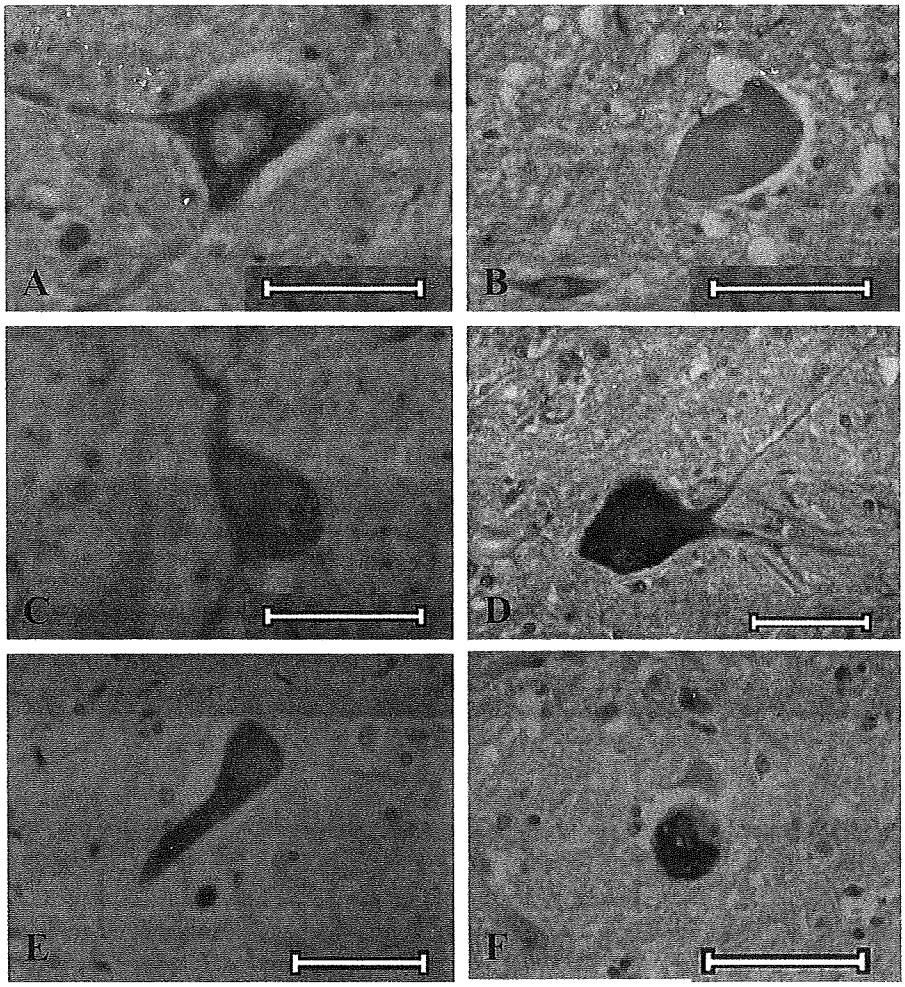

Fig. 2 A normal-looking neuron from a Guam control (G-control-13) was positive for anti-IGF-I antibody (A, bar indicates 30 μm). A chromatolytic neuron from a Guam amyotrophic lateral sclerosis (ALS) patient (MND-16) (B, bar indicates 30 μm) was almost negative for anti-IGF-I antibody. Chromatolytic neurons from Japanese sporadic ALS patients were positive for anti-glycogen synthase kinase-3b (anti-GSK-3β) (C, bar indicates 50 μm, MND-11) and anti-p-GSK-3α/β antibody (D, bar indicates 50 μm, MND-4). An atrophic neuron from a Japanese sporadic ALS patient (MND-5) was positive for anti-GSK-3β (E, bar indicates 50 μm) and an atrophic neuron from a Kii ALS patient (MND-1) was positive for anti-p-GSK-3α/β antibody (F, bar indicates 50 μm). Immunohistochemical examinations were performed using the ABC system and visualization with DAB, and were counterstained with hematoxylin.

3α/β antibodies (Fig. 1J), and showed marked positive staining for anti-GSK-3β antibodies (Fig. 1I). In Kii ALS patients, anterior horn neurons were markedly positive for anti-IGF-I (Fig. 1K), anti-IGF-IR (Fig. 1L), anti-p-Thr(308) Akt (Fig. 1M) and anti-p-GSK-3α/β antibodies (Fig. 1O); however, they were weak for anti-GSK-3β antibody (Fig. 1N). Anterior horn neurons from Guam ALS patients were weakly positive for anti-IGF-I (Fig. 1U) and markedly positive for anti-IGF-IR (Fig. 1V), anti-p-(Thr308)-Akt (Fig. 1W) and anti-p-GSK-3α/β antibodies (Fig. 1Y). However, they were weak for anti-GSK-3β antibody (Fig. 1X). Anterior horn neurons from Guam ALS and Kii ALS patients characteristically showed weak staining for anti-GSK-3β antibody but were markedly positive for anti-pGSK-3α/β antibody.

