approach [25] to obtain a three-dimensional tract reconstruction. Identification of fibre tracts was initiated by placing a seed area in anatomical regions through which the particular fibres were expected to course [26]. Tract measurements were performed by two of the authors (K.S., K.K.), who were blinded to the disease status of the subjects.

Tractography of the genu of the corpus callosum was performed according to Hofer and Frahm's scheme [27], as the most anterior segment covers the first sixth of the corpus callosum and contains fibres projecting into the prefrontal region (Hofer and Frahm defined CC1). The seed ROI was placed manually, including the entirety of the genu of the corpus callosum (*light blue area*), on a reconstructed mid-sagittal image with a non-diffusion-weighted image (b= 0 s/mm^2) (Fig. 1a). Tractographic images of the genu of the corpus callosum were generated with threshold values of line-tracking termination FA>0.18 (Fig. 1b). The genu of the corpus callosum fibre tracts was defined as follows: anterior–posterior, including the first sixth of the corpus callosum; above and below, including the upper and lower border of the genu of the corpus callosum; and right–left, between the anterior horns of the lateral ventricles (Fig. 1c, d). Voxelisation along the genu of the corpus callosum was then performed. To reduce the partial volume effect of the peripheral portion of the tract and to eliminate small incidental artefactual lines, we used a shape-processing technique based on mathematical morphology [28]. In this shape-processing technique, we dilated the voxels once and eroded twice. FA and MD values in co-registered voxels were calculated (Fig. 1e).

Statistical analysis

Statistical analysis of demographic and clinical data was performed by using analysis of variance with Tukey's HSD (honestly significant difference) test for continuous variables and a χ^2 test for categorical data. The criterion of statistical significance was $P<0.05$. Statistical analyses were performed with SPSS for Windows, Release 8.0.

We used the Kolmogorov-Smirnov test for analysis of normal distribution. Because only the MD of the PD group was not normally distributed, we used non-parametric (Kruskal-Wallis) analysis of variance and the Mann–Whitney U test to test for differences between groups. A Bonferroni correction was applied for the number of comparisons (n=3: [normal vs PD, normal vs PD, PD vs PDD], setting the level of significance at $P<0.05/3=0.016$).

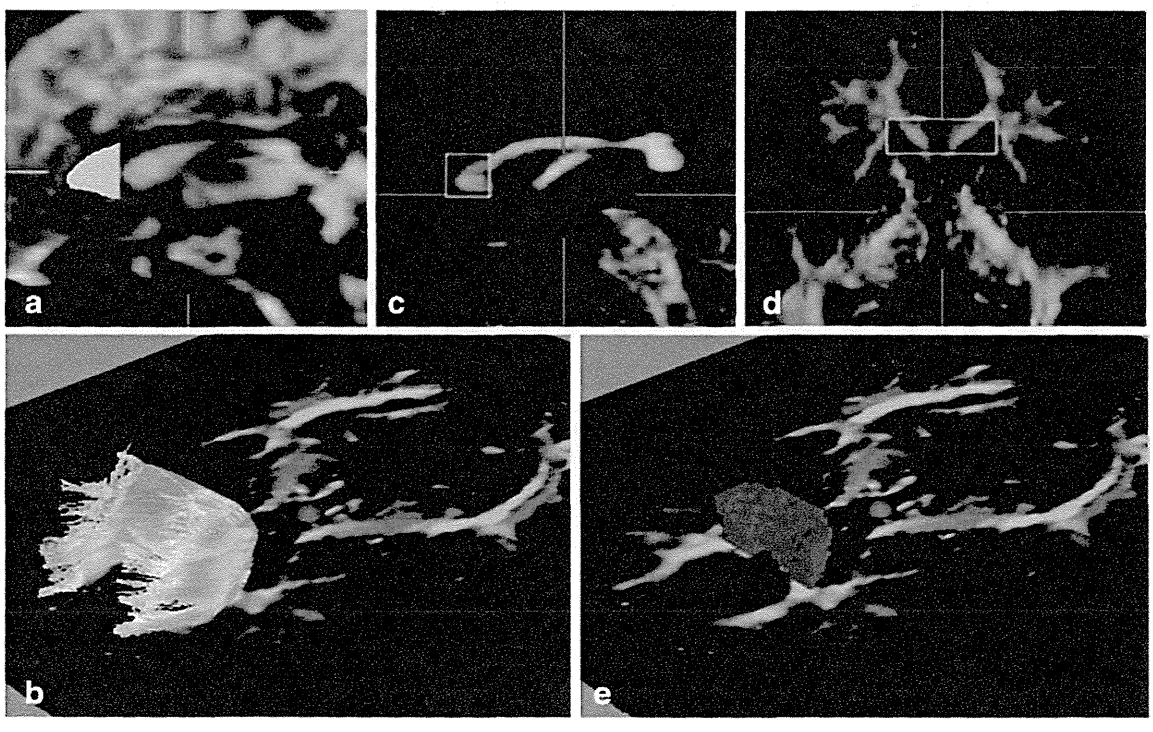

Fig. 1 Diffusion tensor tractography images of the genu of the corpus callosum and fibre tracts, and voxelisation. **a** The seed region of interest was placed manually including the entire genu of the corpus callosum (*light blue area*) on a reconstructed mid-sagittal image with a non-diffusion-weighted image (b=0 s/mm^2). **b** Tractographic image of the genu of the corpus callosum was generated with threshold values of line-tracking termination as fractional anistropy (FA)>0.18. **c, d** Fibre tracts of the genu of the corpus callosum were defined as follows: anterior–posterior, including the first sixth of the corpus callosum; above and below, including the upper and lower border of the genu of the corpus callosum; right–left, between the anterior horns of the lateral ventricles. **e** Voxelisation was performed along the genu of the corpus callosum (*blue voxels*). FA and mean diffusivity (MD) values in co-registered voxels were calculated

Spearman's rank-order correlation test was used to investigate correlations between the imaging measurements and continuous clinical variables.

Results

Demographic and clinical features

The three groups did not differ by age ($P>0.70$, ANOVA) or gender ($P>0.76$, χ^2) (Table 1). As expected, PDD patients scored significantly lower than PD patients and control subjects on the MMSE ($P<0.01$, $P<0.01$, ANOVA with Tukey's HSD test), but PD and control subjects did not differ significantly on the MMSE. There were significant differences in disease duration, Hoehn–Yahr stage, and levodopa dosage (mg/day) between PD and PDD patients (Table 1).

White-matter alteration assessed by using TBSS

FA and MD values were not significantly altered in the cerebral white matter of patients with PD compared with control subjects.

In patients with PDD, major white-matter tracts had significantly reduced FA values compared with the control group (Fig. 2a). The affected white-matter tracts included the superior and inferior longitudinal fasciculus, the inferior fronto-occipital fasciculus, the uncinate fasciculus, the cingulum, the anterior limb of the internal capsule and the substantia nigra. The reductions in FA were seen bilaterally in all of the affected white-matter tracts. Increased MD was found in major white-matter tracts in the PDD patients compared with the control group (Fig. 2b). MD was increased in almost the same white-matter tracts as those in which FA was decreased; in addition, MD was increased in the posterior limb of the internal capsule.

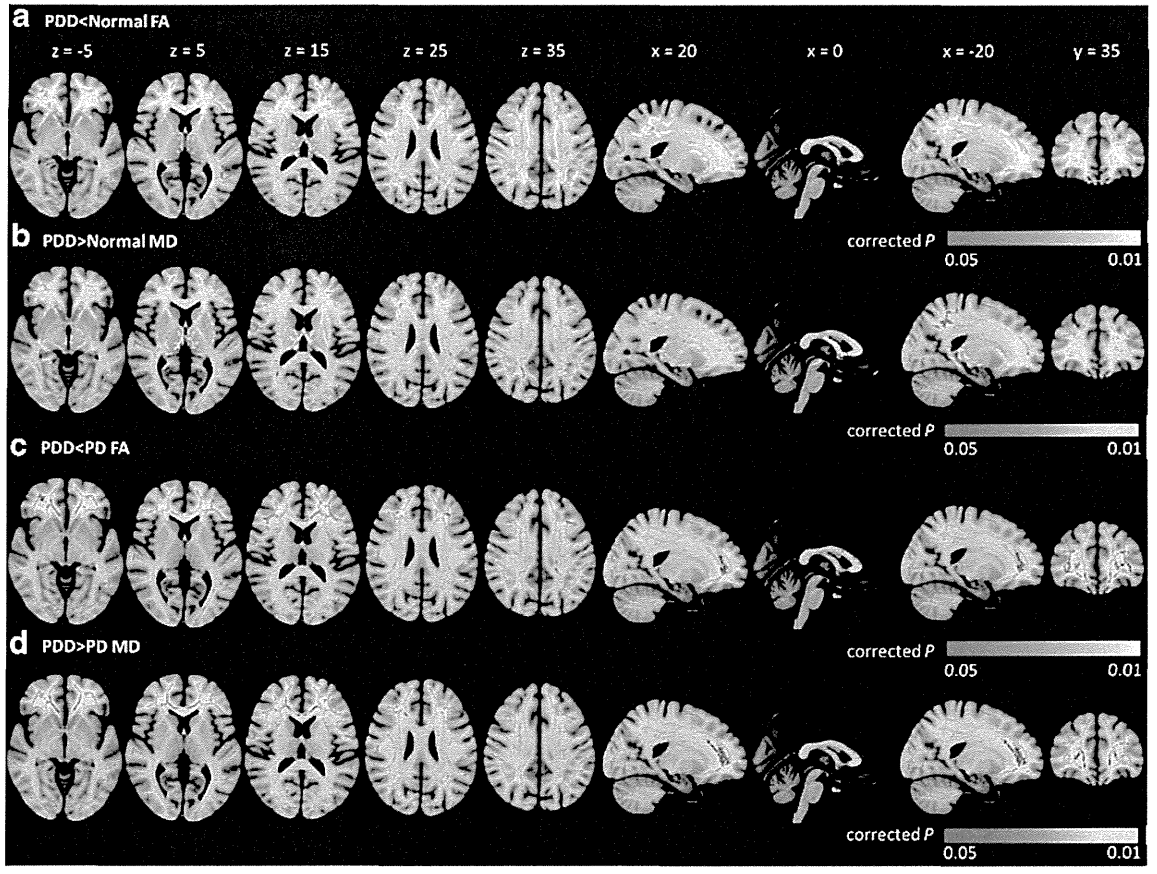

Fig. 2 Corrected *P* maps. Tract-based spatial statistics (TBSS) analysis of the FA of normal control vs Parkinson's disease with dementia (*PDD*) (**a**), MD of normal controls vs PDD (**b**), FA of Parkinson's disease (*PD*) vs PDD (**c**), MD of PD vs PDD (**d**). All images are displayed in Montreal Neurological Institute space. **a** TBSS analysis demonstrated significantly decreased FA (*red–yellow voxels*) in several major white-matter tracts in the PDD group compared with the control group. **b** MD was increased in almost the same white-matter tracts as those in which FA was decreased in the PDD group compared with the control group (*blue-light blue voxels*). **c** In patients with PDD, FA values in the anterior part of the inferior fronto-occipital fasciculus (i.e. the white matter adjacent to the prefrontal area) and in part of the genu of the corpus callosum were significantly lower than those in PD patients (*red-yellow voxels*). **d** MD was increased in almost the same white-matter tracts as those in which FA was decreased in PDD patients relative to PD patients (*blue-light blue voxels*)

In patients with PDD, FA values in the anterior part of the inferior fronto-occipital fasciculus (i.e. the white matter adjacent to the prefrontal area) and in part of the genu of the corpus callosum were significantly lower than in PD patients (Fig. 2c). MD was increased in almost the same white-matter tracts as those in which FA was decreased in PDD patients relative to PD patients (Fig. 2d).

In the PD and PDD groups combined, FA values correlated with MMSE scores. FA correlated positively with MMSE score in the anterior part of the inferior fronto-occipital fasciculus, in part of the genu of the corpus callosum bilaterally, and in smaller areas in the right anterior and left posterior parts of the superior longitudinal fasciculus (precuneus) and in the left part of the corpus callosum (Fig. 3). FA and MD did not correlate with MMSE score in the separate PD and PDD groups. In the PD group, the PDD group, and the combined PD and PDD group, FA and MD did not correlate with disease duration, Hoehn–Yahr stage or levodopa dosage.

Because in PDD the FA values in the white matter adjacent to the prefrontal area and in part of the genu of the corpus callosum were significantly decreased and correlated positively with MMSE scores, we hypothesised that the genu of the corpus callosum, which contains fibres projecting into the prefrontal area, is involved in the pathological processes responsible for dementia in PD. We therefore compared diffusion abnormalities in the genu of the corpus callosum in PDD and PD patients with those in normal controls using diffusion tensor tractography.

White-matter alteration assessed by using tract-specific analysis

Reproducibility was determined on the basis of fibre counts and expressed as an intraclass correlation coefficient; the coefficient was 0.96 for the genu of the corpus callosum. Averaged values were therefore used for further statistical analyses.

