重症度」をON時のSHY重症度，「症状変動のある患者のOFF時の重症度」をOFF時のSHY重症度と表記する。

PD治療薬の服用状況は，レボドパ，ドパミンアゴニスト（dopamine agonist：DA），MAO-B（monoamine oxidase-B）阻害薬，COMT（cathechol-*O*-methyltransferase）阻害薬については1日量を，そのほかについては服用の有無のみを尋ねた。薬効の切れる時間の有無を尋ね，「あり」と答えた患者では1日のOFF時間の合計を調査した。ジスキネジアについても同様に，その有無と1日の合計時間を調査した。

日常生活の活動レベルは5段階（レベル1：仕事，2：趣味・クラブ活動，3：散歩・買い物，4：通院，5：どれもなし）で判定し，患者が行っている最も高いレベルの活動をその患者の活動レベルとした。介助レベルも5段階（レベル1：介助なし，2：掃除・炊事・買い物，3：外出時の付き添い・食事・着替え，4：入浴・寝返り・洗顔・歯磨き，5：排泄・車椅子）で評価し，患者が受けている最も重度の介助をその患者の介助レベルとした。

薬物治療に対する患者の気持ちは，「薬を増やさないこと」と「動きやすさ」のどちらを優先するか，「副作用の回避」と「動きやすさ」のどちらを優先するか，「ジスキネジアの回避」と「動きやすさ」のどちらを優先するかについて尋ねた。

2．面接調査

面接調査は2008年8～12月に実施した。郵送調査への回答で面接調査に同意した患者の中から，COMT阻害薬（エンタカポン）の服用患者203例と非服用患者204例を無作為に抽出し，調査員が直接患者を訪問して約30分間の面接調査を実施した。面接調査ではまず服薬・食事の状況，「動きやすい」「動きにくい」「動けない」の3段階で評価した運動能力，そして「あまり気にならないジスキネジア」「つらいジスキネジア」の2段階で評価したジスキネジアの出現時間を，訪問前日の症状日誌をもとに確認した。

次に郵送調査で回答した薬物治療に対する気持ちを再確認し，その理由を尋ねた。また，現在の薬物治療に対する満足度を「満足」，「まあ満足」，「どちらともいえない」，「やや不満」，「不満」の5段階で評価してもらった。さらに増薬について，医師から「薬を増やせない」と言われた経験，あるいは「薬を増やさないで欲しい」と自ら医師にお願いした経験とその理由についても尋ねた。

3．解析

解析にあたり服用中のPD治療薬の1日量を，文献7～10を参考にしてレボドパ相当量（levodopa equivalent dose：LED）に換算し総LEDを算出した。DAはブロモクリプチン10 mg，ペルゴリド1 mg，カベルゴリン2 mg，タリペキソール1.6 mg，プラミペキソール2 mg，ロピニロール9 mgをレボドパ・DCI（dopa decarboxylase inhibitor）合剤100 mg相当とした。セレギリンは服用量にかかわらずレボドパ・DCI合剤の1日量×30%，エンタカポンは服用量にかかわらずレボドパ・DCI合剤の1日量×20%とした。

有意差検定は，評価項目に応じて分散分析（1元配置

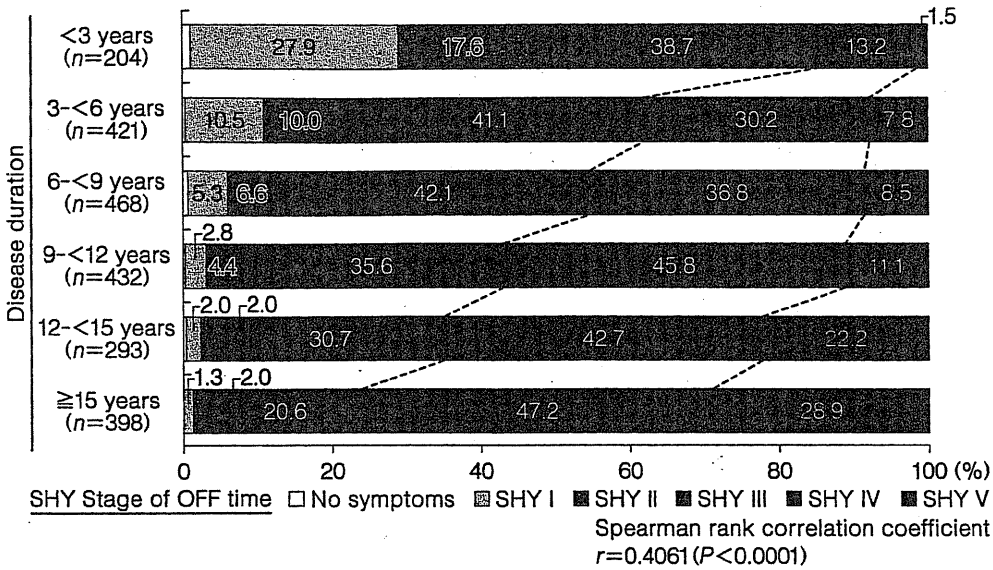

Fig. 1 Parkinson disease duration and Self-diagnosed Hoehn-Yahr Stage of OFF time
Self-diagnosed Hoehn-Yahr (SHY) Stage is shown every 3 years of disease duration. SHY Stage of OFF time increased in accordance with longer duration of disease.
Spearman rank correlation coefficient $r=0.4061$ ($P<0.0001$)

および2元配置），傾向性検定（コクラン・アミテージ傾向性検定）を用い，相関性についてはSpearman順位相関係数を算出し，$|r|>0.3$を強い相関があるとした。

Ⅱ．郵送調査の結果

郵送した約8,200例中4,011例（友の会会員3,568例，会員以外443例）が回収され，記載漏れなどで使用できない76例を除く3,935例を解析対象とした。脳深部電気刺激を実施している398例は薬物治療の解析から除外した。

1．背景（重症度，罹病期間，ウェアリングオフ現象，活動レベル，介助レベル）

対象の平均年齢は69.2±8.7歳で，診断時の平均年齢は60.2±10.5歳であった。女性の割合が53%，平均罹病期間は9.3±6.4年であった。3,935例中1,558例がウェアリングオフ現象（以下，W/O）を伴い，1,787例は伴わず，590例は不明であった。年齢別のW/Oの合併率は80歳以上で22%，70～79歳で33%，60～69歳で47%，59歳以下で56%と，年齢が若くなるに従ってW/Oの合併率は高くなった。罹病期間別のW/Oの合併率は3年未満で13%，3～6年で29%，6～9年で45%，9年以上で51%と，罹病期間が長くなるに従ってW/Oの合併率は高くなった。