Many normal-looking neurons from Japanese sporadic ALS, Kii ALS and Guam ALS patients, as well as from Japanese and Guam controls, were positive for anti-IGF-I antibody (Fig. 2A), although some normal-looking neurons were negative for anti-IGF-I antibody (Table 3, Fig. 3). Chromatolytic neurons from these ALS patients were almost negative for anti-IGF-I antibody (Fig. 2B), and some were positive for anti-GSK-3β (Fig. 2C) and anti-p-GSK-3α/β antibodies (Fig. 2D). Many atrophic neurons from these ALS patients showed positive staining for anti-GSK-3β (Fig. 2E) and anti-p-GSK-3α/β antibodies (Fig. 2F).

Immunological co-localization of IGF-I, GSK-3β and p-GSK-3α/β was seen in anterior horn neurons of the spinal cord from Japanese and Guam controls by a confocal laser scanning technique (Fig. 4A–D). In Kii and Guam ALS patients, anterior horn neurons showed the immunological co-localization of IGF-I and p-GSK-3α/β (Fig. 4E,G,H), while they were negative for anti-GSK-3β antibody Fig. 4F).

NFTs in the hippocampus from Kii ALS patients were positive for anti-paired helical filament (PHF)-tau and anti-p-GSK-3α/β antibodies, but negative for anti-GSK-3β. Co-localization of PHF-tau and p-GSK-3α/β was found in NFTs by a confocal laser scanning technique (Fig. 5A–D)

Table 3 Immunoreactivities (IR) for anti-IGF-I, glycogen synthase kinase (GSK)-3β, and phosphor (p)-GSK-3α/β antibodies were examined by the percentages of positive neurons in the anterior horn of the spinal cord from Japanese sporadic amyotrophic lateral sclerosis (JALS), Kii ALS (KALS), Guam ALS (GALS), and controls (Japanese [JC] and Guam controls [GC]). The percentages of positive neurons for each antibody in total, normal-looking and abnormal neurons, including chromatolytic, atrophic and degenerating neurons, are shown

Cases	Total neurons		Normal-looking neurons		Abnormal neurons	
	N	IR score	N	IR score	N	IR score
IR scors for anti-IGF-I antibody						
JC ($n=14$)	56.0 ± 19.7	37.8 (0–67.5)	54.9 ± 19.3	38.3 (0–67.8)	1.1 ± 1.3	0 (0–66.7)*
JALS ($n=10$)	30.0 ± 10.0	30.0 (11.1–60.7)	16.4 ± 5.7	41.0 (14.3–57.1)	13.9 ± 9.1	17.7 (0–75)*
KALS ($n=3$)	20.0 ± 2.6	65.2 (61.1–68.4)	10.3 ± 2.5	87.5 (84.6–100)	9.7 ± 1.5	40.0 (12.5–54.5)*
GC ($n=4$)	63.5 ± 38.8	40.5 (26.9–75.6)	62.5 ± 38.7	40.9 (26.9–75.6)	1.0 ± 0.8	0 (0–100)*
GALS ($n=3$)	28.0 ± 6.6	45.7 (31.8–51.9)	16.3 ± 3.2	60.0 (28.6–65.0)	11.7 ± 3.5	37.5 (20–41.7)*
IR scores for anti-GSK-3β antibody						
JC ($n=14$)	42.9 ± 20.4	54.3 (13.6–71.4)	42.6 ± 19.9	53.2 (13.6–63.8)	0.3 ± 0.7	0 (0–100)
JALS ($n=10$)	35.1 ± 16.2	67.1 (33.3–84.7)	25.3 ± 14.7	66.7 (33.3–82.0)	9.8 ± 7.3	75.0 (0–100)
KALS ($n=3$)	47.0 ± 15.0	29.8 (12.5–40.3)	35.7 ± 7.5	25.0 (7.4–25.0)	11.3 ± 9.3	57.1 (40–68.2)*
GC ($n=4$)	36.8 ± 12.7	54.7 (18.8–62.5)	36.3 ± 12.5	59.1 (19.4–71.4)	0.5 ± 0.6	0 (0–100)
GALS ($n=3$)	21.3 ± 13.7	26.7 (16.7–37.8)	16.7 ± 9.8	18.2 (9.1–25.0)	4.7 ± 4.0	77.8 (50–100)*
IR scores for anti-p-GSK-3α/β antibody						
JC ($n=14$)	35.2 ± 15.2	31.5 (18.6–91.7)	34.2 ± 14.8	31.5 (19.0–81.8)	1.0 ± 1.5	0 (0–50)
JALS ($n=10$)	26.9 ± 10.4	38.9 (17.2–100)	19.0 ± 9.5	39.4 (16.7–100)	7.9 ± 4.3	51.9 (6.7–100)
KALS ($n=3$)	28.7 ± 27.2	80.0 (66.7–100)	20.7 ± 20.2	79.5 (77.8–100)	8.0 ± 7.0	81.3 (33.3–100)
GC ($n=4$)	39.8 ± 12.4	87.3 (39.3–100)	39.0 ± 12.3	97.0 (74.0–100)	0.8 ± 1.0	25.0 (0–100)
GALS ($n=3$)	25.0 ± 4.4	90.0 (81.8–95.7)	21.7 ± 7.6	90.0 (80.0–99.3)	3.3 ± 4.1	100 (0–100)

Numbers were shown as mean ± SD, and IR scores (percentages of positive neurons) were shown as median (ranges).
* $P < 0.05$, comparison between normal-looking neurons and abnormal neurons by Wilcoxon test.