There was a significant correlation between MMSE score and FA and MD values in the genu of the corpus callosum (FA: r=0.472; MD: r=−0.453, P<0.005) in the PD and PDD patient groups combined (Fig. 4). FA and MD did not correlate with MMSE score in the separate PD and PDD groups (FA in the PD group: r=0.303, P=0.194; MD in the PD group: r=−0.165, P=0.488; FA in the PDD group: r =0.313, P=0.178; MD in the PDD group: r=−0.223, P= 0.344). However, we did observe a trend toward a positive correlation between FA in the genu of the corpus callosum and MMSE score. FA and MD values of the genu of the corpus callosum did not correlate significantly with disease duration or Hoehn–Yahr stage (P>0.05) in patients with either PD or PDD.

FA and MD values in the genu of the corpus callosum were significantly lower in patients with PDD than in those with PD (P=0.0050, P=0.0013) or in normal controls (P= 0.0049, P = 0.00014) (Table 2). There were no significant differences in diffusion in the genu of the corpus callosum between PD patients and normal controls.

Discussion

Our study yielded three major findings. First, comparison of patients with PDD with a group of healthy individuals revealed diffusion abnormalities over a wide area of cerebral white matter. Second, a comparison of PDD patients with PD patients without dementia revealed diffusion abnormalities in the anterior superior longitudinal fasciculus (i.e. the cerebral white matter adjacent to the prefrontal area) and the genu of the corpus callosum. Third, multiple linear regression analysis

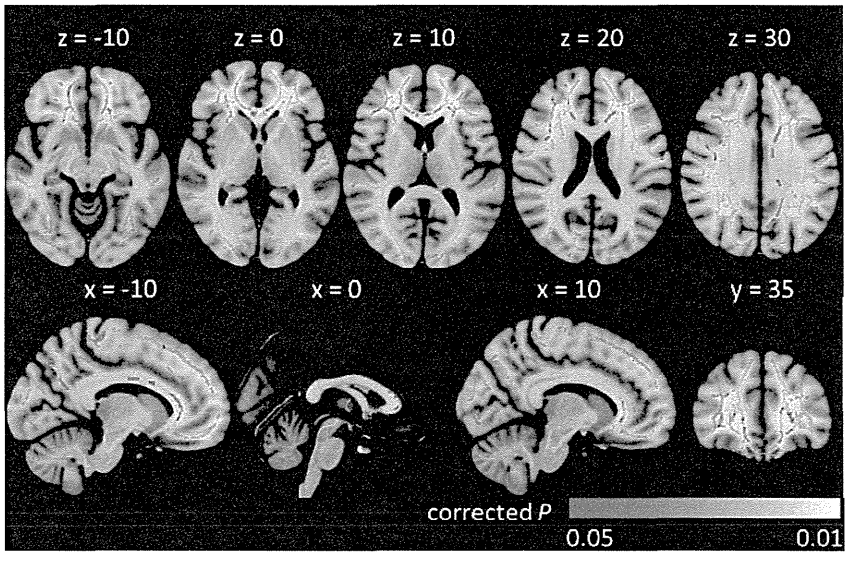

Fig. 3 In PD and PDD patients, TBSS analysis identified a significant positive correlation between FA and MMSE score. (P<0.05, corrected for multiple comparisons, gender and age at the time of MRI). *Red–yellow voxels* demonstrate a significant correlation between the MMSE score and FA

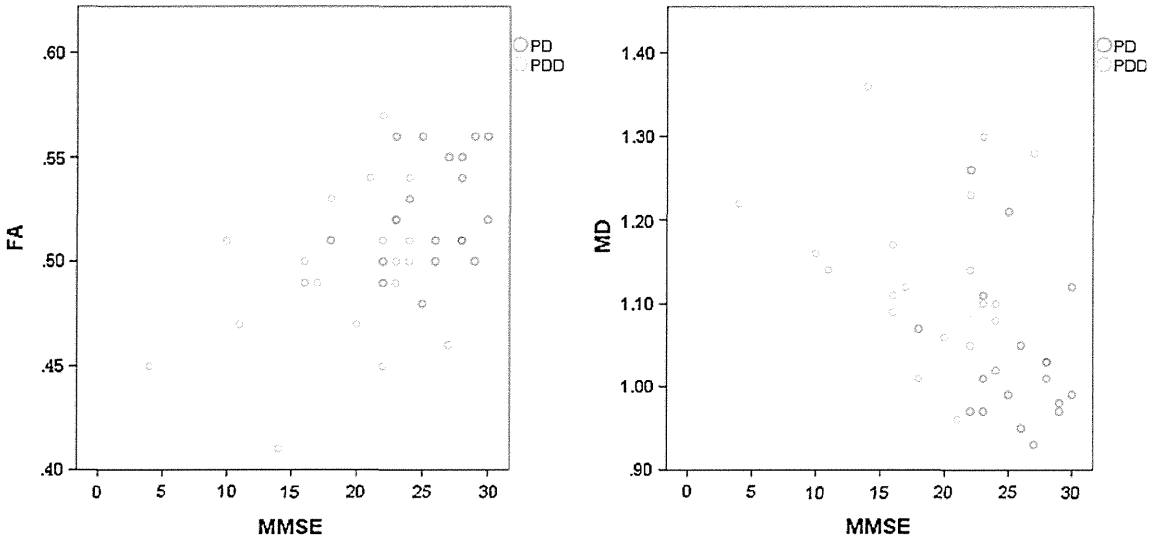

Fig. 4 FA and MD values in the tracts of the genu of the corpus callosum in the PD and PDD patient groups combined were significantly correlated with MMSE score (FA: r=0.472, P=0.002; MD: r=−0.453, P=0.003)

of TBSS revealed a significant correlation between the MMSE score and FA values of the cerebral white matter adjacent to the prefrontal area and the genu of the corpus callosum. Tract-specific analysis also detected a significant correlation between the FA values of the genu of the corpus callosum and the MMSE score, confirming the robustness of our results.

The widespread deterioration of cerebral white matter in the PDD group agrees with the results of the previous study by Hattori et al. [14]. Although the pathological features of white matter in PD are not well established, previous neuropathological studies suggest that white-matter damage is a multifaceted process. There are small Lewy abnormalities, such as Lewy neurites and Lewy axons, in the cerebral white matter in PD [5, 29]. Such accumulated Lewy abnormalities may have altered the axonal structure, resulting in FA values that were significantly lower in the major tracts in our PDD patients than in the controls.

Our comparison between the PDD and PD groups also revealed significant diffusion abnormalities in the genu of the corpus callosum and the white matter adjacent to the prefrontal area, uncovering a correlation between the MMSE score and the diffusion abnormality in these domains. These findings suggest that such changes could be used in assessing the onset of dementia in patients with PD.

However, FA and MD did not correlate with MMSE score in the separate PD and PDD groups when analysed by using TBSS and TSA. When we included both the PD and the PDD group combined, the FA values correlated positively with the MMSE scores in almost the same white matter (prefrontal white matter and genu of the corpus callosum) as that in which FA was decreased in PDD patients relative to PD patients. The finding that PDD patients had significantly lower MMSE scores than PD patients affected the result (FA values correlated positively with MMSE scores in the prefrontal white matter and the genu of the corpus callosum); however, the smaller patient number in this subgroup (n=20, <40) may have influenced this finding.

There were significant differences in disease duration, Hoehn-Yahr stage, and levodopa dosage between the PD

Table 2 Comparison of mean diffusivity (MD) and fractional anisotropy (FA) in the genu of the corpus callosum in patients and control subjects

	CN	PD	PDD			
GCC				CN > PD	CN > PDD	PD > PDD
FA	0.52±0.03[a]	0.52±0.03	0.49±0.04	NS	P<0.005[c]	P<0.005[c]
				CN < PD	CN<PDD	PD<PDD
MD[b]	1.01±0.07	1.04±0.08	1.13±0.10	NS	P<0.00014[c]	P<0.0013[c]

GCC genu of the corpus callosum, *PD* Parkinson's disease, *PDD* Parkinson's disease with dementia, *CN* control subjects

[a] Values are means ± standard deviation

[b] Diffusivity values are expressed as 10^{-3} mm^2/s

[c] Statistical significance (P<0.05)

and PDD patients, and this may have affected the white matter alterations in the PDD group. However, FA and MD did not correlate with disease duration, Hoehn–Yahr stage, or levodopa dosage in the PD and PDD groups. This finding suggests that Hohen-Yahr stage, disease duration and levodopa dosage have little influence on white matter alteration compared with MMSE score.

The most consistent finding of structural MRI studies that have compared PDD patients with normal individuals or with PD patients has been atrophy of the entorhinal cortex, hippocampus, prefrontal cortex and posterior cingulate gyrus [9–11]. In recent studies in particular, atrophy of the white matter in the prefrontal area has been reported in addition to atrophy of the prefrontal cortex [30]. The pattern of atrophy of the entorhinal cortex, hippocampus and posterior cingulate gyrus is similar to the pattern reported in Alzheimer's disease, suggesting that Alzheimer-like disease abnormalities are part of the cause of the cognitive impairment in PD [31, 32]. The atrophy of the prefrontal cortex and white matter in PDD patients may also be related to the presence of Lewy abnormalities of the cortex and white matter. In fact, a neuropathological study has reported a link between the number of Lewy bodies in the cortex and the degree of dementia [33, 34]. In the Braak stages, the deposition of Lewy bodies on the prefrontal cortex is classified as Stage 5, which is a relatively early stage for the neocortex. Neurite abnormalities, parallel with Lewy bodies, are also found in PD [35]; these are called Lewy neuritis [36, 37]. Lewy abnormalities, such as Lewy neurites, are believed to spread to the adjacent white matter in addition to the prefrontal cortex. These pathological changes may be a cause of cognitive impairment in PD.

The corpus callosum is by far the largest fibre bundle in the human brain, interconnecting the two cerebral hemispheres with more than 300 million fibres and playing a primary role in both high-level cognitive integration and sensory integration [38]. Hofer and Frahm [27] defined five vertical partitions of the corpus callosum. Region I, the most anterior segment, covers the first sixth of the corpus callosum and contains fibres that project into the prefrontal region. The genu of the corpus callosum, which we defined here as equivalent to Region I, contains fibres that project into the prefrontal area [39]. In our study, the diffusion abnormalities of the genu of the corpus callosum therefore probably reflected prefrontal cortical Lewy abnormality and prefrontal white-matter damage.

Hattori et al. [14] compared a PDD group with a PD group and reported significant correlations between reduced FA and MMSE score in the superior and inferior longitudinal fasciculus, the lower frontal occipital fasciculus, the uncinate fasciculus, the cingulate fasciculus and the corpus callosum. They further reported significant correlations between the MMSE score and the decrease in FA values in the same domains. An examination of the figures included in their paper reveals that the alteration of the white matter was found largely in the parietal lobe. This finding differs considerably from our study results.

The difference between the results of our study and that of Hattori et al. may reflect the fact that our study used 3-T MRI and the diffusion tensor was imaged with a 32-axis MPG. Examinations of Monte Carlo simulations are said to require at least a 20-axis MPG to measure FA values and a 30-axis MPG to obtain more refined elements of the tensor [40]. Furthermore, in vivo examinations are said to require a 21-axis MPG for the calculation of FA values [41]. Thus the 12-axis MPG used in the study by Hattori et al. does not appear to meet these requirements; our study, which used a 32-axis MPG, may have produced more precise results. One limitation of our study, however, is that our patient group was smaller than that used by Hattori et al. Compared with 1.5-T MRI, 3-T MRI amplifies the distortion owing to the unevenness of the magnetic field. However, it produces high-resolution tensor images because of the increased SNR and a reduction in noise-related errors [42]. Compared with the PDD group in the report by Hattori et al. [14], our PDD group had a somewhat lower MMSE score; this may also have affected the results.

Hattori et al. reported significant correlations between reduced FA and MMSE score in the parietal lobe bilaterally, including in the precuneus; however, our results showed a significant correlation between the FA value of only the left side of the precuneus and the MMSE score. One possible reason why the right precuneus did not produce the same result could be that the FA changes in the precuneus were small and at the threshold value, i.e. the limit of detection (TFCE-corrected $P<0.05$). Figure 3 shows that major sections in the left precuneus are almost entirely red, indicating the significant correlation between MMSE and FA. Another possible reason why this change was found only on one side is that our results may reflect the laterality of cognitive-related white alterations. Hence, further studies are needed to clarify whether cognitive impairment is associated with laterality of white matter alterations.

We previously reported reduced FA in the anterior cingulate fibre tracts in PD patients and a significant correlation between FA in the anterior cingulate fibre tracts and MMSE score by using tract-specific analysis in PDD patients [17]. In the present study, we detected reduced FA bilaterally in the cingulate fibre tracts of PDD patients compared with in normal controls, but we did not detect any reduced FA in PD patients or a significant correlation between FA in the anterior cingulate fibre tracts and MMSE score when we used TBSS in PDD patients.

Compared with TSA, TBSS can influence the outcome by multiple comparisons, whereas TSA has the advantage of detecting abnormalities in specific white matter tracts.

Therefore, our use of TBSS may have been the reason why we did not detect reduced FA in the anterior cingulate fibre tracts in PD patients.

The limitations of our study need to be addressed. Because the diagnoses of PD and PDD were not histopathologically confirmed, the possibility of misdiagnosis remains. However, the validity of the diagnoses is supported by the finding that, 24 months or more after undergoing imaging, all of the patients continued to respond satisfactorily to anti-parkinsonian therapy and remained free of atypical parkinsonism.