ON時のSHY重症度は症状なし307例，Ⅰ度823例，Ⅱ度710例，Ⅲ度1,191例，Ⅳ度405例，Ⅴ度180例，OFF時のSHY重症度は症状なし14例，Ⅰ度177例，Ⅱ度167例，Ⅲ度929例，Ⅳ度1,039例，Ⅴ度368例であった。罹病期間が長くなるに従ってOFF時のSHY重症度は上昇したが（Fig. 1），ON時のSHY重症度との間には一定の傾向を認めなかった。活動レベルはON時のSHY重症度の上昇に伴い低下した（Fig. 2）。介助レベルはOFF時間が長くなるにつれて悪化する傾向を認めた（Fig. 3）。

2．治療薬の服用状況

PD治療薬の服用率は，レボドパ95%，DA 85%，MAO-B阻害薬42%，COMT阻害薬25%であった。服用率をON時のSHY重症度別にみると，レボドパはすべてのSHY重症度で93%以上の服用率であるのに対し，DAは症状なし82%，Ⅰ度86%，Ⅱ度87%，Ⅲ度88%，Ⅳ度80%，Ⅴ度68%で，Ⅲ度を超えると服用率が減少していた。MAO-B阻害薬は症状なし44%，Ⅰ度38%，Ⅱ度44%，Ⅲ度46%，Ⅳ度40%，Ⅴ度26%，COMT阻害薬は症状なし28%，Ⅰ度23%，Ⅱ度29%，Ⅲ度27%，Ⅳ度24%，Ⅴ度13%と，ともにⅤ度で服用率が減少していた。

服用患者における平均1日量は，レボドパが370 mgで，ON時“症状なし”を除きON時およびOFF時の

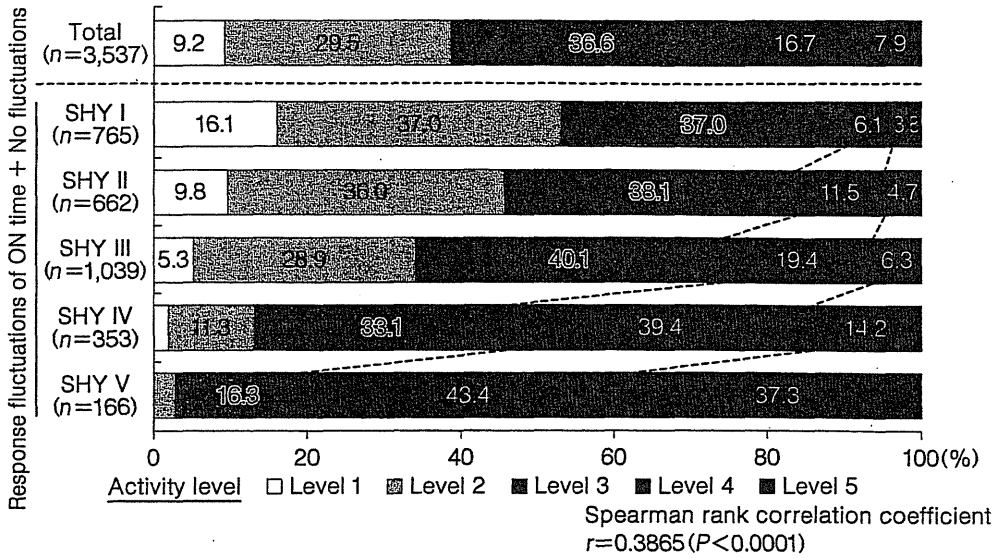

Fig. 2 Activity level of daily life and Self-diagnosed Hoehn-Yahr Stage of ON time

The relationship between activity level of daily life and SHY Stage of ON time was investigated by evaluating activity level of daily life in 5 levels (Level 1: work,Level 2: hobby and club activities, Level 3: walking and shopping, Level 4: Hospital visits, Level 5: No activities). Activity level decreased in accordance with the increase of SHY Stage of ON time.
Spearman rank correlation coefficient $r=0.3865$ ($P<0.0001$)

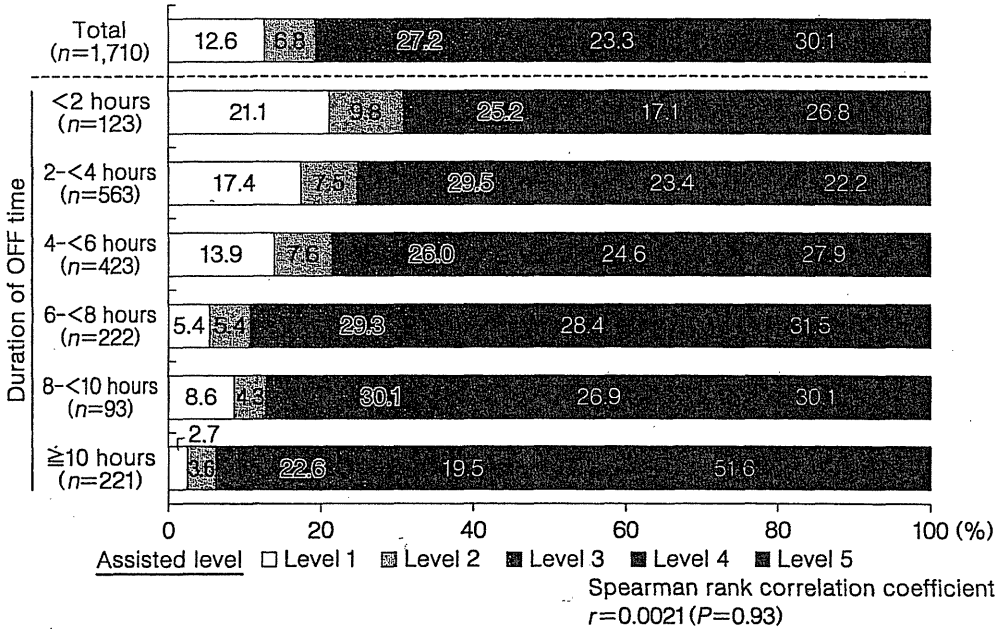

Fig. 3 Assisted level of daily life and daily OFF time

The relationship between assisted level of daily life and daily OFF time was investigated by evaluating assisted level of daily life in 5 levels (Level 1: No assistance, Level 2: Cleaning/Cooking/Shopping, Level 3: Outside assistance/Eating/Change clothing, Level 4: Bathing/Turn over in bed/Washing face/Brushing teeth, Level 5: Toileting/Assisted wheelchairs). It was found that the assisted level tended to decrease in accordance with longer duration of OFF time.
Spearman rank correlation coefficient $r=0.0021$ ($P=0.93$)