NFTs in the spinal cord from Guam ALS patients were also positive for anti-PHF-tau and anti-p-GSK-3α/β antibodies (Fig. 5E–H).

Histometry

Immunoreactivity (IR) for anti-IGF-I, GSK-3β, and p-GSK-3α/β antibodies was compared using the percentage of positive neurons in the anterior horn of the spinal cord among Japanese sporadic ALS, Kii ALS, Guam ALS, and the controls (Japanese and Guam controls). IR scores (percentages of positive neurons) for each antibody in normal-looking neurons and abnormal neurons, including chromatolytic, atrophic and degenerating neurons, are shown in Table 3. The IR score for anti-IGF-I antibody was not significantly different between Japanese sporadic ALS patients and Japanese controls, or between Guam ALS patients and Guam controls, when they were compared with both total and normal-looking neurons (Table 3, Fig. 3A–C). In Kii ALS patients of long clinical duration, IR scores for anti-IGF-I antibody of both the total neurons and the normal-looking neurons were significantly higher than those of Japanese controls ($P < 0.05$, $P < 0.01$, respectively Mann-Whiney test, Fig. 3A,B). In abnormal neurons, the IR score for anti-IGF-I antibody was lower than those of normal-looking neurons ($P < 0.05$, Wilcoxon test, Table 3).

A positive correlation between IR scores for anti-IGF-I antibody in total neurons and the clinical durations was found in Japanese ALS patients (Fig. 6, Pearson's correlation coefficient: 0.648, $P = 0.04$, 95% IC: 0.031–0.907). Although in Kii and Guam ALS patients the IR scores for IGF-I antibody were not significantly correlated to their clinical durations, they showed higher IR scores for IGF-I antibody than those of Japanese ALS patients (Fig. 6).

In total neurons, the median IR scores for the anti-GSK-3β antibody of Japanese controls and Guam controls were 54.3% and 54.7%, respectively, but those of Kii ALS and Guam ALS patients tended to be low (27.8% and 26.7%, respectively, not significant, Table 3, Fig. 3D). In Japanese sporadic ALS patients, the median IR score for anti-GSK-3β was significantly higher than that of Japanese controls ($P < 0.01$, Fig. 3E). In Kii ALS and Guam ALS patients, IR scores for anti-GSK-3β antibody in normal-looking neurons were lower than those of each Japanese control or Guam control ($P < 0.01$, $P < 0.01$ respectively, Fig. 3E). When they were compared between normal-looking neurons and abnormal neurons, IR scores for anti-GSK-3β antibody in abnormal neurons from Japanese sporadic ALS, Kii ALS and Guam ALS were higher than those in normal-looking neurons (Table 3, $P < 0.05$, Wilcoxon test, Fig. 3F).

Concerning the anti-p-GSK-3α/β antibody in normal-looking neurons from Kii ALS patients, the median IR score (79.5%) was higher than that of Japanese controls (31.5%, $P < 0.05$) and Japanese sporadic ALS patients (39.4%, $P < 0.05$, Table 3, Fig. 3H). The median IR score for