In conclusion, we consider that the finding of diffusion abnormalities in the cerebral white matter of PDD patients reflects structural changes resulting from Lewy abnormalities in the cerebral white matter. Our study also found a relationship between cognitive impairment and alteration of white matter adjacent to the prefrontal area and in the genu of the corpus callosum. These changes may be useful in assessing the onset of dementia in PD patients.

Acknowledgments We thank Nozomi Hamasaki and Syuji Sato, MRI technologists, for their skilful performance in data acquisition; Toshino Suzuki, Tomomi Okamura and Yasmin Hasina for their research assistance; and Yuriko Suzuki and Masaru Takashima, Philips Healthcare for their technical assistance. We also thank Narisumi Cho for administrative assistance. This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas (Comprehensive Brain Science Network) from the Ministry of Education, Science, Sports, and Culture of Japan, and MEXT/JSPS KAKENHI Grant Number 24591787.

Note that some of these patients also participated in our previous study. However, overlap of the case is below a half and the main analysis methods in the present study differ from our previous report. Only the cingulate fibre tract was evaluated by tract-specific analysis in our previous study, but the main analysis techniques in the present study is a whole-brain analysis by using TBSS. Tract-specific analysis was used to confirm the robustness of our results in present study.

References

1. Winter Y, von Campenhausen S, Arend M et al (2011) Health-related quality of life and its determinants in Parkinson's disease: results of an Italian cohort study. Parkinsonism Relat Disord 17:265–269
2. Muslimovic D, Post B, Speelman JD, Schmand B (2005) Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology 65:1239–1245
3. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG (2008) The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord 23:837–844
4. Svenningsson P, Westman E, Ballard C, Aarsland D (2012) Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment. Lancet Neurol 11:697–707
5. Braak H, Sandmann-Keil D, Gai W, Braak E (1999) Extensive axonal Lewy neurites in Parkinson's disease: a novel pathological feature revealed by alpha-synuclein immunocytochemistry. Neurosci Lett 265:67–69
6. Braak H, Rub U, Jansen Steur EN, Del Tredici K, de Vos RA (2005) Cognitive status correlates with neuropathologic stage in Parkinson disease. Neurology 64:1404–1410
7. Caviness JN, Lue L, Adler CH, Walker DG (2011) Parkinson's disease dementia and potential therapeutic strategies. CNS Neurosci Ther 17:32–44
8. Aarsland D, Kurz MW (2010) The epidemiology of dementia associated with Parkinson's disease. Brain Pathol 20:633–639
9. Burton EJ, McKeith IG, Burn DJ, Williams ED, O'Brien JT (2004) Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls. Brain 127:791–800
10. Song SK, Lee JE, Park HJ, Sohn YH, Lee JD, Lee PH (2011) The pattern of cortical atrophy in patients with Parkinson's disease according to cognitive status. Mov Disord 26:289–296
11. Weintraub D, Doshi J, Koka D et al (2011) Neurodegeneration across stages of cognitive decline in Parkinson disease. Arch Neurol 68:1562–1568
12. Beaulieu C (2002) The basis of anisotropic water diffusion in the nervous system—a technical review. NMR Biomed 15: 435–455
13. Abe O, Aoki S, Hayashi N et al (2002) Normal aging in the central nervous system: quantitative MR diffusion-tensor analysis. Neurobiol Aging 23:433–441
14. Hattori T, Orimo S, Aoki S et al (2012) Cognitive status correlates with white matter alteration in Parkinson's disease. Hum Brain Mapp 33:727–739
15. Wiltshire K, Concha L, Gee M, Bouchard T, Beaulieu C, Camicioli R (2010) Corpus callosum and cingulum tractography in Parkinson's disease. Can J Neurol Sci 37:595–600
16. Matsui H, Nishinaka K, Oda M, Niikawa H, Kubori T, Udaka F (2007) Dementia in Parkinson's disease: diffusion tensor imaging. Acta Neurol Scand 116:177–181
17. Kamagata K, Motoi Y, Abe O et al (2012) White matter alteration of the cingulum in Parkinson disease with and without dementia: evaluation by diffusion tensor tract-specific analysis. AJNR Am J Neuroradiol 33:890–895
18. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55:181–184
19. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198
20. Goetz CG, Emre M, Dubois B (2008) Parkinson's disease dementia: definitions, guidelines, and research perspectives in diagnosis. Ann Neurol 64:S81–S92
21. Smith SM, Jenkinson M, Johansen-Berg H et al (2006) Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31:1487–1505
22. Nichols TE, Holmes AP (2002) Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 15:1–25
23. Mori S, Wakana S, Van Zijl PCM (2004) MRI atlas of human white matter. Elsevier, Amsterdam
24. Masutani Y, Aoki S, Abe O, Hayashi N, Otomo K (2003) MR diffusion tensor imaging: recent advance and new techniques for diffusion tensor visualization. Eur J Radiol 46:53–66
25. Mori S, Crain BJ, Chacko VP, van Zijl PC (1999) Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann Neurol 45:265–269
26. Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PC, Mori S (2004) Fiber tract-based atlas of human white matter anatomy. Radiology 230:77–87
27. Hofer S, Frahm J (2006) Topography of the human corpus callosum revisited—comprehensive fiber tractography using

diffusion tensor magnetic resonance imaging. Neuroimage 32: 989–994
28. Yasmin H, Nakata Y, Aoki S et al (2008) Diffusion abnormalities of the uncinate fasciculus in Alzheimer's disease: diffusion tensor tract-specific analysis using a new method to measure the core of the tract. Neuroradiology 50:293–299
29. Saito Y, Kawashima A, Ruberu NN et al (2003) Accumulation of phosphorylated alpha-synuclein in aging human brain. J Neuropathol Exp Neurol 62:644–654
30. Takahashi R, Ishii K, Miyamoto N et al (2010) Measurement of gray and white matter atrophy in dementia with Lewy bodies using diffeomorphic anatomic registration through exponentiated lie algebra: a comparison with conventional voxel-based morphometry. AJNR Am J Neuroradiol 31:1873–1878
31. Weintraub D, Dietz N, Duda JE et al (2012) Alzheimer's disease pattern of brain atrophy predicts cognitive decline in Parkinson's disease. Brain 135:170–180
32. Sabbagh MN, Adler CH, Lahti TJ et al (2009) Parkinson disease with dementia: comparing patients with and without Alzheimer pathology. Alzheimer Dis Assoc Disord 23:295–297
33. Hurtig HI, Trojanowski JQ, Galvin J et al (2000) Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. Neurology 54:1916–1921
34. Aarsland D, Perry R, Brown A, Larsen JP, Ballard C (2005) Neuropathology of dementia in Parkinson's disease: a prospective, community-based study. Ann Neurol 58:773–776
35. Gai WP, Blessing WW, Blumbergs PC (1995) Ubiquitin-positive degenerating neurites in the brainstem in Parkinson's disease. Brain 118:1447–1459
36. Gai WP, Blumbergs PC, Blessing WW (1996) Microtubule-associated protein 5 is a component of Lewy bodies and Lewy neurites in the brainstem and forebrain regions affected in Parkinson's disease. Acta Neuropathol 91:78–81
37. Kanazawa T, Adachi E, Orimo S, Nakamura A, Mizusawa H, Uchihara T (2012) Pale neurites, premature alpha-synuclein aggregates with centripetal extension from axon collaterals. Brain Pathol 22:67–78
38. Gazzaniga MS (2000) Cerebral specialization and interhemispheric communication: does the corpus callosum enable the human condition? Brain 123:1293–1326
39. Witelson SF (1989) Hand and sex differences in the isthmus and genu of the human corpus callosum. A postmortem morphological study. Brain 112:799–835
40. Jones DK (2004) The effect of gradient sampling schemes on measures derived from diffusion tensor MRI: a Monte Carlo study. Magn Reson Med 51:807–815
41. Ni H, Kavcic V, Zhu T, Ekholm S, Zhong J (2006) Effects of number of diffusion gradient directions on derived diffusion tensor imaging indices in human brain. AJNR Am J Neuroradiol 27:1776–1781
42. Hunsche S, Moseley ME, Stoeter P, Hedehus M (2001) Diffusion-tensor MR imaging at 1.5 and 3.0 T: initial observations. Radiology 221:550–556

Parkinsonism and Related Disorders 19 (2013) 725–731

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

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

Editor's comment: By systematically obtaining information from the charts of an impressively large number of patients with Parkinson's disease (PD) followed in an outpatient neurology clinic, Yoritaka and colleagues have provided us a treasure trove of information and data that will serve as a valuable reference point for both clinicians and researchers. In addition to useful demographic and treatment information, they also have accumulated very interesting data on a number of aspects of PD that often receive scant attention, such as the frequency of camptocormia and pneumonia in PD patients.

Ronald F. Pfeiffer, Editor-in-Chief Department of Neurology, University of Tennessee HSC, 875 Monroe Avenue, Memphis, TN 38163, USA

Motor and non-motor symptoms of 1453 patients with Parkinson's disease: Prevalence and risks

Asako Yoritaka [a,b,*], Yasushi Shimo [a], Masashi Takanashi [a], Jiro Fukae [a,c], Taku Hatano [a], Toshiki Nakahara [a], Nobukazu Miyamato [a], Takao Urabe [a,d], Hideo Mori [a,b], Nobutaka Hattori [a]

[a] Department of Neurology, Juntendo University School of Medicine, Japan
[b] Department of Neurology, Juntendo University Koshigaya Hospital, Japan
[c] Department of Neurology, Fukuoka University Hospital, Japan
[d] Department of Neurology, Juntendo University Urayasu Hospital, Japan

ARTICLE INFO

Article history:
Received 2 January 2013
Received in revised form
22 March 2013
Accepted 2 April 2013

Keywords:
Parkinson's disease
Natural history studies
Wearing-off
Camptocormia
Psychosis

ABSTRACT

Purpose: We examined the prevalence and risk of clinical symptoms in a large number of Japanese patients with Parkinson's disease (PD) ($n = 1453$; 650 males).
Methods: Events were analyzed using Kaplan–Meier survival curves, logistic regression, and Cox proportional-hazards models.
Results: The mean age (SD) was 67.7 (10.0), age of onset was 58.0 (11.5), and disease duration was 9.7 (6.6) years. The mean modified Hoehn and Yahr stage was 2.8 (1.2). Most patients (88.9%) received levodopa (547.7 (257.6) mg/day). A large proportion (81.3%) received dopamine agonists (136.2 (140.7) mg/day). About 23.4% received pain treatment 6.9 (5.1) years after the onset; females ($p < 0.05$) and patients with late-onset PD (≥60 years, $p < 0.001$) were more likely to be affected. About 44.7% of patients had wearing-off 7.5 (4.7) years after the onset, and it was more common in females ($p < 0.001$) and patients with early-onset PD ($p < 0.001$). Camptocormia was found in 9.5% of patients 8.1 (6.2) years after the onset, and it was more common in females ($p < 0.05$) and patients with late-onset PD ($p < 0.05$). About 28.6% of patients developed psychosis 9.0 (5.4) years after the onset, and it was more likely to occur in patients with late-onset PD ($p < 0.001$). Late-onset PD and cerebrovascular disease were also associated with increased risk of pneumonia.
Conclusions: Considering that very few studies have assessed numerous clinical symptoms in the same report, these data provide a useful reference for the clinical course of PD.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. Dopamine replacement with levodopa or dopamine agonists (DA) results in marked improvement of motor symptoms and alleviation of disability; these treatments have also improved patient survival [1,2]. However, levodopa use is also associated with the development of motor complications that substantially contribute to disability in patients with advanced PD. Various motor and non-motor symptoms (NMS) and side effects of anti-parkinsonian drugs limit the medication dose and the ability to prescribe other drugs. Here, we have described the prevalence and risk

* Corresponding author. Department of Neurology, Juntendo University Koshigaya Hospital, Fukuroyama 560, Saitama 343-0032, Japan. Tel.: +81 48 975 0321; fax: +81 48 975 0346.
E-mail addresses: ayori@juntendo.ac.jp, yyykoro@yahoo.co.jp (A. Yoritaka).

1353-8020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.parkreldis.2013.04.001

Table 1
Baseline demographic and clinical characteristics of patients with Parkinson's disease.