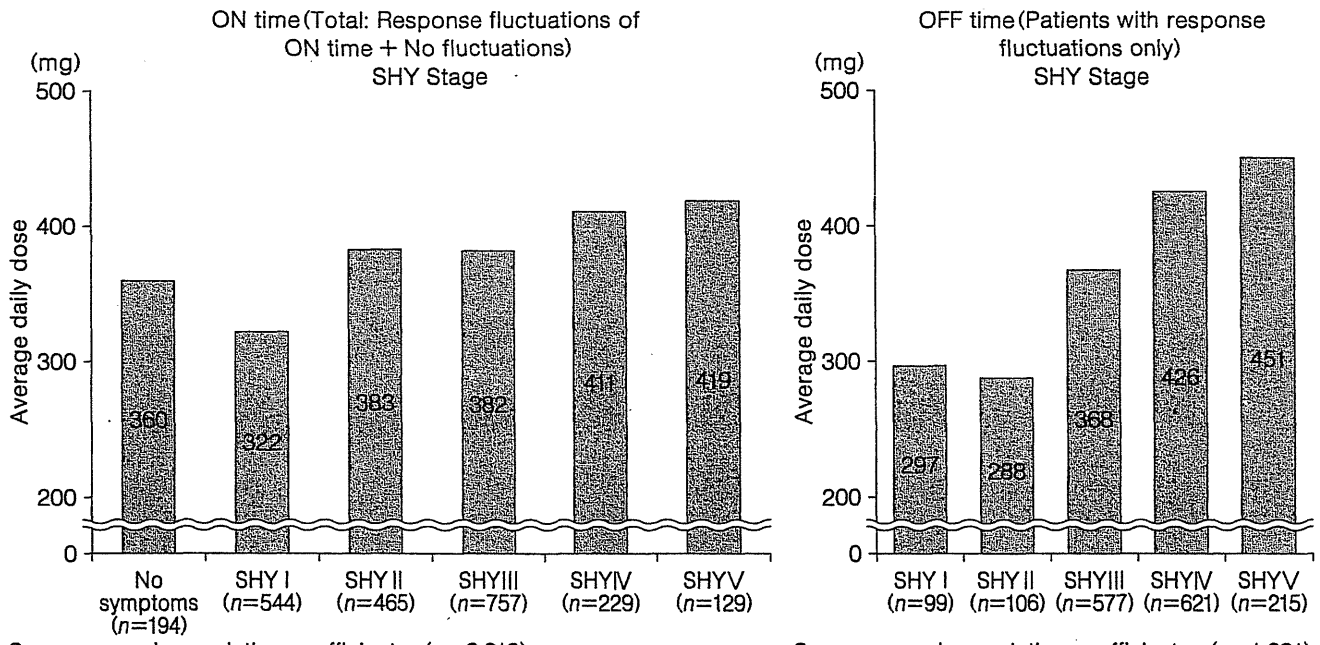

Fig. 4 Average daily dose of levodopa in Self-diagnosed Hoehn-Yahr Stage of ON and OFF time

In ON time, total average daily dose of the patients with no fluctuations (n=697) and the patients with response fluctuations (n=1,621) in SHY Stage. In OFF time, total average daily dose of the only patients with response fluctuations in SHY Stage. Average daily dose of levodopa increased with worsening of SHY stage in ON and OFF time, except no symptoms of ON time.

Spearman rank correlation coefficient of ON time r=0.1686

Spearman rank correlation coefficient of OFF time r=0.3141

SHY 重症度の上昇に伴って増加していた（Fig. 4）。DA の平均 1 日量は LED として 106 mg で，OFF 時の SHY 重症度の上昇に伴ってⅣ度まで増加し，Ⅴ度で減少していたが，ON 時の SHY 重症度との間には一定の傾向を認めなかった（Fig. 5）。MAO-B 阻害薬の平均 1 日量は 4.7 mg で，SHY 重症度の上昇に伴ってわずかに増加傾向を示した。COMT 阻害薬の平均 1 日量は 365 mg で，SHY 重症度との関連は認められなかった。

レボドパの平均 1 日量は罹病期間が長くなるほど増加する傾向がみられた。しかし，平均 1 日量を 100 mg ごとに区切ってその患者数を集計したところ，罹病期間にかかわらず 300～400 mg を服用している患者が最も多かった（Fig. 6）。総 LED も罹病期間とともに有意に増加したが，総 LED に占めるレボドパの割合は減少傾向を示した（Fig. 7）。一方，MAO-B 阻害薬や COMT 阻害薬などのレボドパ補助薬が総 LED に占める割合は，罹病期間とともに増加した。レボドパとその補助薬を合わせた LED が総 LED に占める割合は，罹病期間に関係なく 83～84％と一定であった。

W/O の有無に着目すると，レボドパ平均 1 日量は，W/O を伴わない例の 253.3±222.5 mg に対して，伴う例は 366.8±267.1 mg と 113.5 mg 多かった。総 LED 量も W/O を伴わない例の 364.8±286.0 mg に対して，伴う例は 567.1±377.6 mg と 202.3 mg 多かった。レボドパとその補助薬を合わせた LED の総 LED に占める割合は，W/O の有無にかかわらず約 83％と一定であった。

DA のみで治療されている患者は，服薬期間 3 年未満に限れば 49 歳以下で 39％，50～59 歳で 23％，60～69 歳で 14％，70～79 歳で 9％と高齢になるにつれて減少した。一方 80 歳以上では，服薬期間 3 年未満であっても，55％がレボドパのみで治療されていた。なお，服薬期間が 3 年を超えると，各年齢層ともレボドパと DA の併用が増え，70％を超えていた。