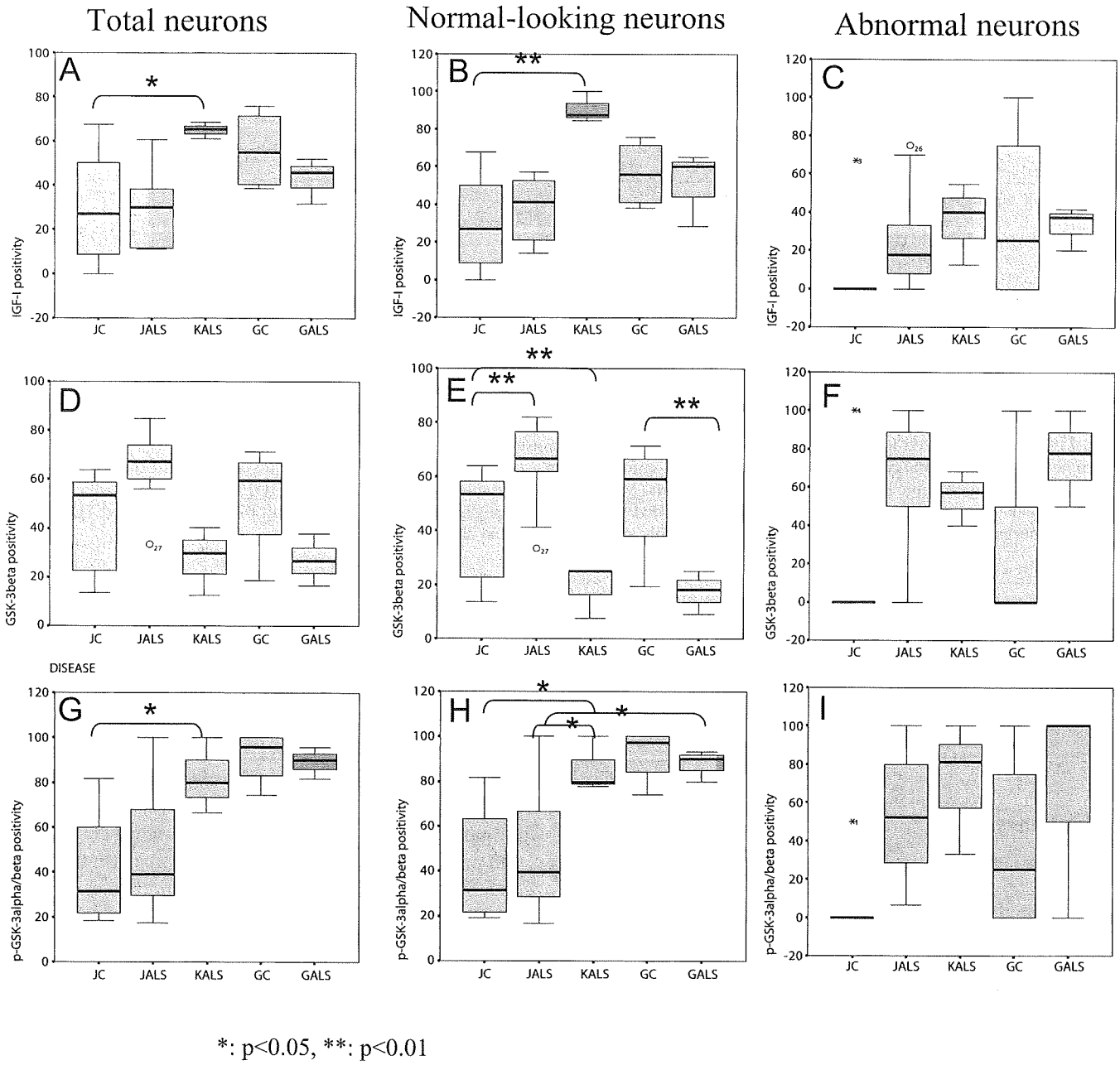

Fig. 3 Percentages of positive neurons for anti-IGF-I (A–C), glycogen synthase kinase-3b (GSK-3β) (D–F), and anti-p-GSK-3α/β antibody (G–I) immunostaining are shown in boxplot graphs. Boxes indicate interquartile ranges (25th percentile and 75th percentile), and horizontal bars in boxes indicate median values. Vertical lines indicate ranges of maximal and minimal values except for extreme values and outliers. Anterior horn neurons were divided into total, normal-looking and abnormal neurons. In Kii amyotrophic lateral sclerosis (ALS) patients, the median percentage of positive neurons for anti-IGF-I antibody was significantly higher than in Japanese controls when compared in total neurons ($P < 0.05$, A) and also in normal-looking neurons ($P < 0.01$, B). The median percentages of positive neurons for the anti-GSK-3β antibody of Kii ALS and Guam ALS patients tended to be low (not significant, D). In Japanese sporadic ALS patients, the percentages of positive neurons for anti-GSK-3β were significantly higher than those of Japanese controls ($P < 0.01$, E). In Kii ALS and Guam ALS patients, the percentages of positive neurons for anti-GSK-3β antibody in normal-looking neurons were lower than those of each Japanese control or Guam control (E). The values for anti-GSK-3β antibody in abnormal neurons from Kii ALS and Guam ALS were higher than those in normal-looking neurons ($P < 0.05$, Wilcoxon test, F). The values for anti-p-GSK-3α/β antibody in both total neurons and normal-looking neurons from Kii ALS patients were higher than those of Japanese controls ($P < 0.05$, G) and Japanese sporadic ALS patients ($P < 0.05$, H). The values for anti-p-GSK-3α/β antibody of Guam controls and Guam ALS patients were similar to those of Kii ALS (G), and were significantly higher than those of Japanese controls ($P < 0.05$, $P < 0.05$, respectively, H). GALS, Guam ALS; GC, Guam controls; JALS, Japanese ALS; JC, Japanese controls; KALS, Kii ALS. *$P < 0.05$, **$P < 0.01$.