Variable	Category	*n* or mean	SD	Median
Total		1453		
Age		67.7	10.0	68.5
Age at onset		58.0	11.5	59.3
Sex	Male	650 (44.7%)		
	Female	803 (55.3%)		
Disease duration	Mean	9.7	6.6	8.5
Hoehn and Yahr stage on		First visit	Enrollment	
	0	10 (0.7%)	48 (3.3%)	
	0.5 and 1.0	241 (16.6%)	101 (7.0%)	
	1.5 and 2.0	685 (47.1%)	428 (29.5%)	
	2.5 and 3.0	414 (28.5%)	438 (30.1%)	
	4	68 (4.7%)	294 (20.2%)	
	5	10 (0.7%)	99 (6.8%)	
	Not described	25 (1.7%)	45 (3.1%)	
Hypertension		258 (17.8%)		
Dyslipidemia		174 (12.0%)		
Diabetes mellitus		79 (5.4%)		
Cerebral vessel disease		86 (5.9%)		
Malignant tumor		87 (6.0%)		
Therapy in another hospital before our hospital		802 (55.2%)		
Anti-parkinsonian drugs				
Levodopa		1292 (88.9%)		
Duration from onset to start of treatment	Years	2.9	3.2	2.0
Daily dose at enrollment day	mg	547.7	257.6	600.0
Cumulative dose	g	1259.2	1190.0	933.4
Pramipexole		900 (61.9%)		
Duration from onset to start of treatment	Years	6.4	5.6	5.0
Daily dose ($n = 900$)	mg	2.1	2.6	1.7
Ropinirole		212 (14.6%)		
Duration from onset to start of treatment	Years	7.5	6.1	6.0
Daily dose ($n = 212$)	mg	7.5	4.7	3.3
Pergolide		414 (28.5%)		
Duration from onset to start of treatment	Years	4.9	4.9	3.5
Daily dose ($n = 414$)	mg	941.4	2.0	1.6
Cabergoline		405 (27.9%)		
Duration from onset to start of treatment	Years	4.9	5.2	3.3
Daily dose ($n = 405$)	mg	2.3	1.3	2.0
Bromocriptine		99 (6.8%)		
Duration from onset to start of treatment	Years	4.3	4.2	3.4
Daily dose ($n = 99$)	mg	16.2		7.5
Dopamine agonist		1182 (81.3%)		
Duration from onset to start of treatment	Years	4.0	4.4	2.6
Daily dose ($n = 1453$)	mg	136.2	140.7	120.0
Entacapone		314 (21.6%)		
Duration from onset to start of treatment	Years	10.3	5.8	9.3
Daily dose ($n = 314$)	mg	490.3	249.3	400.0
Trihexyphenidyl		561 (38.6%)		
Duration from onset to start of treatment	Years	4.0	4.0	2.7
Daily dose ($n = 561$)	mg	3.3	1.6	3.0
Amantadine		598 (41.2%)		
Duration from onset to start of treatment	Years	5.6	5.8	3.9
Daily dose ($n = 598$)	mg	166.0	63.6	150.0
Zonisamide		98 (6.7%)		
Duration from onset to start of treatment	Years	9.9	7.2	8.2
Daily dose ($n = 98$)	mg	47.3	34.9	25.0
Droxidopa		134 (9.2%)		
Duration from onset to start of treatment	Years	7.0	5.1	5.9
Daily dose ($n = 134$)	mg	380.6	178.7	300.0
Selegiline		620 (42.7%)		
Duration from onset to start of treatment	Years	6.7	5.0	5.6
Daily dose ($n = 620$)	mg	7.2	6.0	5.0

of clinical symptoms in a large number of Japanese patients with PD.

2. Patients and methods

Between January and June 2010, we retrospectively reviewed the charts of patients who had visited our outpatient neurology clinic at Juntendo Hospital in Tokyo, and had been diagnosed with PD by a board-certified neurologist. Diagnoses were based on the UK Brain Bank diagnostic criteria for PD [3], and patients with dementia with Lewy bodies [4], progressive supranuclear palsy, corticobasal degeneration, vascular parkinsonism, and other forms of parkinsonism were excluded. Hospital charts were systematically reviewed by A.Y. This study was approved by the Juntendo Hospital institutional ethics committee, and informed consent was obtained.

The following data were collected from patients: sex; date of birth, first visit, and onset; initial symptoms, side of initial symptoms, order of medications taken from the time of initial medication, approximate date of start or stop of each medication, and modified Hoehn and Yahr (H & Y) stage for the initial and final evaluations; and dates of important events (pain, wearing-off, camptocormia, sleep attack, orthostatic hypotension, psychosis, electrical convulsive therapy [ECT] for severe psychosis, neuroleptic malignant syndrome, pneumonia, and tube feeding).

"Onset" was defined as the date of appearance of the first symptoms of parkinsonism (bradykinesia, rest tremor, and/or rigidity). "Pain" was defined as pain that required treatment, including pain related to wearing-off and excluding pain related to bone fracture, myocardial infarction, respiratory disease, and abdominal disease. "Camptocormia" was defined as marked anterior flexion of the thoracolumbar spine in the recumbent position without evidence of fixed kyphosis. "Sleep Attack" was an acute and irresistible episode of sleep occurring without warning signs [5]. "Orthostatic hypotension" was defined as a greater than 20 mmHg decrease in systolic pressure. "Psychosis" included reports of illusion, false sense of presence, hallucinations, or delusions that continued or recurred for at least 1 month [6]. Diagnosis of "neuroleptic malignant syndrome" was based on Levenson's criteria [7]. Other NMS like depression, cognition, apathy, and excessive daytime sleepiness were not selected, because their onset was not clear, and the patients were not regularly examined using tools like the NMS questionnaire (NMSQuest) [8], Scale for Outcomes in Parkinson's Disease-Psychiatric Complications (SCOPA-PC) [9], or SCOPA-Cognition (SCOPA-COG) [10]. NMS in early PD like REM sleep behavior disorder (RBD), olfactory dysfunctions, or constipation were not analyzed.

The daily levodopa equivalent dose was calculated on the basis of the following equivalences: 100 mg standard levodopa = 10 mg bromocriptine = 1 mg pergolide = 5 mg ropinirole = 1 mg pramipexole [11].

2.1. Statistical analyses

SAS (ver. 9.1.3; SAS Institute Inc., Cary, NC, USA) and SPSS (ver. 16.1; SPSS Inc., Chicago, IL, USA) were used for statistical analyses. The data are presented as mean (standard deviation [SD]) values for age, age at onset, H & Y stage of the "on" phase, daily dose of drugs, and duration from the onset of PD for important events. H & Y stages without parkinsonism symptoms in the "on" phase were considered as "0". Point prevalences were calculated, and Kaplan–Meier (K–M) time-to-event curves and log-rank tests were used to estimate the absolute risk of each event. The factors chosen were as follows: onset age (early onset < 60 years or late onset ≥ 60 years), sex, hypertension (HT), diabetes mellitus (DM), dyslipidemia (DL), cerebrovascular disease (CVD), and malignant tumor. These were selected because they are the most frequently seen diseases in the Japanese. Logistic regression was performed to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for each event. Cox proportional-hazard modeling was used to calculate hazard ratios (HRs) and 95% CIs for differences among subgroups embedded into the following variables: age at onset, sex, order of drugs (levodopa or other anti-parkinsonism drugs), and duration to the start of drugs (levodopa, other drugs, or all anti-parkinsonism drugs). Proportional hazards were assessed with graph log–log plots. Statistical tests were two-sided, and the significance level was set at $p < 0.05$.

3. Results

We evaluated 1453 patients with PD (650 males) (Table 1). Their mean age (SD) was 67.7 (10.0), age of onset was 58.1 (11.5), and disease duration was 9.7 (6.6) years. The mean follow-up at our hospital was 5.9 (5.7) years. Age and age at onset were 67.2 (10.2) and 57.5 (11.8) years, respectively, for males and 68.3 (9.6) and 58.6 (11.2) years, respectively, for females. The mean H & Y stages were 2.2 (0.8) at the first visit and 2.8 (1.2) at the final evaluation. Patients with H & Y stages of 0, I (0.5 and 1.0), II (1.5 and 2.0), III (2.5 and 3.0), IV (4.0), V (5), and unknown (not described) were 3.3%, 7.0%, 29.5%, 30.1%, 20.2%, 6.8%, and 1.7%, respectively. The percentages of patients with PD who also had HT, DL, DM, CVD, and malignant tumor were 17.8%, 12.0%, 5.4%, 5.9%, and 6.0%, respectively.

Most patients (1292, 88.9%) received levodopa, and the average daily dose at enrollment was 547.7 (257.6) mg/day. The average levodopa doses for patients with H & Y stages of 0, I, II, III, IV, and V were 504.2 (252.8) mg, 498.0 (283.5) mg, 511.5 (304.2) mg, 484.9 (303.8) mg, 461.9 (283.4) mg, and 475.3 (270.1) mg, respectively (including unmedicated patients). In total, 1182 patients (81.3%) also received DAs; the average equivalent dose at enrollment was 136.2 (140.7) mg/day. The equivalent DA doses were 134.4 (142.4) mg, 136.9 (138.1) mg, 136.6 (139.0) mg, 140.8 (142.3) mg, 129.5

Table 2
Kaplan–Meier survival of events in the patients with Parkinson's disease.

Factors	Category	*N*	*n* (%)	Disease duration and prevalence: Kaplan–Meier (%)						Log-rank test
				2nd year	4th year	6th year	8th year	10th year	12th year	
				n						
				1356	1162	965	760	583	426	
Pain	Total	1453	340 (23.4)	3.2%	7.1%	13.2%	19.8%	25.0%	30.2%	–
Age of onset	<60	711	178 (25.0)	1.6%	4.4%	9.8%	15.1%	21.1%	25.5%	$P < 0.001^{***}$
	≥60	742	162 (21.8)	4.8%	9.9%	16.9%	25.7%	29.4%	37.0%	
Sex	Male	650	133 (20.5)	2.5%	6.2%	11.7%	17.6%	21.0%	26.5%	$P = 0.018^{*}$
	Female	803	207 (25.8)	3.7%	7.9%	14.5%	21.6%	28.0%	33.1%	
Wearing-off	Total	1453	649 (44.7)	1.8%	9.9%	22.7%	40.5%	50.9%	61.8%	–
Sex	Male	650	253 (38.9)	1.3%	8.5%	18.6%	34.5%	40.9%	52.9%	$P < 0.001^{***}$
	Female	803	396 (49.3)	2.2%	11.1%	26.0%	45.4%	58.8%	68.7%	
Camptocormia	Total	1453	138 (9.5)	0.7%	2.7%	5.2%	7.5%	9.3%	11.8%	–
Age of onset	<60	711	80 (11.3)	0.7%	1.5%	3.5%	5.5%	7.0%	10.0%	$P = 0.034^{*}$
	≥60	742	58 (7.8)	0.7%	4.1%	7.2%	9.9%	12.1%	13.4%	
Sex	Male	650	47 (7.2)	0.2%	1.6%	3.9%	6.4%	7.5%	9.1%	$P = 0.010^{*}$
	Female	803	91 (11.3)	1.1%	3.6%	6.3%	8.5%	10.7%	13.9%	
Sleep attack	Total	1453	65 (4.5)	0.4%	1.3%	2.4%	4.4%	6.7%	10.5%	–
Orthostatic hypotension	Total	1453	95 (6.5)	0.5%	1.6%	3.0%	4.8%	6.0%	8.3%	–
Age of onset	<60	711	45 (6.3)	0.1%	0.4%	1.4%	2.5%	3.0%	5.3%	$P < 0.001^{***}$
	≥60	742	50 (6.7)	0.8%	2.8%	4.9%	7.9%	10.5%	12.8%	
Hypertension	–	1195	88 (7.4)	0.5%	1.8%	3.4%	5.5%	6.8%	9.5%	$P = 0.005^{**}$
	+	258	7 (2.7)	0.4%	0.9%	0.9%	1.5%	2.3%	2.3%	
Psychosis	Total	1453	416 (28.6)	1.7%	5.8%	11.1%	18.0%	25.6%	33.8%	–
Age of onset	<60	711	207 (29.1)	0.7%	2.5%	5.8%	11.2%	16.0%	22.1%	$P < 0.001^{***}$
	≥60	742	209 (28.2)	2.7%	9.4%	17.2%	26.6%	39.8%	53.9%	
Malignant syndrome	Total	1453	32 (2.2)	0.1%	0.2%	0.3%	1.1%	2.2%	2.8%	–
Diabetes mellitus	–	1374	27 (2.0)	0.1%	0.2%	0.3%	1.1%	1.7%	2.4%	$P = 0.032^{*}$
	+	79	5 (6.3)	0.0%	0.0%	0.0%	2.0%	9.0%	9.0%	
Pneumonia	Total	1453	63 (4.3)	0.1%	0.2%	0.7%	1.5%	2.8%	3.3%	–
Age of onset	<60	711	27 (3.8)	0.0%	0.0%	0.3%	0.3%	0.6%	0.8%	$P < 0.001^{***}$
	≥60	742	36 (4.9)	0.1%	0.5%	1.1%	3.1%	6.6%	7.9%	
Cerebrovascular disease	–	1367	51 (3.7)	0.1%	0.2%	0.5%	1.0%	2.1%	2.7%	$P < 0.001^{***}$
	+	86	12 (14.0)	0.0%	1.3%	4.1%	7.6%	11.7%	11.7%	

All events were analyzed with all factors. The factors were designed as follows, onset age, sex, hypertension, diabetes mellitus, dyslipidemia, cerebrovascular disease, and malignant tumor. Table indicates only factors with significant differences. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

Table 3
Logistic regression of the events in patients with Parkinson's disease.