3．薬物治療に対する患者自身の気持ち

「薬を増やさないこと」と「動きやすさ」のどちらを優先するかは，全体としてみればそれぞれ 38.0％と 42.4％で拮抗していたが，OFF 時の SHY 重症度の上昇に伴って「動きやすさ」を優先する患者が増加した（Fig. 8）。また，「副作用の回避」と「動きやすさ」に関しては，全

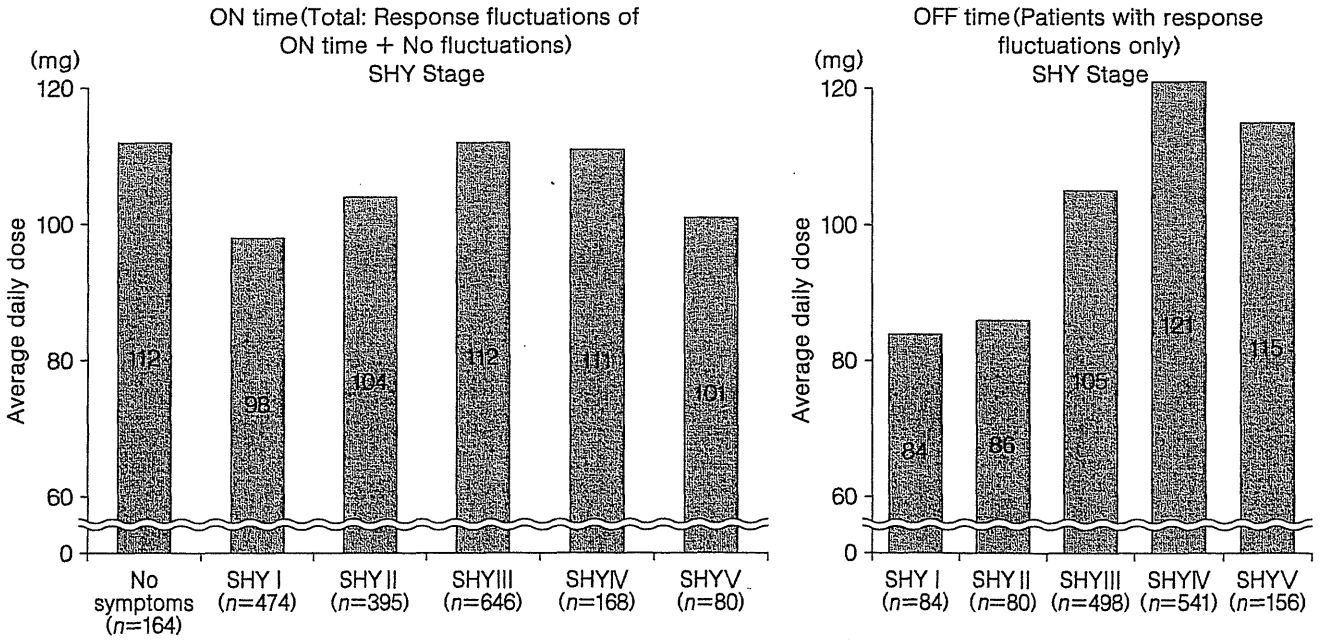

Fig. 5 Average daily dose of dopamine agonist in Self-diagnosed Hoehn-Yahr Stage of ON and OFF time

In ON time, total average daily dose of the patients with no fluctuations (n=567) and the patients with response fluctuations (n=1,360) in SHY Stage. In OFF time, total average daily dose of the only patients with response fluctuations in SHY Stage. Average daily dose of dopamine agonist increased to SHY IV stage, and decreased in SHY V stage in accordance with worsening of SHY stage of OFF time. It was not found that constant relationship between average daily dose of dopamine agonist and SHY stage of ON time.

Spearman rank correlation coefficient of On time r=0.0386

Spearman rank correlation coefficient of OFF time r=0.1409

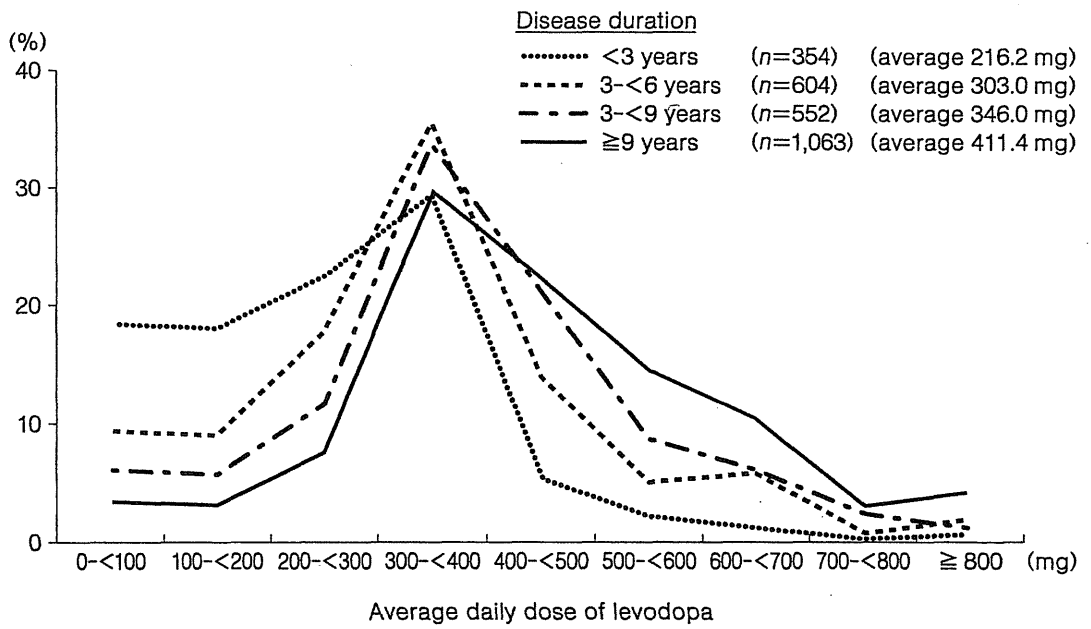

Fig. 6 Average daily dose of levodopa in duration of Parkinson disease

Average daily dose of levodopa is shown every 3 years of disease duration. It was found that average daily dose tended to increase with longer duration of disease. However, the patients taking 300-400mg was highest regardless of disease duration when counting patients by 100mg group of average daily dose.