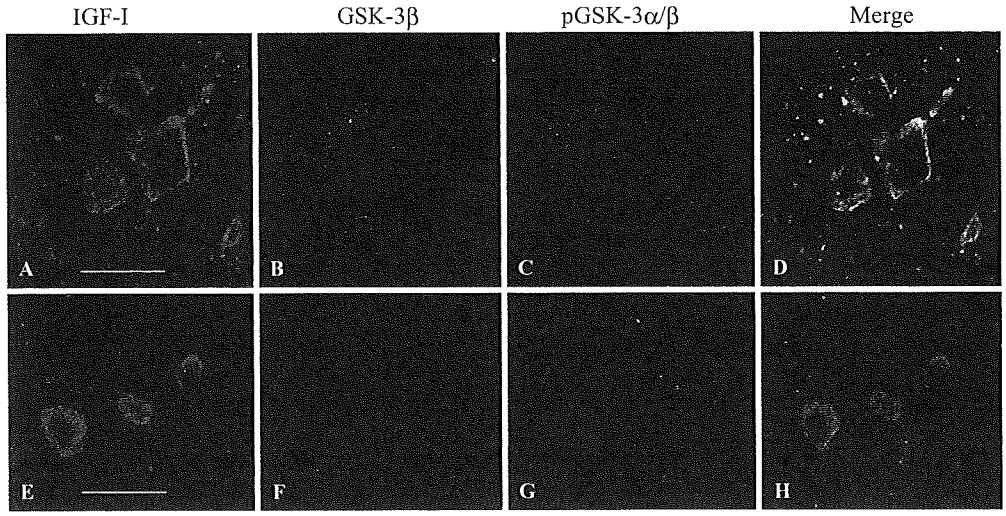

Fig. 4 Immunological co-localization of IGF-I, glycogen synthase kinase-3b (GSK-3β) and phospho (p)-GSK-3α/β was seen in anterior horn neurons of the spinal cord from a Guam control (G-control-14) by a confocal laser scanning technique (A–D). Anterior horn neurons from a Guam amyotrophic lateral sclerosis (ALS) patient (MND-14) showed marked co-localization of IGF-I and p-GSK-3α/β (E, G and H), but weak staining for anti-GSK-3β antibody (F). IGF-I was visualized in green, GSK-3β in blue, and p-GSK-3α/β in red. (D and H) shows a merged image by confocal laser scanning. Details are shown in Table 2b. A bar indicates 50 μm.

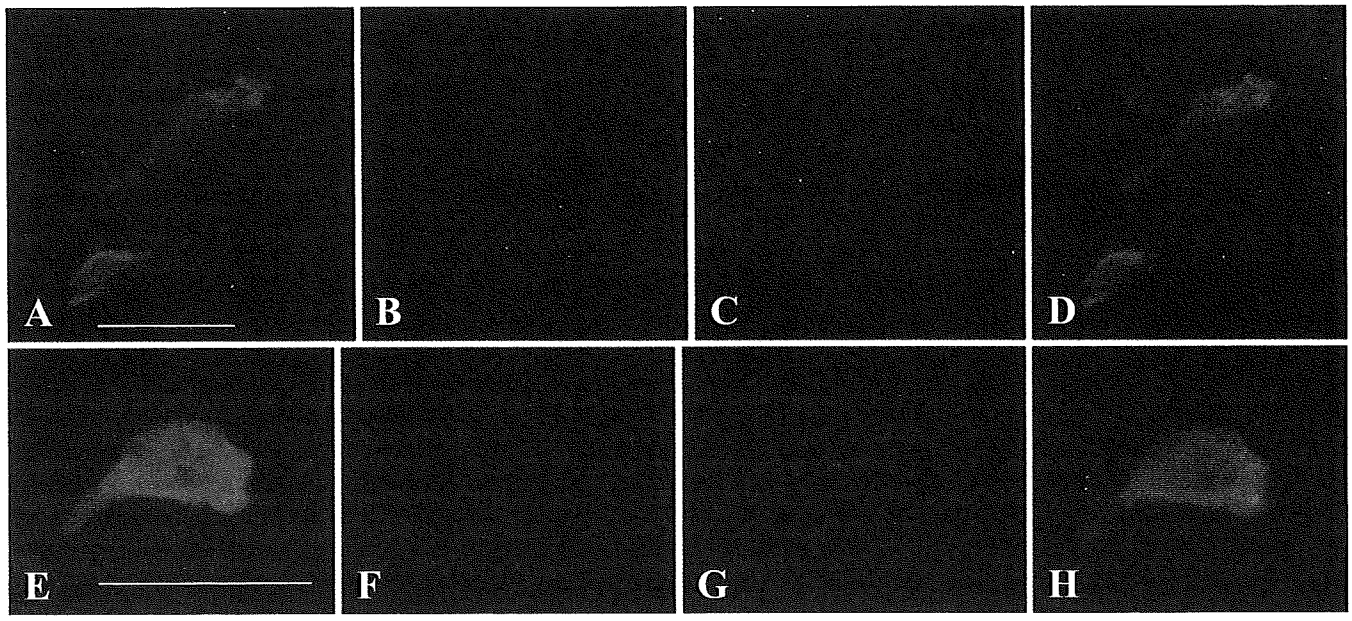

Fig. 5 Neurofibrillary tangles in the hippocampus from a Kii amyotrophic lateral sclerosis (ALS) patient (MND-2) were positive for anti-paired helical filament (PHF)-tau (A) and anti-phospho-glycogen synthase kinase-3α/β (anti-p-GSK-3α/β) antibodies (C), and co-localized by a confocal laser scanning technique (A–D) An NFT-laden neuron in the spinal cord of a Guam ALS patient (MND-14) was also positive for anti-PHF-tau (E) and anti-p-GSK-3α/β antibodies (G), but weak for GSK-3β antibody (F). A and E: PHF-tau, B and F: GSK-3β, C and G: p-GSK-3α/β, D and H: merged image. Bar indicates 50 μm.

anti-p-GSK-3α/β antibody of Guam controls (97.0%) and Guam ALS patients (90%) were similar to those of Kii ALS (Fig. 3G), and were significantly higher than that of Japanese controls ($P < 0.05$, $P < 0.05$ respectively, Fig. 3H).