Factors	Statistical analysis	Age at onset	Age	Sex (female)	Disease duration	Modified Hoehn and Yahr stage	Daily levodopa (mg)	Duration to start of levodopa	Duration start of the drugs except levodopa	First start of the drugs	Hypertension
Pain	Odds ratio	0.85	1.18	1.42	0.83	1.00	1.00	0.10	0.96	0.83	
	CI	0.66–1.08	0.92–1.51	1.08–1.87	0.65–1.06	0.87–1.15	1.00–1.00	1.00–1.00	0.92–1.01	0.60–1.16	NE
	p	0.177	0.191	0.013*	0.128	0.996	<0.001***	0.099	0.090	0.283	
Wearing-off	Odds ratio	0.97	0.97	2.13	1.00	0.93	1.00	1.00	0.99	1.28	
	CI	0.75–1.27	0.75–1.23	1.61–280	0.77–1.29	0.82–1.07	1.00–1.00	1.00–1.00	0.93–1.04	0.91–1.79	NE
	p	0.840	0.815	<0.001***	0.989	0.316	<0.001***	<0.001***	0.592	0.156	
Camptocormia	Odds ratio	0.88	1.12	1.56	0.87	1.37	1.00	1.00	0.95	1.00	
	CI	0.68–1.14	0.86–1.45	1.07–2.28	0.68–1.12	1.13–1.66	1.00–1.00	1.00–1.00	0.88–1.02	0.63–1.57	NE
	p	0.319	0.403	0.022*	0.278	0.002**	0.113	0.681	0.144	0.860	
Sleep attack	Odds ratio	0.98	1.00	0.60	NE	1.01	1.00	0.93	0.88	1.21	NE
	CI	0.93–1.03	0.95–1.06	0.36–1.00		0.78–1.30	0.99–1.00	0.78–1.11	0.76–1.02	0.93–1.58	
	p	0.980	0.970	0.048*		0.967	0.889	0.434	0.101	0.151	
Orthostatic hypotension	Odds ratio	0.86	1.19	0.95	0.82	1.32	1.00	1.00	1.03	1.25	4.47
	CI	0.66–1.11	0.91–1.54	0.60–1.51	0.64–1.05	1.03–1.69	1.00–1.00	1.00–1.00	0.97–1.09	0.71–2.21	1.01–19.75
	p	0.235	0.200	0.826	0.117	0.028*	0.190	0.016*	0.386	0.433	0.048*
Psychosis	Odds ratio	0.98	1.06	1.20	1.01	1.49	1.00	1.04	0.94	0.68	
	CI	0.91–1.05	0.98–1.14	0.79–1.81	0.94–1.08	1.21–1.88	1.00–1.00	0.96–1.13	0.88–1.00	0.41–1.14	NE
	p	0.505	0.136	0.401	0.845	<0.001***	<0.001***	0.360	0.061	0.144	

CI: confidence interval, *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, NE: not examined.

(134.2) mg, and 131.4 (156.3) mg for H & Y stages 0, I, II, III, IV, and V, respectively (including unmedicated patients). Equivalent DA doses in H & Y stages I and II were not significantly different between patients with wearing-off (159.8 (156.0) mg) and those without wearing-off (131.6 (137.0) mg). The average levodopa dose for H & Y stage I and II patients was 538.8 (214.6) mg with wearing-off and 278.0 (247.4) mg without wearing-off; this difference was statistically significant ($p < 0.001$). H & Y stage I and II patients with psychosis were on higher doses of levodopa (535.9 (220.2) mg) compared to patients without psychosis (336.9 (263.5) mg) ($p < 0.001$). The average DA dose was 119.5 (151.6) mg in patients with psychosis and 146.9 (143.3) mg in those without ($p > 0.05$).

The onset of events was significantly ($p < 0.001$) earlier in patients with late onset than in those with early onset (Additional Table 1S). The prevalence and mean duration of each symptom from onset of PD are shown in Additional Fig. 1. The data obtained from K–M curves, logistic regression, and Cox HRs are shown in Tables 2–4, respectively.

3.1. Pain

About 23.4% of patients had pain at a mean duration of 6.94 (5.12) years from PD onset. In the twelfth year, 37.0% of late-onset and 25.5% of early-onset patients reported pain ($p < 0.001$); there was a statistically significant sex difference ($p < 0.05$). Logistic regression showed that the pain OR was 1.42 (95% CI, 1.08–1.87; $p < 0.05$) for females. Cox modeling yielded an HR of 1.26 (95% CI, 1.08–1.58; $p < 0.05$) for females and 1.02 (95% CI, 1.01–1.03; $p < 0.001$) for age at onset.

Table 4
Cox proportional hazards models for clinical events in patients with Parkinson's disease.

Events	Variables	Age at onset	Sex (female)	Duration to start of levodopa	Duration to start of the drugs except levodopa	First start of the drugs	No hyper-tension	Diabetes mellitus+	Cerebro-vascular disease+
Pain	HR	1.02	1.26	0.93	0.95	1.06			
	95%CI	1.01–1.03	1.08–1.58	0.86–1.00	0.91–0.99	0.79–1.41	NE	NE	NE
	p	<0.001***	0.043*	0.059	0.01*	0.701			
Wearing off	HR	0.99	1.46	0.89	0.97	0.86			
	95%CI	0.98–0.99	1.24–1.71	0.84–0.94	0.95–0.99	0.70–1.04	NE	NE	NE
	p	<0.001***	<0.001***	<0.001***	0.006**	0.123			
Camptocormia	HR	1.02	1.46	1.01	0.94	1.08			
	95%CI	1.01–1.04	1.03–2.08	0.90–1.12	0.88–1.00	0.70–1.68	NE	NE	NE
	p	0.012*	0.033*	0.909	0.053	0.723			
Sleep attack	HR	1.02	0.55	0.89	0.85	1.20			
	95%CI	0.99–1.05	0.33–0.90	0.75–1.05	0.74–0.98	0.93–1.53	NE	NE	NE
	p	0.085	0.017*	0.152	0.021*	0.160			
Orthostatic hypotension	HR	1.04	0.87	0.93	1.03	0.94	1.63		
	95%CI	1.02–1.06	0.57–1.34	0.79–1.09	0.98–1.08	0.53–1.66	0.97–2.74	NE	NE
	p	0.001**	0.532	0.345	0.332	0.834	0.063		
Psychosis	HR	1.05	1.04	0.99	0.97	1.16			
	95%CI	1.04–1.07	0.85–1.26	0.93–1.06	0.94–1.01	0.90–1.51	NE	NE	NE
	p	<0.001***	0.714	0.781	0.096	0.253			
Malignant syndrome	HR	1.05	0.73	0.94	1.01	2.05		2.47	
	95%CI	0.99–1.06	0.35–1.53	0.74–1.21	0.93–1.09	0.70–6.01	NE	0.87–6.97	NE
	p	0.176	0.404	0.646	0.883	0.189		0.088	
Pneumonia	HR	1.13	0.63	1.07	0.99	2.00			1.98
	95%CI	1.09–1.16	0.83–1.06	0.91–1.26	0.93–1.05	0.93–4.29	NE	NE	1.03–3.80
	p	<0.001***	0.083	0.435	0.771	0.076			0.041*

HR: hazard rate, CI: confidence interval, *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, NE: not examined.

3.2. Wearing-off

About 44.7% of patients experienced wearing-off an average of 7.52 (4.66) years after PD onset. The prevalence of dyskinesia was 27.1%, and all of these patients had wearing-off. Wearing-off was more common in females ($p < 0.001$); 58.8% of female and 40.9% of male patients had experienced it by the tenth year. Logistic regression analysis revealed a significantly higher OR for female sex, daily dose of levodopa, and disease duration to the start of levodopa. HRs were 1.46 (95% CI, 1.24–1.71; $p < 0.001$) for female sex, 0.99 (95% CI, 0.98–0.99; $p < 0.001$) for age at onset, 0.89 (95% CI, 0.84–0.94; $p < 0.001$) for disease duration to the start of levodopa, and 0.97 (95% CI, 0.95–0.99; $p < 0.01$) for the duration to the start of other drugs.

3.3. Camptocormia

Camptocormia was found in 9.5% of patients an average of 8.05 (6.16) years after PD onset. Prevalence was higher in late-onset patients than in early-onset patients ($p < 0.05$), and more females developed the symptom ($p < 0.01$). Logistic regression analysis revealed significantly higher ORs for female sex and higher H & Y stages. HRs were 1.02 (95% CI, 1.01–1.04; $p < 0.05$) for age at onset and 1.46 (95% CI, 1.03–2.08; $p < 0.05$) for female sex. In 34 patients, we stopped pramipexole and their camptocormia improved; therefore, we also assessed camptocormia risk in patients who did or did not receive non-ergot DAs. Among patients who received pramipexole, females showed a higher prevalence of camptocormia (7.7% in the second year and 14.8% in the fourth year), and males had lower prevalence in the early stage of disease (3.8% in the second year, 6.5% in the fourth year) ($p < 0.01$). The HRs for patients on pramipexole were 1.82 (95% CI, 1.21–2.72; $p < 0.001$) for female sex and 0.67 (95% CI, 0.54–0.83; $p < 0.001$) for disease duration. For those who experienced camptocormia without non-ergot DAs, no differences were observed for age at onset, sex, or accompanying disease.

3.4. Sleep attack

An average of 8.50 (6.52) years from PD onset, 4.5% of patients had sleep attack without warning signs. Daily DA doses were not correlated to the prevalence of sleep attack. Logistic regression analysis revealed significantly higher ORs for male sex. HRs were 0.60 (95% CI, 0.36–1.00; $p < 0.05$) for female sex.

3.5. Orthostatic hypotension

An average of 8.83 (6.04) years from PD onset, 6.5% of patients developed orthostatic hypotension that required treatment. Notably, 12.8% of late-onset patients had orthostatic hypotension by the twelfth year compared to just 5.3% of early-onset patients. Logistic regression revealed that the OR was significantly higher for higher H & Y stages and patients without hypertension. The HR was 1.039 (95% CI, 1.02–1.06; $p < 0.01$) for age at onset.

3.6. Psychosis

About 28.6% of patients had symptoms of psychosis an average of 9.03 (5.38) years after PD onset. Interestingly, 53.9% of late-onset patients and 22.1% of early-onset patients had experienced symptoms of psychosis by the twelfth year ($p < 0.001$). Logistic regression tests revealed that the OR was significantly larger for higher H & Y stages and greater levodopa doses. The HR was 1.05 (95% CI, 1.04–1.07; $p < 0.001$) for age of onset. Seventeen patients underwent ECT for the treatment of psychotic symptoms that were refractory to medication. ECT took place an average of 8.24 (6.07) years after PD onset. The prevalence rate for ECT was 1.8% in the twelfth year. More patients with DM than without DM (3.8% vs. 1.0%) received ECT ($p < 0.05$). Logistic regression revealed no OR effects for ECT (data not shown).

3.7. Neuroleptic malignant syndrome

About 2.2% of patients developed neuroleptic malignant syndrome an average of 11.44 (7.79) years after PD onset. Among patients with DM, 9.0% developed malignant syndrome, whereas only 1.7% of patients without DM had experienced malignant syndrome by the tenth year ($p < 0.05$). Logistic regression and HR assessments did not reveal any risk factors that predisposed patients to developing malignant syndrome.

3.8. Pneumonia

About 4.3% of patients developed pneumonia, which occurred an average of 13.87 (8.04) years after PD onset. Late-onset patients ($p < 0.001$) and those with CVD ($p < 0.001$) were more likely to develop pneumonia. The HR was 1.13 (95% CI, 1.09–1.16; $p < 0.001$) for age at onset and 1.98 (95% CI, 1.03–3.80; $p < 0.05$) for CVD. Tube feeding was necessary in 2.1% of patients after an average of 16.03 (9.36) years after PD onset. Tube feeding prevalence rates were 0.1%, and 1.8% in the sixth and twelfth years, respectively.

4. Discussion

In Western countries, the prevalence and incidence of PD are greater in males than in females [12,13]. In our study, there were more female patients, which is similar to what was previously reported in a Japanese PD study (male:female, 1:1.2–1.7) [14,15]. In this retrospective non-interventional study, we assessed symptom prevalence and duration in a large cohort of Japanese patients with PD. The duration to the onset of events, except for malignant syndrome, in the early-onset group was 1.5–2 times greater than that in the late-onset group.

The questionnaire-based study by Chaudhuri et al. [16] revealed no differences in pain rate (27% for patients with PD vs. 30.2% for age matched-controls). Other studies have described higher pain rates in patients with PD [17,18]; however, the studies utilized different pain scales. We found that females and late-onset patients had increased pain rates, but other reports have stated that younger age at onset [17] and female sex [19–21] were risk factors for pain.

Female patients were more likely to experience wearing-off, and the average female daily dose of levodopa was higher (11.5 (5.8) mg/kg compared to 8.8 (3.9) mg/kg for males; Fisher's test, $p < 0.01$). The DATATOP clinical trial showed that more females developed dyskinesia and that this was likely due to the higher amount of levodopa ($p < 0.01$) [22]. In our study, younger age at onset was a risk for wearing-off. Which drug was prescribed first (levodopa or other drugs) did not affect wearing-off. A prospective study reported that motor complication prevalence was not significantly different between patients initially treated with levodopa and those first treated with DA [23–25]. Although there were no statistical differences, the time without motor complications was longer in the group initially treated with DA; however, these patients often experienced sleepiness, edema, and hallucinations [23–25]. In our 2002 study, the prevalence of wearing-off was 21.3% at the fifth year and 59.4% at the tenth year

from PD onset [15], which was slightly higher than what we found here. In the interim between the studies, new anti-parkinsonian drugs were marketed in Japan, including pramipexole (2004), ropinirole (2006), entacapone (2007), and zonisamide (2009). The availability of these drugs may have prolonged wearing-off onset because we could select from different DAs.