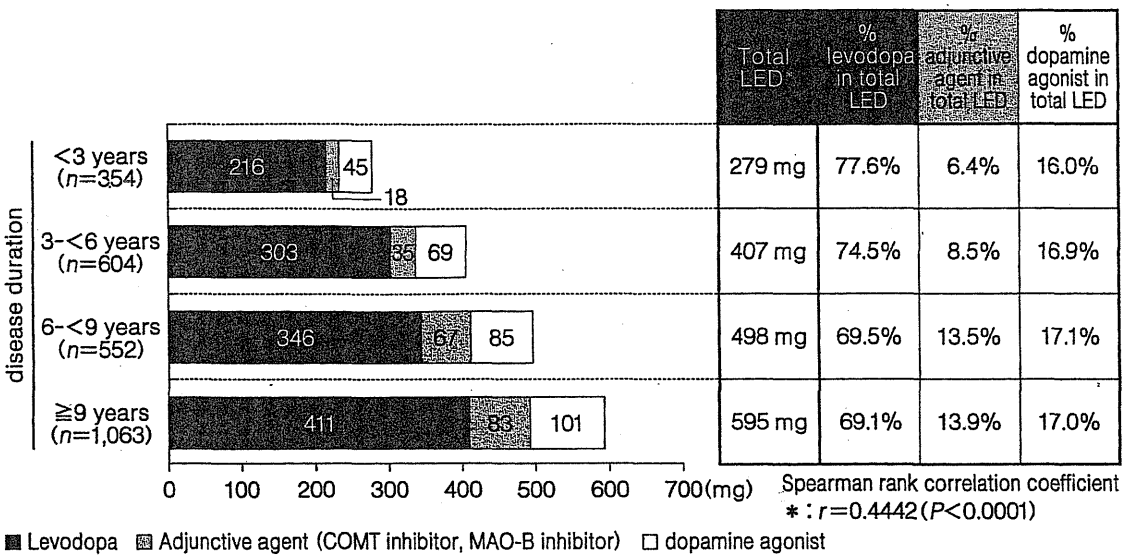

Fig. 7 Duration of Parkinson disease and total levodopa equivalent dose

Total LED (levodopa equivalent dose) in every 3 years of disease duration and percentage of each agents in tatal LED are shown. Total LED increased in accordance with longer duration of disease. [Spearman rank correlation coefficient $*: r=0.4442(P<0.0001)$]

Percentage of levodopa in total LED decreased in accordance with longer duration of disease, however percentage of adjunctive agents such as COMT inhibitor and MAO-B inhibitor increased. It was stable that LED percentage of levodopa and adjunctive agents in total LED was 83-84 % in all disease duration.

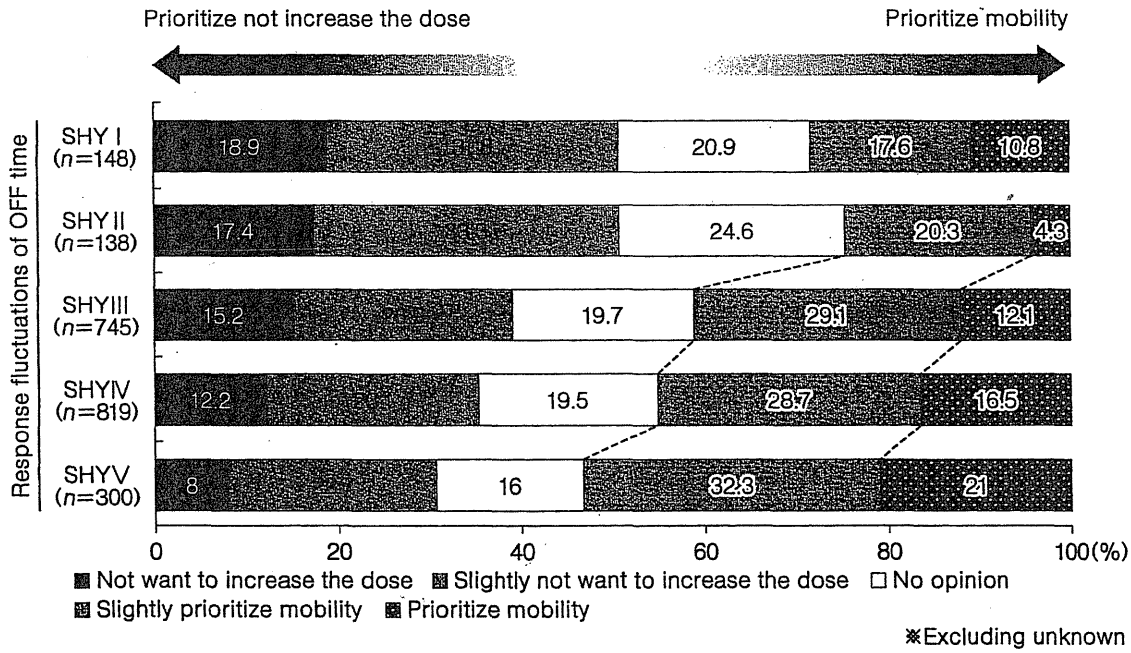

Fig. 8 Patients' feeling regarding drug therapy

The results of mail survey about whether the priority is "Not increase the dose" or "mobility" in SHY stage of OFF time are shown. "Mobility" in priority increased with worsening of SHY stage of OFF time.