DISCUSSION

We studied the immunoreactivity of IGF-I and GSK signaling pathways in the spinal cords and hippocampus of ALS patients with special reference to Kii and Guam ALS

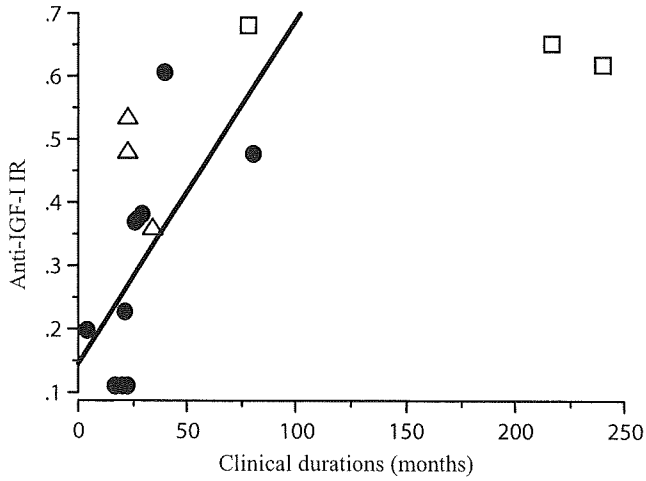

Fig. 6 The relationship between IGF-I immunoreactivity and clinical duration in amyotrophic lateral sclerosis (ALS) patients is shown. In Japanese ALS patients (●), the IR score for anti-IGF-I antibody was positively correlated with the clinical duration ($Y = 0.144 + 0.005 \times X$; R^2 = 0.42, Pearson's correlation coefficient: 0.648, $P = 0.04$, 95% IC: 0.031–0.907). Three Kii ALS patients (□) and two Guam ALS patients (△) showed higher IR scores for IGF-I antibody than Japanese ALS patients, although no correlation between IR scores and the clinical duration in each subgroup of Kii and Guam ALS patients was seen.

patients. Spinal anterior horn neurons from long-surviving Kii ALS patients tended to show positive staining with anti-IGF-I antibody, while ALS patients with a short clinical duration were weakly positive. Three Kii ALS patients and two Guam ALS patients showed higher IR scores for IGF-I antibody than Japanese ALS patients, although a correlation between IR scores and the clinical duration of each Kii and Guam ALS patient group was not seen, probably due to the small sample size. In Japanese ALS patients, the IR score for anti-IGF-I antibody was positively correlated with the clinical duration. In the future the relationship between IGF-I immunoreactivity and the clinical duration of ALS patients should be pursued in patients with matching clinical features, including age at onset, sex and geographical history.

IGF-I is a potent neuroprotective survival factor for motor neurons, acting as a major neurotrophic factor, exerting a protective effect against motor neuron degeneration in organotypic spinal cord cultures and cultured motor neurons,[12] and is also capable of preventing motor neuron loss following sciatic nerve axotomy in rat pups.[18] The biological functions of IGF-I are mediated by the IGF-I receptor.[19] Its neuroprotective roles may be coordinated by the activation of Akt, inhibition of GSK-3β, and thus inhibition of tau phosphorylation.[20] Inhibition of GSK-3β reduced the degree of spinal cord inflammation and tissue injury, cellular infiltration and apoptosis in experimental spinal cord trauma.[13] GSK-3β inhibitor VIII injection in a G93A-superoxide dismutase 1 (SOD1) mouse model of ALS delayed the onset of symptoms and prolonged the life span.[21] In the present study, we found a positive correlation between the IR score for the anti-IGF-I antibody and clinical duration in Japanese sporadic ALS patients. This suggested that IGF-I might have a protective effect on ALS degeneration.

Abnormal as well as normal-looking neurons from Japanese sporadic ALS patients showed significantly higher IR score for anti-GSK-3β antibody than controls. Abnormal neurons from Kii ALS and Guam ALS patients were also positive for anti-GSK-3β antibody. GSK-3β of which p-GSK-3α/β is an inactive form, is a critical downstream element of the PI3 kinase/P-Akt cell survival pathway, and its activity can be involved in ALS degeneration by modulating inflammatory responses by regulating nuclear factor of κ light polypeptide gene enhancer in B-cells (NfκB)-mediated inflammatory gene expression.[22,23] In sporadic ALS patients, GSK-3β was upregulated in the spinal cord homogenate.[24] We also found that abnormal neurons from ALS patients showed positive staining for anti-GSK-3β and anti-p-GSK-3α/β antibodies. Overall, these results indicated that the GSK-3β signaling pathway might be involved in ALS degeneration.

We found in the present study that spinal anterior horn neurons from Kii and Guam ALS patients showed low IR scores of GSK-3β but significantly high IR scores of p-GSK-3α/β compared to Japanese sporadic ALS patients and controls. We also found co-localization of hyperphosphorylated tau and p-GSK-3α/β in NFT-laden neurons of the hippocampus from Kii ALS patients and in the spinal cord from Guam ALS patients. NFT, mainly composed of hyperphosphorylated tau, has been identified as a marker of Kii and Guam ALS neuropathology. GSK-3β, a serine threonine kinase with a broad array of cellular targets, such as cytoskeletal proteins and transcription factors, is a potential candidate mediating tau hyperphosphorylation in cortical cultured neurons and hippocampal slices from the adult rat brain.[25] It was difficult to explain why p-GSK-3α/β IR scores were higher but GSK-3β IR scores were lower in Kii ALS and Guam ALS patients compared to Japanese ALS patients, and also why p-GSK-3α/β and hyperphosphorylated tau were co-localized in NFT-laden neurons. Although the reason is not clear, it might be that: (i) the anti-GSK-3β antibody used in the present study did not fully recognize the hyperphosphorylated form of GSK, and high IR score for the anti-p-GSK-3α/β antibody might indicate an upregulation of the GSK signaling pathway; (ii) the elevation of p-GSK-3α/β IR score was ascribed to functions of the IGF-I signaling pathway to inhibit GSK-3β through p-Akt activation, especially in Kii ALS and Guam ALS patients; or (iii) GSK-3β in Kii and Guam ALS patients

was hyperphosphorylated in concert with tau hyperphosphorylation by unknown mechanisms.