The prevalence of camptocormia and duration from PD onset to camptocormia in our study were nearly identical to those previously described [26,27]. We found that female sex, older age at onset, and disease severity were risk factors for camptocormia. In our patient population, camptocormia was more severe during walking or standing and tended to increase with fatigue and decrease when non-ergot drug use was ceased. Camptocormia was considered to be axial dystonia [28] rather than a myopathic change [26,27]. Levodopa [29] or pramipexole [30] induced or worsened camptocormia in some cases, but they may also have beneficial effects in cases in which it is due to PD. We investigated the risk of camptocormia in patients with PD receiving non-ergot DAs.

Sleep attack and excessive daytime sleepiness were more common in males [31]. Disease duration, DA therapy, excessive daytime sleepiness [32] and RBD [33] were risks of sleep attack. Varying frequencies of sleep attack (0–43%) have been reported [34].

A previous report showed that 60% of patients developed psychosis during a 12-year study period [35]. The analysis revealed that the risk of psychosis (mainly hallucinations) increased in patients with older age at onset and greater disease severity. In other studies, older age [36] and longer disease duration [37,38] were associated with psychosis, and disease severity was linked to the presence of hallucinations [38]. Moreover, hallucinations were more frequent among patients with early PD treated with DA compared with those who received placebo or levodopa [39]. In our study, patients with psychosis were treated with lower doses of DAs and higher doses of levodopa, and other drugs were stopped due to psychosis.

The risk of neuroleptic malignant syndrome has been previously associated with CVD, cerebral contusion, physical stress [40], infection, hot weather, and severe wearing-off [41]. In this study, CVD was not a risk factor. Many patients experienced dehydration or severe off-phases before neuroleptic malignant syndrome onset. Although malignant syndrome and dopamine agonist withdrawal syndrome [42] were both acute syndromes caused by a sudden change in dopaminergic stimulation, the risk factors for these syndromes were different.

Respiratory infection is one of the leading causes of death in patients with PD [15]. Patients with late-onset PD or CVD were at risk for developing pneumonia, and the mean duration of tube feeding was 2 years after the first episode of pneumonia.

The limitation of our retrospective study is that we did not include patients who died early. Furthermore, this study was a retrospective chart review study and certain treatment outcomes differed from those of previously reported controlled prospective studies.

NMSQuest studies [8,43] and the PRIAMO study [20] that used self-completed NMS questionnaire have reported that NMS were prevalent across all stages of PD disease. These studies broadly included a broad spectrum of NMS that patients may not be aware of as PD-related symptoms or clinicians ignored. However, until recently, NMS were known to clinicians treating PD and patients with PD, and many of the unrecognized NMS need treatment because these reduce the quality of life.

In conclusion, we investigated the duration and prevalence rates of various symptoms and complications in a large cohort of patients with PD and determined that age and sex might predict the onset of some events. Moreover, the onset or duration of levodopa use might influence the onset of wearing-off, but the order of levodopa or other drugs did not predict symptoms.

Full financial disclosure

A. Yoritaka, Y. Shimo, M. Takanashi, J. Fukae, T. Hatano, T. Nakahara, N. Miyamoto, T. Urabe, and H. Mori report no disclosures. N. Hattori is a consultant for Boehringer Ingelheim, FP Pharmaceutical Company, Ohtsuka Pharmaceutical Company, Kyowa Hakko Kirin Pharmaceutical Company, GlaxoSmithKline, Novartis, Abbot, Hisamitsu, and Schering-Plough. He received personal compensation for attending advisory board meetings.

Study funding

None.

Author roles

1. Research Projects: A. Conception, Organization, B. Execution
2. Statistical Analysis: A. Design and Execution, Review and Critique
3. Manuscript: A. Writing of the First draft, B. Review and Critique.

A. Yoritaka: 1A, 1B, 2A, 3A, and 3B; Y. Shimo, M. Takanashi, J. Fukae, T. Hatano, T. Nakahara, N. Miyamoto, H. Mori, and N Hattori: 1B; T. Urabe: 1B and 3B.

Acknowledgments

We thank Dr. K. Matsuoka, Juntendo Clinical Research Center, for advice regarding the statistical analysis. We thank Dr. A. Mori, Department of Neurology, Juntendo University School of Medicine, as well as the nurses and office workers for their assistance reviewing charts.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2013.04.001.

References

[1] Ben-Shlomo Y, Marmot MG. Survival and cause of death in a cohort of patients with parkinsonismI: possible clues to aetiology? J Neurol Neurosurg Psychiatr 1995;58:293–9.
[2] Diem-Zangerl A, Seppi K, Wenning GK, Trinka E, Ransmayr G, Oberaigner W, et al. Mortality in Parkinson's disease: a 20-year follow-up study. Mov Disord 2009;24:819–25.
[3] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatr 1992;55:181–4.
[4] 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 DLB Consortium. Neurology 2005;65:1863–72.
[5] Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 1999;52:1908–10.
[6] Ravina B, Marder K, Fernandez HH, Friedman JH, McDonald W, Murphy D, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. Mov Disord 2007;22:1061–8.
[7] Levenson JL. Neuroleptic malignant syndrome. Am J Psychiatry 1985;142:1137–45.
[8] Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. Mov Disord 2007;22:1901–11.

[9] Visser M, Verbaan D, van Rooden SM, Stiggelbout AM, Marinus J, van Hilten JJ. Assessment of psychiatric complications in Parkinson's disease: the SCOPA-PC. Mov Disord 2007;22:2221–8.
[10] Marinus J, Visser M, Verwey NA, Verhey FR, Middelkoop HA, Stiggelbout AM, et al. Assessment of cognition in Parkinson's disease. Neurology 2003;61: 1222–8.
[11] Chung SJ, Jeon SR, Kim SR, Sung YH, Lee MC. Bilateral effects of unilateral subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. Eur Neurol 2006;56:127–32.
[12] Wright Willis A, Evanoff BA, Lian M, Criswell SR, Racette BA. Geographic and ethnic variation in Parkinson disease: a population-based study of US Medicare beneficiaries. Neuroepidemiology 2010;34:143–51.
[13] Linder J, Stenlund H, Forsgren L. Incidence of Parkinson's disease and parkinsonism in northern Sweden: a population-based study. Mov Disord 2010;25:341–8.
[14] Harada H, Nishikawa S, Takahashi K. Epidemiology of Parkinson's disease in a Japanese city. Arch Neurol 1983;40:151–4.
[15] Sato K, Hatano T, Yamashiro K, Kagohashi M, Nishioka K, Izawa N, et al. Prognosis of Parkinson's disease: time to stage III, IV, V, and to motor fluctuations. Mov Disord 2006;21:1384–95.
[16] Chaudhuri KR, Martinez-Martin P, Schapira AH, Stocchi F, Sethi K, Odin P, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Mov Disord 2006;21:916–23.
[17] Negre-Pages L, Regragui W, Bouhassira D, Grandjean H, Rascol O. Chronic pain in Parkinson's disease: the cross-sectional French DoPaMiP survey. Mov Disord 2008;23:1361–9.
[18] Beiske AG, Loge JH, Ronningen A, Svensson E. Pain in Parkinson's disease: prevalence and characteristics. Pain 2009;141:173–7.
[19] Scott B, Borgman A, Engler H, Johnels B, Aquilonius SM. Gender differences in Parkinson's disease symptom profile. Acta Neurol Scand 2000; 102:37–43.
[20] Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord 2009;24: 1641–9.
[21] Martinez-Martin P, Pecurariu CF, Odin P, van Hilten JJ, Antonini A, Rojo-Abuin JM, et al. Gender-related differences in the burden of non-motor symptoms in Parkinson's disease. J Neurol 2012;259:1639–47.
[22] Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa. Ann Neurol 1996;39:37–45.
[23] Hely MA, Morris JG, Reid WG, Trafficante R. Sydney multicenter study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. Mov Disord 2005;20:190–9.
[24] Hauser RA, Rascol O, Korczyn AD, Jon Stoessl A, Watts RL, Poewe W, et al. Ten-year follow-up of Parkinson's disease patients randomized to initial therapy with ropinirole or levodopa. Mov Disord 2007;22:2409–17.
[25] Katzenschlager R, Head J, Schrag A, Ben-Shlomo Y, Evans A, Lees AJ. Fourteen-year final report of the randomized PDRG-UK trial comparing three initial treatments in PD. Neurology 2008;71:474–80.
[26] Margraf NG, Wrede A, Rohr A, Schulz-Schaeffer WJ, Raethjen J, Eymess A, et al. Camptocormia in idiopathic Parkinson's disease: a focal myopathy of the paravertebral muscles. Mov Disord 2010;25:542–51.
[27] Spuler S, Krug H, Klein C, Medialdea IC, Jakob W, Ebersbach G, et al. Myopathy causing camptocormia in idiopathic Parkinson's disease: a multidisciplinary approach. Mov Disord 2010;25:552–9.
[28] Fahn S. Current concept and classification of dystonia. Adv Neurol 1976;14: 177–86.
[29] Djaldetti R, Mosberg-Galili R, Sroka H, Merims D, Melamed E. Camptocormia (bent spine) in patients with Parkinson's disease–characterization and possible pathogenesis of an unusual phenomenon. Mov Disord 1999;14:443–7.
[30] Nakayama Y, Miwa H. Drug-induced camptocormia: a lesson regarding vascular parkinsonism. Intern Med 2012;51:2843–4.
[31] Ondo WG, Dat Vuong K, Khan H, Atassi F, Kwak C, Jankovic J. Daytime sleepiness and other sleep disorders in Parkinson's disease. Neurology 2001;57:1392–6.
[32] Paus S, Brecht HM, Köster J, Seeger G, Klockgether T, Wüllner U. Sleep attacks, daytime sleepiness, and dopamine agonists in Parkinson's disease. Mov Disord 2003;18:659–67.
[33] Yoritaka A, Ohizumi H, Tanaka S, Hattori N. Parkinson's disease with and without REM sleep behaviour disorder: are there any clinical differences? Eur Neurol 2009;61:164–70.
[34] Ghorayeb I, Loundou A, Auquier P, Dauvilliers Y, Bioulac B, Tison F. A nationwide survey of excessive daytime sleepiness in Parkinson's disease in France. Mov Disord 2007;29:1567–72.
[35] Forsaa EB, Larsen JP, Wentzel-Larsen T, Goetz CG, Stebbins GT, Aarsland D, et al. A 12-year population-based study of psychosis in Parkinson disease. Arch Neurol 2010;67:996–1001.
[36] Sanchez-Ramos JR, Ortoll R, Paulson GW. Visual hallucinations associated with Parkinson disease. Arch Neurol 1996;53:1265–8.
[37] Graham JM, Grunewald RA, Sagar HJ. Hallucinosis in idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatr 1997;63:434–40.
[38] Barnes J, David AS. Visual hallucinations in Parkinson's disease: a review and phenomenological survey. J Neurol Neurosurg Psychiatr 2001;70:727–33.
[39] Baker WL, Silver D, White CM, Kluger J, Aberle J, Patel AA, et al. Dopamine agonists in the treatment of early Parkinson's disease. Parkinsonism Relat Disord 2009;15:287–94.
[40] Hashimoto T, Tokuda T, Hanyu N, Tabata K, Yanagisawa N. Withdrawal of levodopa and other risk factors for malignant syndrome in Parkinson's disease. Parkinsonism Relat Disord 2003;9:S25–30.
[41] Takubo H, Harada T, Hashimoto T, Inaba Y, Kanazawa I, Kuno S, et al. A collaborative study on the malignant syndrome in Parkinson's disease and related disorders. Parkinsonism Relat Disord 2003;9:S31–41.
[42] Cunnigton AL, White L, Hood K. Identification of possible risk factors for the development of dopamine agonist withdrawal syndrome in Parkinson's disease. Parkinsonism Relat Disord 2012;18:1051–2.
[43] Chaudhuri KR, Prieto-Jurcynska C, Naidu Y, Mitra T, Frades-Payo B, Tluk S, et al. The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals: an international study using the nonmotor symptoms questionnaire. Mov Disord 2010;25:704–9.