体としてみればそれぞれ52.9%と24.5%で「副作用の回避」が多かったが，SHY重症度の上昇に伴って「動きやすさ」を優先する患者が増加した。「ジスキネジアの回避」と「動きやすさ」に関しても，全体でみればそれぞれ47.3%と23.9%で「ジスキネジアの回避」を優先する患者が多かったが，SHY重症度の上昇に伴って「動きやすさ」を優先する患者が増加した。

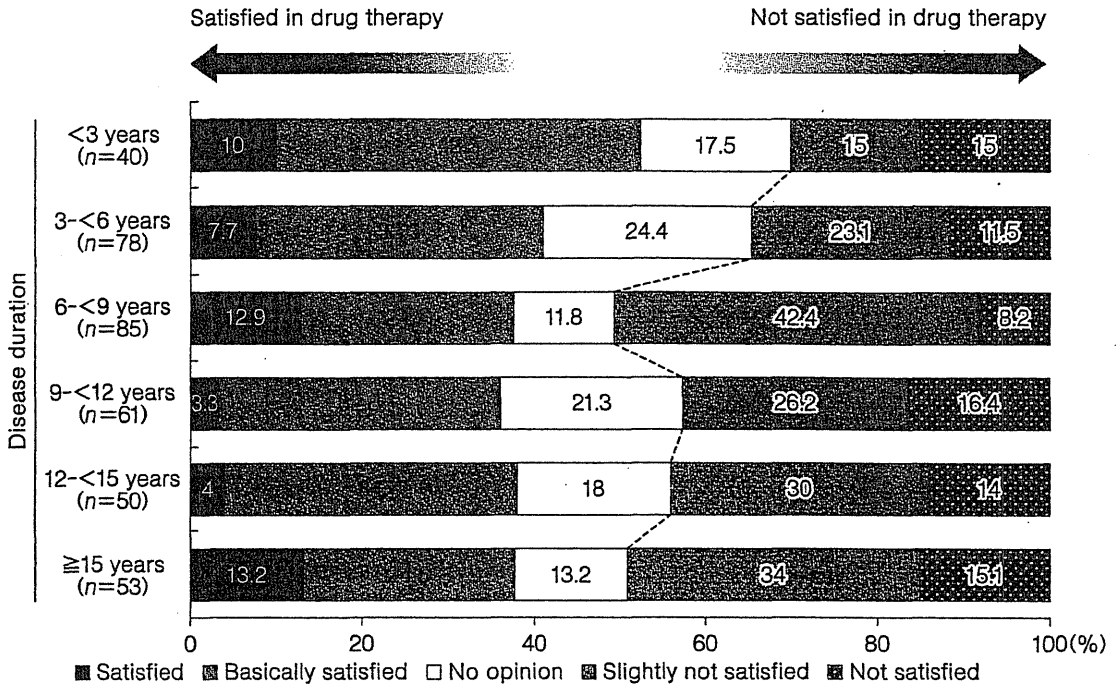

Fig. 9 Parkinson disease duration and the degree of satisfaction

The degree of satisfaction regarding drug therapy every 3 years of disease duration confirmed in interview survey is shown in 5 levels. The percentage of "Not satisfied" increased gradually as longer duration of disease. In disease duration of 6-<9 yrs, the percentage of "Not satisfied" and "Slightly not satisfied" increased transiently.

Ⅲ. 面接調査の結果

1. 現在の薬物治療に対する満足度

現在の薬物治療に対する満足度はW/Oの有無によって異なり，「満足」あるいは「まあ満足」はW/Oのない群では49%であったのに対し，W/Oのある群では36%であった。罹病期間を3年ごとに区切ると，罹病期間が長くなるに従って「不満」「やや不満」を感じる割合が徐々に増加した。その中にあって，罹病期間6～9年の群では一過性に不満を感じる患者が増加し，「不満」「やや不満」を合わせた割合は最大であった（Fig. 9）。なお，患者満足度と総LED，年齢との間には相関を認めなかった。

2. 薬物治療における優先順位，副作用に対する考え方

「薬を増やさないこと」と「動きやすさ」のどちらを優先するかは，「動きやすさ」を優先する患者が47.7%，「薬を増やさないこと」を優先する患者が40.7%であった。「薬を増やさないこと」を優先する理由として「副作用が心配」が56.3%と最も多く，「薬が効かなくなるから」8.6%，「体によくないから」5.3%，「飲むのが大変」4.0%，「薬漬けは嫌だから」3.3%，「病気が進行するから」2.6%，「治癒力が低下するから」2.0%であった。

「副作用の回避」と「動きやすさ」のどちらを優先するかは，「動きやすさ」を優先する患者が29.8%，「副作用の回避」を優先する患者が47.8%であった。回避したい副作用は「幻覚」が18.6%と最も多く，「便秘」5.1%，「眠気」4.0%，「悪心」「臓器障害」がそれぞれ2.8%，「妄想」2.3%，「不眠」「立ちくらみ」「息苦しさ」がそれぞれ1.7%，「むくみ」1.1%であった。なお，患者が思い浮かべる治療薬の副作用は「便秘」が53.1%と最も多く，次いで「幻覚」45.7%，「眠気」34.9%，「吐き気」15.2%，「浮腫」15.2%，「不眠」13.8%，「突発的睡眠」12.3%，ジスキネジア7.4%，「歩行障害」6.4%，「話しにくさ」4.7%，「立ちくらみ」4.4%，「痛み」4.7%，「心臓弁膜症」3.4%であった。

3. 治療薬の追加・増量に対する医師側・患者側双方の意見

医師から「薬を増やせない」といわれた経験のある患者は15.6%（58/371例）であり，その理由として「副作用が出るから」と説明を受けた患者が27例（46.6%）と

最も多かった。その際に説明された副作用は「幻覚」が15例で最多であった。医師から「薬を増やせない」といわれた経験のある患者とない患者それぞれの総LEDは655 mg対562 mg，レボドパの平均1日量は436 mg対371 mg，平均年齢は69.8歳対67.2歳，平均罹病期間は10.5年対8.6年であった。

患者自身が「薬を増やさないで欲しい」と希望した経験のある患者は18.6%（69/371例）であったが，その理由も「副作用が心配」が39例（56.5%）と最も多く，その中で最も多かったのは「幻覚」の12例であった。なお，総LEDやレボドパの平均1日量は，「薬を増やさないで欲しい」と希望した経験の有無により差を認めなかった。

4．ジスキネジアと効果に対する考え方

「ジスキネジアの回避」と「動きやすさ」のどちらを優先するかの質問に対して，ジスキネジアの経験がない患者ではそれぞれ34.4%対17.5%，軽度のジスキネジアのある患者では32.6%対43.4%，重度のジスキネジアのある患者では42.4%対36.9%であった。「ジスキネジアの回避」を選択した理由を尋ねると，ジスキネジアの経験がない患者では「周りの人の目が気になる」，「ジスキネジアのある人をみると嫌だ」，「精神的に苦痛，症状がひどい」，「仕事・家事・趣味などに支障」などと回答したが，軽度のジスキネジアのある患者では「ジスキネジアのある人をみると嫌だ」と回答した患者は半減した。重度のジスキネジアのある患者では「精神的に苦痛，症状がひどい」が圧倒的に多く，「ジスキネジアのある人をみると嫌だ」と回答したのは1例のみであった。