Tau phosphorylation is regulated developmentally and functionally, and it is speculated that responsive transit hyperphosphorylation of tau may be neuroprotective but prolonged hyperphosphorylation/accumulation of tau may be a cause of neurodegeneration, and tau abnormal hyperphosphorylation is the result of upregulation of tau kinases and/or downregulation of tau phosphatases.[15] Among kinases that have been shown to phosphorylate tau in vitro, GSK-3β is most implicated in the abnormal hyperphosphorylation of tau.[15,26–29] Tau hyperphosphorylation in concert with GSK phosphorylation can be caused by S100B in cultured human neural stem cells[27] and β-amyloid peptide 1-42 [Aβ (1-42)] in cell lines and transgenic mice.[28,29] NFTs from Kii and Guam ALS patients were not associated with the accumulation of β-amyloid peptide. Although the mechanism is not clear, we suspected that different mechanisms, including the upregulation of kinases and/or downregulation of phosphatases of both GSK and tau, such as the accumulation of aluminium or other trace metals,[30–32] might have important roles in the hyperphosphorylation of tau in concert with GSK-3β phosphorylation in Kii and Guam ALS patients.

It is noteworthy that Guam controls also showed high IR scores for p-GSK-3α/β antibody, similar to Guam and Kii ALS patients. Oyanagi *et al.* reported that NFTs were widely found among the Guam people, not only in those having ALS and/or Parkinson–dementia complex (PDC) but also in controls.[33] Chronic exposure to exogenous factors might have various roles in NFT dispersion among people living in the focus area of ALS.[30–33] High IR scores for p-GSK-3α/β in Guam controls might be related to the background characteristics similar to the formation of NFT. We indicated that the predominant expression of p-GSK-3α/β compared to GSK-3β in spinal motor neurons and the co-localization of p-GSK-3α/β and PHF-tau in NFT-laden neurons in the hippocampus and spinal cord were characteristic findings of Kii and Guam ALS patients.

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Journal of the Neurological Sciences 288 (2010) 117–122

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Dietary fat intake and risk of Parkinson's disease: A case-control study in Japan

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ARTICLE INFO

Article history:
Received 27 June 2009
Received in revised form 31 August 2009
Accepted 22 September 2009
Available online 12 October 2009

Keywords:
Arachidonic acid
Case-control studies
Cholesterol
Diet
Fatty acids
Japan
Parkinson disease

ABSTRACT

The present case-control study examined the relationship between dietary intake of individual fatty acids and the risk of Parkinson's disease (PD) in Japan. Included were 249 cases within 6 years of onset of PD. Controls were 368 inpatients and outpatients without a neurodegenerative disease. Information on dietary factors was collected using a validated self-administered diet history questionnaire. Compared with arachidonic acid intake in the first quartile, consumption of that in the fourth quartile was significantly related to an increased risk of PD: the adjusted odds ratio between extreme quartiles was 2.09 (95% confidence interval: 1.21−3.64, P for trend = 0.008). Cholesterol intake was also significantly positively associated with the risk of PD: the adjusted odds ratio between extreme quartiles was 1.78 (95% confidence interval: 1.04−3.05, P for trend = 0.01). Consumption of total fat, saturated fatty acids, monounsaturated fatty acids, n-3 polyunsaturated fatty acids, α-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid, n-6 polyunsaturated fatty acids, and linoleic acid and the ratio of n-3 to n-6 polyunsaturated fatty acid intake were not associated with PD. Higher consumption of arachidonic acid and cholesterol may be related to an increased risk of PD.

1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders and is characterized clinically by resting tremor, rigidity, bradykinesia, and postural instability. The incidence rate was estimated to be 16.9 per 100,000 person-years in one Japanese study [1]. With aging of the population, an increase in the prevalence of PD is expected. A cure for PD is not yet available, although symptomatic treatment has improved in recent years. Because the cause of onset is unknown, epidemiology is important in defining the cause of PD and in evaluating preventive measures. The exact mechanisms underlying the process of the massive death of dopaminergic nigrostriatal neurons are unclear, but oxidative stress, inflammation, and mitochondrial dysfunction may play a large role [2–4].

There remains much to be learned about the effects of dietary factors on the development of PD. Fatty acids play a critical role in brain function. Evidence from animal models has indicated that fatty acids, especially docosahexaenoic acid, regulate oxidative stress in the brain [5–7]. Other potential mechanisms of the neuroprotective effects of docosahexaenoic acid include regulation of the inflammatory process, postsynaptic dendritic scaffold proteins, gene transcription, cell signaling, caspase activation, and cell membrane properties [8–14]. On the other hand, because of the high concentration of polyunsaturated fatty acids in the brain, reactive products of lipid peroxidation are likely contributors to neurodegeneration [15]. Laboratory studies in rats showed that the brain content of fatty acids such as polyunsaturated fatty acids depends on dietary intake [16–18].