Parkinsonism and Related Disorders 19 (2013) 350–354

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

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

Short communication

Long-term effect of repeated lidocaine injections into the external oblique for upper camptocormia in Parkinson's disease

Yoshihiko Furusawa [a,d,*], Yohei Mukai [a], Tomoya Kawazoe [a], Terunori Sano [a], Harumasa Nakamura [a], Chikako Sakamoto [b], Yasuyuki Iwata [b], Mizuki Wakita [b], Yasuhiro Nakata [c], Kohei Kamiya [c], Yoko Kobayashi [b], Takashi Sakamoto [a], Yoshihisa Takiyama [d], Miho Murata [a]

[a] Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-higashi-cho, Kodaira, Tokyo 187-8551, Japan
[b] Department of Rehabilitation, National Center Hospital, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-higashi-cho, Kodaira, Tokyo 187-8551, Japan
[c] Department of Radiology, National Center Hospital, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-higashi-cho, Kodaira, Tokyo 187-8551, Japan
[d] Department of Neurology, Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Kofu, Japan

ARTICLE INFO

Article history:
Received 12 May 2012
Received in revised form
11 August 2012
Accepted 18 September 2012

Keywords:
Parkinson's disease
Camptocormia
Dystonia
External oblique muscle
Lidocaine

ABSTRACT

Background: Parkinson's disease (PD) is occasionally complicated by camptocormia. In a previous study, we classified camptocormia into upper and lower types based on the inflection point, and reported that lidocaine injection into the external oblique muscle, but not into the internal oblique or rectus abdomen, improved upper camptocormia in PD. The effect of a single lidocaine injection disappeared over a period of few days. In this study, we used repeated lidocaine injections into the external oblique for 4–5 days and evaluated the effects of such treatment for up to 90 days.
Methods: The study subjects were 12 patients with PD and upper camptocormia who were treated with repeated lidocaine injections into the bilateral external oblique followed by rehabilitation. The effect of treatment was evaluated by measuring the angle of truncal flexion before and after the injection. Patients who showed improvement with repeated injections were evaluated during a 90-day period.
Results: Eight out of 12 patients showed significant improvement in posture after a single lidocaine injection. However, the effect subsided several days after treatment. Repeated injections produced long-term improvement in 9 out of 12 patients, which was maintained during the 90-day observation period in eight of these patients.
Conclusions: Our results showed that repeated lidocaine injections into the external oblique improved upper camptocormia, and that the effect was maintained in the majority of patients during the 90-day observation period, indicating that repeated lidocaine injections into the external oblique have therapeutic effect on upper camptocormia in patients with Parkinson's disease.

1. Introduction

Camptocormia (from the Greek *kamptos* or to bend, and *kormos* or trunk) is defined as an abnormal thoracolumbar flexion that appears on standing or walking but disappears in the supine position. There is a strong relationship between camptocormia and Parkinson's disease (PD) [1]. The possible causes of camptocormia include myopathy, myositis [2], and truncal dystonia [1]; however, the exact etiology of camptocormia in PD has not been determined. In camptocormia, several flexion patterns exist, which include bending at an upper position or hip joint and scoliosis or rotation of the trunk. However, there is little information on these classification patterns of camptocormia. In a previous study, we categorized camptocormia into upper and lower types and showed that lidocaine injection into the external oblique (EO) muscle, but not into the internal oblique or rectus abdomen, improved posture in PD patients with upper camptocormia [3]. We also reported that the effect of single lidocaine injection disappears over several days [3]. Our results support the notion that dystonia in the EO is involved in the pathogenesis of upper camptocormia [3]. In this study, we confirmed the effects of a single lidocaine injection and evaluated the effect of repeated lidocaine injections into the EO in upper camptocormia for patients with PD.

* Corresponding author. Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-higashi-cho, Kodaira, Tokyo 187-8551, Japan. Tel.: +81 423412711; fax: +81 423446745.
E-mail address: yfuru@ncnp.go.jp (Y. Furusawa).

1353-8020/$ – see front matter
http://dx.doi.org/10.1016/j.parkreldis.2012.09.008

2. Methods

2.1. Classification of camptocormia

Camptocormia was clinically categorized by our group into upper and lower types based on spinal inflection points [3]. Based on X-ray images of the spine, upper camptocormia was defined as abnormal truncal flexion at a point between the lower thoracic and upper lumbar vertebrae, while lower camptocormia represented truncal flexion at the hip joint.

2.2. Patients

PD patients with upper camptocormia (flexion angle >40°) received single and repeated lidocaine injections into the EO between December 2010 and July 2011, and followed for a 90-day period. Patients were diagnosed with PD according to the United Kingdom Parkinson Disease Society Brain Bank criteria. Patients with severe spondylosis associated with kyphosis or other similar conditions arising from truncal muscle weakness were excluded in this study.

Twelve patients (8 women and 4 men, age: 72.8 ± 6.0, mean ± SD, PD duration: 10.0 ± 7.7 years, Hoen & Yahr stage: 3.6 ± 0.7) were included in this study. All patients showed some resistance to passive truncal extension and complained of stiffness and pain in the upper abdomen. The wearing-off phenomenon was noted in 4 patients, and treatment with anti-Parkinson medications in these patients partially corrected upper camptocormia in two patients. The inflection points were located between Th10 and L2 on the spinal X-ray images. Primary pathologies that could affect the paraspinal muscles and potentially explain upper camptocormia (e.g., myopathy or myositis) were evaluated by neurological examination, needle electromyography (EMG), muscle computed tomography (CT), and magnetic resonance imaging (MRI). Although muscle CT showed moderate paraspinal atrophy in 3 patients, and MRI T2-weighted images showed hyperintensity of the paraspinal muscles in one patient, none of the patients showed truncal extension weakness or myogenic response on needle EMG.

The study was approved by the ethics committee of the National Center of Neurology and Psychiatry (NCNP), and informed consent was obtained from all participants.

2.3. Measurement of upper camptocormia flexion angle

The angle of the upper camptocormia was defined as the angle formed between a line perpendicular to the ground and a line linking the C7 vertebra with the inflection point of the trunk (Fig. 1) [3]. The inflection point was defined as the point most distant from another line between C7 and L5. Truncal flexion angle was also measured in 7 age-matched PD patients free of camptocormia (flexion angle: 29.4 ± 3.7°).

2.4. Lidocaine injection and rehabilitation

Lidocaine (50 mg of 1% xylocaine®, Astrazeneca, Japan) was injected in the bilateral EO muscles under ultrasound guidance. A single injection was used first and then repeated lidocaine injections (once a day for 4–5 days) in all patients. Repeated injections were commenced after diminishment of improvement following a single injection or at 2 weeks when improvement following a single injection was maintained or after few days when a single injection failed to induce improvement. The upper camptocormia flexion angle was measured prior to injection, one day after single injection, and three days after repeated injections. Flexion angles were measured during the on-state in four patients who had the wearing-off phenomenon. Patients showing improvement with repeated injections were followed-up for 90 days. In addition, all patients were trained to perform regular daily rehabilitation program that emphasized on truncal extension, during and after repeated injections. Anti-Parkinson drug use was not changed prior to or after the injections.

2.5. Statistical analysis

Values were reported as mean ± standard deviation. Differences in flexion angles prior to and after a single or repeated injections were analyzed using the Wilcoxon signed rank test. A p value < 0.05 was considered statistically significant. To analyze the effect of repeated injections of lidocaine during the 90-day observation period, we calculated the rate of improvement in the flexion angle. For this purpose, the rate measured at 3 days after repeated injections relative to the baseline was considered 100%. Thus, the following equation was used to calculate the improvement rate: Improvement rate (%) = [(flexion angle at baseline − flexion angle at time x)/(flexion angle at baseline − flexion angle at 3 days after repeated injections) × 100].

3. Results

Upper camptocormia improved in 8 out of 12 patients (66.7%) after single injection with lidocaine. The mean camptocormia flexion angle decreased from 62.1 ± 13.4° to 54.0 ± 16.8° ($p = 0.018$;

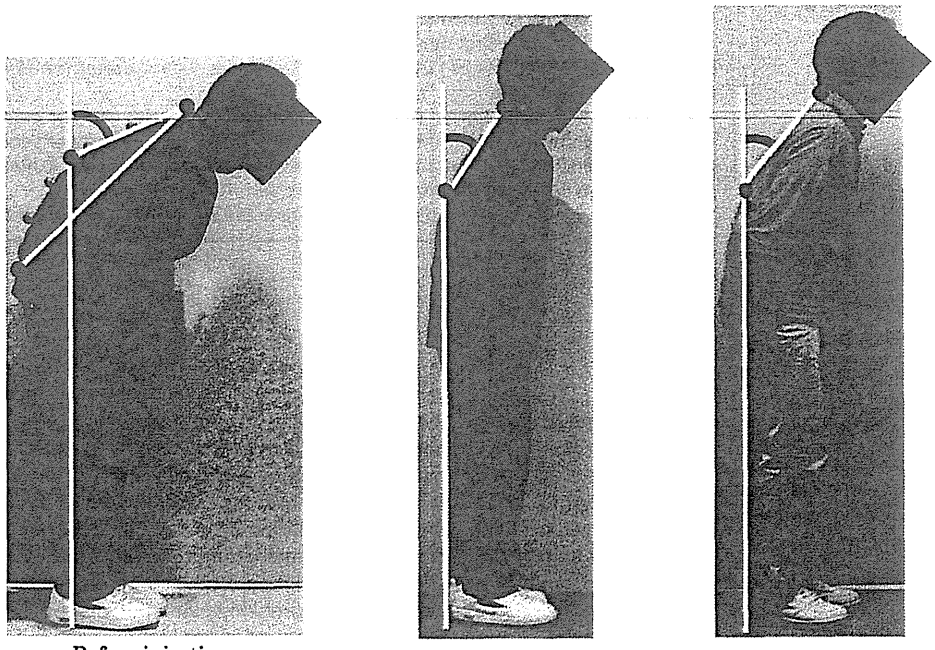

Fig. 1. Measurement of upper camptocormia flexion angle and time course of camptocormia in a representative patient. Patients were instructed to stand during evaluation without exerting any effort. In this patient, the camptocormia flexion angle decreased from 65 to 32° after repeated injections of lidocaine and the improvement was maintained over the 90-day observation period.

Fig. 2a). The observed improvement diminished between 3 and 8 days after the single injection in all but two patients, in whom improvement was maintained for more than 12 days. Repeated injections were performed for 5 days (4 patients) or 4 days (8 patients). Upper camptocormia improved in 9 out of 12 patients (75%) after repeated lidocaine injections, including one patient who had not previously shown improvement with the single injection. The mean camptocormia flexion angle decreased with repeated injections from 62.1 ± 13.4° to 49.0 ± 18.5° ($p = 0.005$; Fig. 2b). In addition, the improvement was maintained for 90 days in 8 of 9 patients who responded to the repeated injection course (Figs. 1 and 2c). Six of these patients maintained over 75% improvement rate during the 90-day observation period.

One patient developed acute lumbago 7 days after receiving the repeated injection course, with subsequent deterioration in posture. No other side effects, such as truncal weakness, were observed after a single injection or repeated injections.

4. Discussion

In our previous study [3], camptocormia in PD patients was classified into upper and lower types based on the inflexion point of the spinal flexion. The results of that study showed improvement of upper camptocormia after a single ultrasound-guided lidocaine injection into the EO muscle, but not into the internal oblique or rectus abdomen, suggesting that the EO muscle is the primary

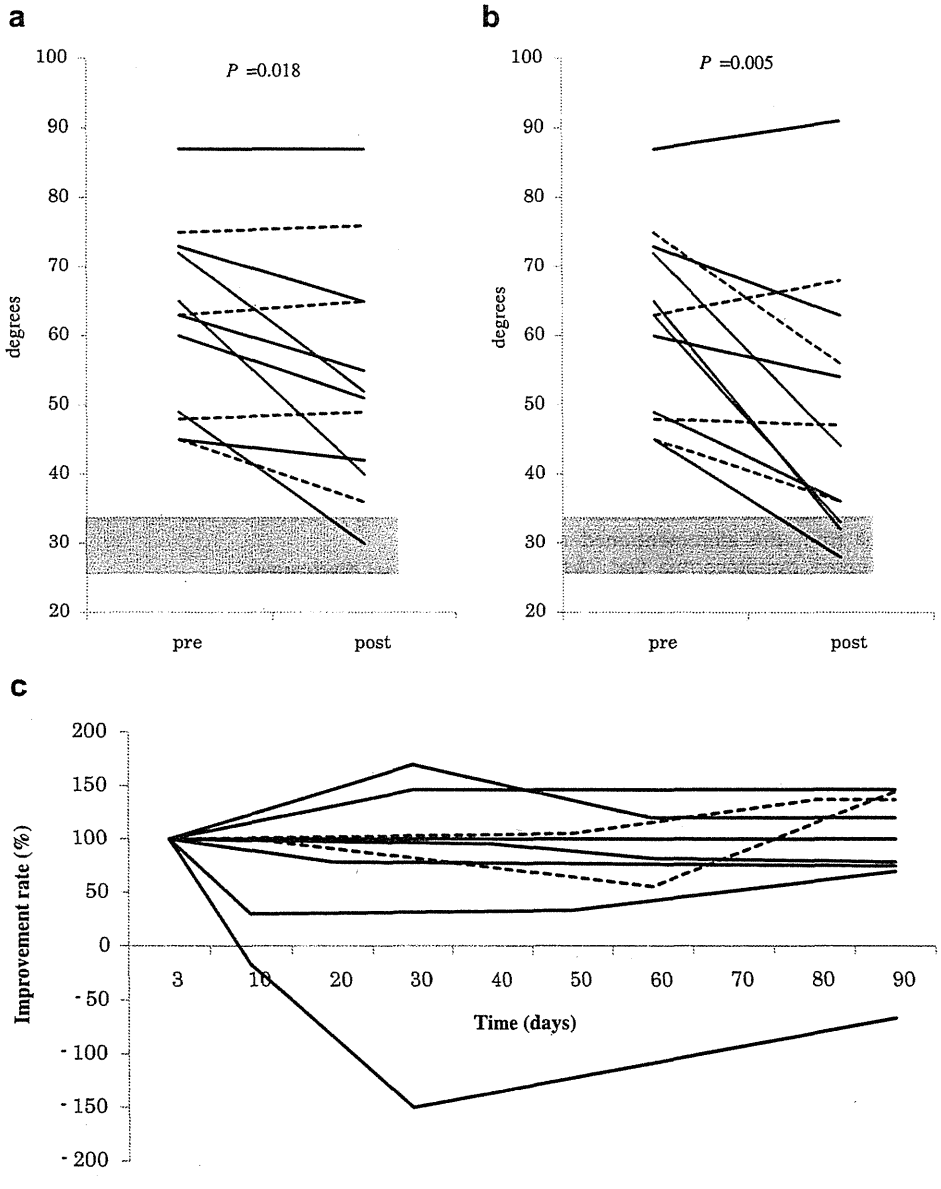

Fig. 2. Changes in upper camptocormia flexion angle after (a) single and (b) repeated injections of lidocaine, and (c) Changes in flexion angle improvement rate following repeated injections of lidocaine. *Post*: one day after a single injection in (a), and 3 days after repeated injections in (b). (c) To analyze the effect of repeated injections of lidocaine during the 90-day observation period, we calculated the rate of improvement in the flexion angle. For this purpose, the rate measured at 3 days after repeated injections relative to the baseline was considered 100%. Thus, the following equation was used to calculate the improvement rate: Improvement rate (%) = [(flexion angle at baseline − flexion angle at time *x*)/(flexion angle at baseline − flexion angle at 3 days after repeated injections) × 100]. *Solid lines*: patients treated with repeated injections for 4 days. *Dotted lines*: patients treated with repeated injections for 5 days. *Gray box*: range of truncal angle of age-matched PD patients free of camptocormia.