Ⅳ．考　　察

本調査は，本邦の全PD患者約145,000人のうち約4,000人（2.8%）から回答を得た。ON時で無症状あるいはSHY重症度がⅠ度かⅡ度の患者が1,840人，Ⅲ度以上の患者が1,776人で，W/Oを発症している患者が1,558人と，重症な患者がやや多いのは「全国パーキンソン病友の会」の会員を中心に郵送調査を実施したためと考えられる。

W/Oは，年齢が若く，罹病期間が長いほど発現しやすいというのは，従来の報告と同じであった。OFF時のSHY重症度が罹病期間とともに上昇したのに対し，ON時ではSHY重症度と罹病期間の間に一定の傾向を認めなかった。これは症状の進行した患者でも，ON時にはパーキンソニズムがある程度は改善されるためと考えられる。PD患者はONの状態で医療機関を受診することが多いが，病状の進行や日常生活活動の障害度の把握にはOFF時のSHY重症度を参考にすることが望ましい。またOFF時間が長くなるに従って介助レベルが悪化することから，OFF時間の短縮，あるいはOFF時の症状緩和が重要である。

レボドパの1日量は海外臨床試験[11~14]では700 mg前後であるのに対し，国内臨床試験[15]では300～400 mgであり，本邦におけるレボドパの1日量は欧米と比べて少ないことが指摘されている[6]。本調査でもレボドパの1日量は罹病期間にかかわらず300～400 mgの患者が最も多く，平均1日量は罹病期間9年以上の患者でも411 mgであり，その傾向が確認された。さらなる治療効果を求める場合，本邦ではレボドパを増量せず，DAあるいはMAO-B阻害薬やCOMT阻害薬などのレボドパ補助薬の追加で，総LEDを補う傾向があることが示された。この傾向はW/Oの有無にかかわらず同じであった。

ドパミンの必要量は病期によって大きく異なり，またレボドパの吸収率は個人差が大きい[16]。レボドパ1日量が罹病期間にかかわらず300～400 mgである患者が最も多いという現状は，進行期の患者での不十分な治療や，患者の症状に合わせたレボドパの用量設定が不十分な状況が危惧される。レボドパの必要量は個人差が大きいので，患者に合わせた柔軟な用量調整が重要である。

治療のガイドライン・アルゴリズムでは，W/O現象やジスキネジアの予防のため，若年患者はDAで治療開始することを推奨している。本調査でも，服薬期間3年未満に限れば49歳以下で39%，50～59歳で23%がDAのみで治療されていた。しかし服薬期間が3年を超えると，各年齢層ともDAとレボドパの併用が70%を超えた。この事実は，長期にわたりDAだけで満足できる治療効果を維持することの難しさを示している。また，SHY重症度Ⅴ度におけるDA服用率の低下は，進行期患者におけるDAの有効率の低下や「幻覚」などの副作用が関与していると推察される。

面接調査は，W/Oの治療薬であるエンタカポンの服用患者と非服用患者が半々になるよう重症度をそろえて無作為に抽出したため，進行期の患者の割合がより高くなった。現在の薬物治療に不満を感じる患者の割合は，W/Oがあると高くなる傾向があった。特に罹病期間が6～9年の患者群で不満を感じる患者が一過性に増えたが，この時期はW/Oなどの運動合併症が問題となる時期に一致する。満足度を高めるには，運動合併症の予防に努めるとともに，早期からW/Oへの対策を取ることが重要と考えられる。

「薬を増やさないこと」と「動きやすさ」のどちらを優

先するかは，郵送調査でそれぞれ38.0%対42.4%，面接調査で40.7%対47.7%であった。面接調査のほうがやや「動きやすさ」を優先する患者の比率が高かったが，これは面接調査で進行期患者の割合がより多かったためと考えられる。「薬を増やさないこと」を優先する理由は「副作用が心配」が最も多く，回避したい副作用として「幻覚」を挙げる患者が最も多かった。薬物療法では，特に「幻覚」を回避する努力が重要であることを示している。

医師に治療薬の追加・増量を断られた経験は，進行期の患者でより多かった。「幻覚」をはじめとする副作用への懸念によって医師に追加・増量を拒まれていることが示された。一方，患者自身が治療薬の追加・増量を拒む場合は，総LEDや罹病期間との間に関連を認めず，副作用，特に「幻覚」を心配していることがわかった。おそらく，患者自身の副作用の経験が影響を及ぼしているものと思われる。

「ジスキネジアの回避」と「動きやすさ」については，全体としては「ジスキネジアの回避」を優先する患者が多かったが，SHY重症度の上昇に伴って「動きやすさ」を優先する患者が増えることが郵送調査から示された。面接調査では，ジスキネジアの経験の有無によってその傾向が異なることが明らかとなった。ジスキネジアを経験したことのない患者は「周りの人の目が気になる」「ジスキネジアのある人をみると嫌だ」などの理由で「ジスキネジアの回避」を優先するが，軽度のジスキネジアを経験すると「ジスキネジアのある人をみること」はあまり気にならず，「動きやすさ」を優先することが示された。ジスキネジアを恐れてレボドパの服用量を過度に抑えることは，患者の希望と逆行している可能性がある。ただし，重度のジスキネジアは患者にとっても苦痛であり，回避する努力が必要である。

まとめ

今回の調査から実際に患者が服用しているレボドパは罹病期間にかかわらず1日300～400 mgの患者が最も多く，平均1日量も370 mgであり，欧米に比べて少ないことが確認された。本邦では少ないレボドパを，DAあるいはMAO-B阻害薬やCOMT阻害薬などのレボドパ補助薬で補っている実態が明らかになった。服薬期間3年未満に限ると，DAのみを服用中の59歳未満の患者は稀でなかったが，服薬期間3年を過ぎるとすべての年齢層でDAとレボドパの併用が70%以上を占めた。

薬物治療に対する患者満足度は，W/Oの有無によって影響を受けた。罹病期間が長くなるほど不満が増えたが，6～9年の患者群で一過性に不満が増え，これは全体を通しても最大であった。

薬物治療の副作用として，患者は「幻覚」を最も恐れており，増薬に対する抑制因子となっていた。一方，医師側も主に副作用としての「幻覚」を理由に増薬を躊躇していた。

ジスキネジアはその経験によって意見が分かれた。未経験者はジスキネジアの回避を望んでいたが，軽いジスキネジアの経験者はむしろ動くことを希望していた。

本邦のPD患者の2.8%を対象とした大規模患者調査の結果，薬物治療の現状とそれに対する患者の希望が明らかとなった。新薬の開発によってPDの治療は飛躍的に進歩したが，患者満足度を高めるためには，今後もさらなる努力が必要と考えられた。

謝辞

本研究は，ノバルティスファーマ株式会社から研究助成金を受けた。

筆者らは，本研究を支援してくださった全国パーキンソン病友の会の会員をはじめとした参加者，医師および関係スタッフならびに共同研究者に感謝の意を表する。

文　献

1）厚生労働省: 平成17年患者調査の概況; 主要な傷病の総患者数. 2005
2）de Lau LM, Giesbergen PC, de Rijk MC, Hofman A, Koudstaal PJ, et al: Incidence of parkinsonism and Parkinson disease in a general population: the Rotterdam Study. Neurology **63**: 1240-1244, 2004
3）Post B, Merkus MP, de Haan RJ, Speelman JD; CARPA Study Group: Prognostic factors for the progression of Parkinson's disease: a systematic review. Mov Disord **22**: 1839-1851, 2007
4）Olanow CW, Watts RL, Koller WC: An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology **56**: S1-S88, 2001
5）Diamond SG, Markham CH, Hoehn MM, McDowell FH, Muenter MD: Multi-center study of Parkinson mortality with early versus later dopa treatment. Ann Neurol **22**: 8-12, 1987
6）水野美邦: パーキンソン病の薬物療法. 難病と在宅ケア **15**: 33-37, 2009
7）長谷川一子: 新規開発薬. 日本臨牀 **58**: 2066-2071, 2000
8）Nutt JG, Woodward WR, Beckner RM, Stone CK, Berggren K, et al: Effect of peripheral catechol-O-methyltransferase inhibition on the pharmacokinetics and pharmacodynamics of levodopa in parkinsonian patients. Neurology **44**: 913-919, 1994

9) Thobois S: Proposed dose equivalence for rapid switch between dopamine receptor agonists in Parkinson's disease: a review of the literature. Clin Ther **28**: 1-12, 2006
10) Linazasoro G, Kulisevsky J, Hernández B; Spanish Stalevo Study Group: Should levodopa dose be reduced when switched to stalevo? Eur J Neurol **15**: 257-261, 2008
11) Parkinson Study Group: A randomized controlled trial comparing pramipexole with levodopa in early Parkinson's disease: design and methods of the CALM-PD Study. Parkinson Study Group. Clin Neuropharmacol **23**: 34-44, 2000
12) Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, et al: A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. N Engl J Med **342**: 1484-1491, 2000
13) Montastruc JL, Rascol O, Senard JM, Rascol A: A randomised controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously untreated patients with Parkinson's disease: a five year follow up. J Neurol Neurosurg Psychiatry **57**: 1034-1038, 1994
14) Rinne UK, Bracco F, Chouza C, Dupont E, Gershanik O, et al: Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications. Results of a double-blind levodopa controlled trial. The PKDS009 Study Group. Drugs **55**: 23-30, 1998
15) Mizuno Y, Kanazawa I, Kuno S, Yanagisawa N, Yamamoto M, et al: Placebo-controlled, double-blind dose-finding study of entacapone in fluctuating parkinsonian patients. Mov Disord **22**: 75-80, 2007
16) 服部信孝: いきなり名医！ パーキンソン病Q&A—押さえておきたいポイント 33. 日本医事新報社, 東京, 2009, p49

5. 麦角系ドパミンアゴニスト：線維症問題からの教訓

山本光利
Mitsutoshi Yamamoto

はじめに

1974年に英国のDonald Calneらにより麦角系ドパミン(DA)アゴニストであるブロモクリプチンのパーキンソン病（PD）に対する有効性が報告されて以来[1]，麦角系及び非麦角系DAアゴニストの開発が行われてきた．図1にはその開発と副作用報告の歴史を示す．我が国では現在，麦角系ではブロモクリプチン，ペルゴリド，カベルゴリンの3種類が使用されているが，欧州では現在でもこれ以外にlisurideが使用されている．

薬剤および規制当局	年号	副作用報告および規制内容
methysergide(偏頭痛治療薬)	1966	心弁膜症
ブロモクリプチン(BR)(UK)	1974	パーキンソン病に使用
Rinne	1981	BRで胸膜肺線維症を報告
BR発売(JP)	1985	日本でPDへの適応症認可
ペルゴリド(PRG)発売(JP)	1994	日本で発売
fenfluramine-fentanile(食欲抑制剤)	1997	心弁膜症報告(N Engl J Med)
プラムペキソール(PPX) & ロピニロール(ROP)	1999	突発的睡眠発作
BR & ペルゴリド(PRG)	2002	心臓弁膜症：症例報告
PPX	2004	日本で発売承認
PRG		高用量での心弁膜症が高頻度
カベルゴリン(CB)	2005	心弁膜症の症例報告(N Engl J Med)
ROP	2006	日本で発売承認
FDA	2007	PRG発売中止
EMEA/PMDA	2007	麦角DAアゴニストの添付文書を改訂
日本神経学会	2007	日本神経学会DAアゴニスト使用上の注意を作成
EMEA/PMDA	2008	突発性睡眠発作対策として薬剤の使用警告
DAアゴニスト等に警告：EMEA & PMDA(JP)	2008	麦角系DAアゴニスト等に対して使用規制

FDA : Federal Drug and Food Agency(米国)
EMEA : 欧州医薬品審査庁　　赤字：麦角系薬剤
PMDA : 医薬品医療機器審査機構(日本)　　緑字：非麦角系薬剤

図1　ドパミン（DA）アゴニスト製剤と副作用の歴史