culprit in upper camptocormia [3]. In this study, posture improved in 8 out of 12 patients with camptocormia after a single lidocaine injection, which was consistent with the previous study [3]. Because our previous study showed that the effect of a single lidocaine injection diminished after several days, a repeat lidocaine injection course was applied in this study. Our findings clearly showed a long-term effect lasting over several months in patients who received repeated injections.

Lidocaine is a class 1B anti-arrhythmic drug that suppresses nerve conduction reversibly by blocking Na^+ channels, thereby inhibiting sensory and motor nerves. Neural excitation arising from dystonia involves the afferent nerves which originate from the muscle spindle and efferent fibers, which include the γ fibers and α motor nerves [4]. Previous studies have suggested that lidocaine suppresses dystonic excitation by blocking type Ia or the γ fiber but not the α motor nerve, thus alleviating dystonia without weakening the targeted muscle [4]. Here we showed that upper camptocormia improved after lidocaine injection without causing truncal weakness. We suspect that EO dystonia was suppressed by lidocaine, leading to improvement of upper camptocormia.

Upper camptocormia in patients treated with a single lidocaine injection improved over a period of 3 to more than 12 days, which is longer than the drug's half-life. The observed duration of improvement cannot be attributed solely to the effect of lidocaine on the target nerve since the half-life of this drug is only 102 min with a 200 mg intramuscular injection [5]. We speculate that it takes several days to reconstruct the neuronal circuit responsible for upper camptocormia once dystonic excitation is blocked by lidocaine. In contrast, improvement by repeated lidocaine injections was maintained over several months in most patients. Irwin et al. [6] reported a patient with corticobasal degeneration whose dystonia was improved by a 5-day intravenous lidocaine infusion. The effect in their patient lasted three months; however, the mechanism of the prolonged action of lidocaine was not discussed. Though the route of lidocaine administration in the present study was different from the aforementioned report, a similar improvement in upper camptocormia was observed. Rehabilitation, which is considered to be partially effective in camptocormia [7], may help prolong the effect of lidocaine. In this regard, Ohara et al. [8] showed that intravenous lidocaine injection prolonged P300 latency. Mexiletine, a derivative oral form of lidocaine is also considered to affect the central process of dystonia [9]. Our results showed that the prolonged improvement observed in four patients was similar to the improvement assessed 3 days after repeated injections. These results suggest that lidocaine acts both peripherally and centrally, thereby modifying the central processes of dystonia and producing long-term effects.

Although camptocormia is defined as abnormal thoracolumbar flexion of at least 45° when standing or walking [10], there is no standard method for the measurement of the angle of camptocormia. Seki et al. [11] assessed camptocormia by measuring the angle between the vertical plane and a line connecting the trochanter and the acromion, but did not take into consideration the flexion point. For this reason, we developed a new method to measure the angle of upper camptocormia (Fig. 1). Compared to the method described by Seki et al. [11], the new method is more sensitive to upper camptocormia, with the inflection point located between the lower thoracic and upper lumbar vertebrae.

Acute lumbago seven days after repeated injections was observed in one patient. This adverse effect may be explained by postural changes occurring after the injection. However, no other side effects were seen during the observation period. Rankin et al. [12] reported that the mean thickness of the EO muscle was 0.67 cm (0.33–1.01) in males, 0.59 cm (0.23–0.95) in females in the supine position. We used ultrasound guide during the injection of lidocaine into the EO muscle for safe and precise injection. Muscle morphological changes (e.g., fibrosis) arising from lidocaine injection were not evaluated in this study. Therefore, the effect of lidocaine injection on muscle morphology needs to be investigated and evaluated in a future study.

The present study has some limitations. Repeated lidocaine injections were performed during a 5-day (4 patients) or 4-day (8 patients) period. The optimal number of days required for repeated lidocaine injections was not analyzed given the small sample size. In addition, the optimal lidocaine dose was not evaluated. The effect of rehabilitation on upper camptocormia was not formally evaluated and thus cannot be ruled out. The study also did not evaluate changes in the quality of life following improvement of camptocormia. Finally, the study is non-blinded, non-control trial and conducted in a small sample size. Though we cannot rule out placebo effect; the improvement was noted only by injection into the EO muscle, but not into the internal oblique or rectus abdomen [3]. Furthermore, the improvement by repeated lidocaine injections was maintained for several months in many patients, suggesting the improvement is not a placebo effect but the true effect on upper camptocormia. Further research, including proper randomized clinical trials in larger number of patients, is required to confirm the effect of lidocaine in camptocormia and develop the best protocol for repeated lidocaine injections for the treatment of upper camptocormia in patients with PD.

Funding source

This work was supported in part by Grants-in-Aid from the Research Committee of CNS Degenerative Disease, the Ministry of Health, Labour and Welfare of Japan, and Intramural Research Grant (21B-4) for Neurological and Psychiatric Disorders of NCNP.

Financial disclosures

None of the authors has any financial disclosure to report, with the exception of Miho Murata, who has received honoraria for consultations and/or lectures from GlaxoSmithKline, Boehringer Ingelheim, Dainippon Sumitomo Pharma, and Novartis Pharma.

Acknowledgments

The authors extend their gratitude to Dr. Atsuo Nakagawa, whose extensive support and insightful comments were invaluable to our study.

References

[1] Djaldetti R, Mosberg-Galili R, Sroka H, Merims D, Melamed E. Camptocormia (bent supine) in patients with Parkinson's disease—characterization and possible pathogenesis of an unusual phenomenon. Mov Disord 1999; 14:443–7.
[2] Margraf NG, Wrede A, Rohr A, Schulz-Schaeffer WJ, Raethjen J, Eymess A, et al. Camptocormia in idiopathic Parkinson's disease: a focal myopathy of the paravertebral muscles. Mov Disord 2010;25:542–51.
[3] Furusawa Y, Mukai Y, Kobayashi Y, Sakamoto T, Murata M. Role of the external oblique muscle in upper camptocormia for patients with Parkinson's disease. Mov Disord 2012;27:802–3.
[4] Kaji R, Rothwell JC, Katayama M, Ikeda T, Kubori T, Kohara N, et al. Tonic vibration reflex and muscle afferent block in writer's cramp. Ann Neurol 1995; 38:155–62.
[5] Adjepon-Yamoah KK, Prescott LF. Lidocaine metabolism in man. Br J Pharmacol 1973;47:672–3.
[6] Irwin D, Revuelta G, Lippa CF. Clinical improvement of secondary focal limb dystonia in neurodegenerative disease following a five-day lidocaine infusion: a case report. J Neurol Sci 2009;277:164–6.

[7] Seze MP, Creuze A, Seze M, Mazaux JM. An orthosis and physiotherapy programme for camptocormia: a prospective case study. J Rehabil Med 2008;40:761–5.
[8] Ohara S, Hayashi R, Momoi H, Miki J, Yanagisawa N. Mexiletine in the treatment of spasmodic torticollis. Mov Disord 1998;13:934–40.
[9] Lucetti C, Nuti A, Gambaccini G, Bernardini S, Brotini S, Manca ML, et al. Mexiletine in the treatment of torticollis and generalized dystonia. Clin Neuropharmacol 2000;23:186–9.
[10] Tiple D, Fabbrini G, Colosimo C, Ottaviani D, Camerota F, Defazio G, et al. Camptocormia in Parkinson disease: an epidemiological and clinical study. J Neurol Neurosurg Psychiatr 2009;80:145–8.
[11] Seki M, Takahashi K, Koto A, Mihara B, Morita Y, Isozumi K, et al. Camptocormia in Japanese patients with Parkinson's disease: a multicenter study. Mov Disord 2011;26:2567–71.
[12] Rankin G, Stokes M, Newham DJ. Abdominal muscle size and symmetry in normal subjects. Muscle Nerve 2006;34:320–6.

Available online at www.sciencedirect.com

SciVerse ScienceDirect

Neuromuscular Disorders 23 (2013) 84–88

www.elsevier.com/locate/nmd

Respiratory dysfunction in patients severely affected by GNE myopathy (distal myopathy with rimmed vacuoles)

Madoka Mori-Yoshimura [a,*], Yasushi Oya [a], Yukiko K. Hayashi [b,c], Satoru Noguchi [b], Ichizo Nishino [b,c], Miho Murata [a]

[a] *Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi, Kodaira, Tokyo 187-8551, Japan*

[b] *Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi, Kodaira, Tokyo 187-8502, Japan*

[c] *Translational Medical Center, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi, Kodaira, Tokyo 187-8502, Japan*

Received 28 March 2012; received in revised form 23 July 2012; accepted 25 September 2012

Abstract

GNE myopathy is a rare and mildly progressive autosomal recessive myopathy caused by *GNE* mutations. Respiratory dysfunction has not been reported in GNE myopathy patients. In this study, we retrospectively reviewed the respiratory function of 39 severely affected GNE myopathy patients (13 men, 26 women) from medical records, and compared these parameters with various other patient characteristics (e.g., *GNE* mutations, age at onset, creatine kinase levels, and being wheelchair-bound) for correlations. The mean % forced vital capacity [FVC] was 92 (26) (range, 16–128). In 12/39 (31%) patients, %FVC was <80%. Of these 12 patients, 11 (92%) were entirely wheelchair-dependent. These patients exhibited significantly earlier onset (20 [4] vs. 30 [8] years, $p < 0.001$) and lower creatine kinase levels (56 [71] vs. 279 [185] IU/L) than patients with normal respiratory function. Two patients exhibited severe respiratory failure and required non-invasive positive pressure ventilation. Patients with a homozygous mutation in the *N*-acetylmannosamine kinase domain exhibited lower %FVC, while only one compound heterozygous patient with separate mutations in the uridinediphosphate-*N*-acetylglucosamine 2-epimerase and the *N*-acetylmannosamine kinase domains had respiratory dysfunction. Our results collectively suggest that GNE myopathy can cause severe respiratory failure. Respiratory dysfunction should be carefully monitored in patients with advanced GNE myopathy characterized by early onset and homozygous homozygous mutations in the *N*-acetylmannosamine kinase domain.

Keywords: GNE myopathy; Distal myopathy with rimmed vacuoles (DMRV); Hereditary inclusion body myopathy; Respiratory dysfunction; Uridinediphosphate-*N*-acetylglucosamine (UDP-GlcNAc) 2-epimerase domain; *N*-acetylmannosamine kinase domain

1. Introduction

GNE myopathy, also known as distal myopathy with rimmed vacuoles (DMRV), Nonaka myopathy, or hereditary inclusion body myopathy (hIBM), is an early adult-onset, slowly progressive myopathy that preferentially affects the tibialis anterior muscle but relatively spares the quadriceps femoris muscles [1,2]. Respiratory dysfunction has not been reported in GNE myopathy [3]. Nonaka et al. reported that respiratory muscles were rarely involved even in bed-ridden patients, but no data were presented [1]. However, we had noticed that a few patients with GNE myopathy exhibited mild but progressive respiratory loss, with some experiencing recurrent pneumonia due to reduced airway clearance. Recent recommendations suggest training patients with neuromuscular disease with respiratory dysfunction using the air stacking technique to increase their thorax capacity and assisted cough peak flow (CPF) from an early stage to maintain lung compliance and chest mobility, and to clean the airways [4]. If respiratory dysfunction is not rare in patients with GNE

* Corresponding author. Tel.: +81 341 2711; fax: +81 342 1852.
E-mail address: yoshimur@ncnp.go.jp (M. Mori-Yoshimura).

0960-8966/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.nmd.2012.09.007