Several epidemiological studies investigated the relationship between dietary fat intake and the risk of PD, but the results were

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doi:10.1016/j.jns.2009.09.021

not consistent [19–28]. In consideration of the paucity of epidemiological information regarding the relationship between dietary intake of individual fatty acids and the risk of PD in Japan where intake of marine origin n-3 polyunsaturated fatty acids is high, we investigated this issue based on a multicenter hospital-based case-control study.

2. Methods

2.1. Study population

Recruitment of PD cases was conducted at 3 university hospitals and 1 national hospital in Fukuoka Prefecture, the largest prefecture in Kyushu Island in southern Japan, and 3 university hospitals, 3 national hospitals, and 1 municipal hospital in Osaka, Kyoto, and Wakayama Prefectures, which are part of the Kinki region located in the midwestern part of Japan. Eligible cases were patients who were within 6 years of the onset of PD and who received treatment at one of the 11 collaborating hospitals during the period from April 1, 2006 to March 31, 2008. The collaborating neurologists were responsible for the diagnosis of PD, which was based on the UK PD Society Brain Bank clinical diagnostic criteria [29]. The neurologists in charge asked 298 eligible PD patients to take part in our case-control study, and 250 patients agreed to answer the questionnaires whereas 48 patients refused (response rate: 84%).

Control subjects were inpatients and outpatients without a neurodegenerative disease who were recruited from departments other than departments of neurology of 3 of the 11 collaborating hospitals: a university hospital in Fukuoka Prefecture and a university hospital and a national hospital in the Kinki region (orthopedic surgery, ophthalmology, otorhinolaryngology, plastic surgery, and oral surgery) during the period from April 1, 2006 to March 31, 2008. Controls were not, individually or in larger groups, matched to cases. A total of 528 patients were approached by their attending physicians or our research nurses to be recruited as control subjects. Finally, 372 patients participated in our study whereas 156 refused (response rate: 70%).

Excluded were 1 case and 4 controls because of missing data on the factors under study. The final analysis comprised 249 cases and 368 controls. The ethics committees of the 11 collaborating hospitals approved this case-control study.

2.2. Measurements

Cases and controls filled out a set of 2 self-administered questionnaires and mailed them to the data management center or handed them to research nurses. Research technicians completed missing or illogical data by telephone or direct interview.

A self-administered, comprehensive, diet history questionnaire (DHQ) was used to assess dietary habits during the preceding month [30,31]. Estimates of daily intake of foods (total of 150 foods), energy, and selected nutrients were calculated using an ad hoc computer algorithm for the DHQ, which was based on the Standard Tables of Food Composition in Japan [32,33]. Information on dietary supplements was not used in the calculation of dietary intake. Detailed descriptions of the methods used for calculating dietary intake and the validity of the DHQ were published elsewhere [30,31]. The correlation coefficients for nutrient intake between those estimated from the DHQ and those observed by a 3-day dietary record were 0.75, 0.50, 0.37, and 0.49 for saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, and cholesterol, respectively, in women [30]. A highly positive correlation was also observed between marine origin n-3 polyunsaturated fatty acid intake estimated by the DHQ and the corresponding concentration in the serum phospholipid fraction in women ($r = 0.69$) [31]. According to another validation study of Japanese men and women, Pearson correlation coefficients between the DHQ and 16-day weighed dietary records were 0.43 and 0.35 for vitamin E, 0.49 and 0.63 for iron, and 0.80 and 0.79 for alcohol, respectively (Sasaki S, unpublished data, 2004). Energy-adjusted intake by the residual method was used for the analyses [34]. Our DHQ also included questions about height and weight. Body mass index was calculated by dividing self-reported body weight (kg) by the square of self-reported height (m).

A second questionnaire elicited information on sex, age, education, and smoking habits.

2.3. Statistical analysis

Dietary factors under investigation were categorized at quartile points based on the distribution of control subjects. Sex, age, region of residence, pack-years of smoking, years of education, intake of vitamin E, iron, and alcohol, and body mass index were selected *a priori* as potential confounding factors. Dietary factors under investigation were categorized at quartile points based on the distribution of control subjects. Region of residence was classified into 2 categories (Fukuoka and Kinki); pack-years of smoking into 3 (none, 0.1 – 29.9, and ≥ 30.0); and years of education into 3 (< 10, 10 – 12, and ≥ 13 years). Age, intake of vitamin E, iron, and alcohol, and body mass index were used as continuous variables.

We used logistic regression analysis to estimate crude odds ratios (ORs) and 95% confidence intervals (CIs) of PD for each category of dietary intake under investigation compared with the lowest intake category. Multiple logistic regression analysis was used to control for the potential confounding factors. Statistical significance for a linear trend was tested by including the median of each quartile of consumption as a continuous variable in the regression model. Statistical computing was conducted by SAS version 9.1 software (SAS Institute, Inc., Cary, NC).

3. Results

About 60% of both cases and controls were female and lived in the Kinki region (Table 1). There was no difference between cases and controls with regard to education. Compared with control subjects, cases were more likely to be old and thin, report never having smoked, and have a high intake of arachidonic acid and cholesterol.

Table 2 gives crude and adjusted ORs and the 95% CIs of the risk of PD according to dietary intake of specific types of fatty acids and cholesterol. Compared with arachidonic acid intake in the first quartile, consumption of that in the fourth quartile was significantly related to an increased risk of PD and the positive linear trend was also significant. After adjustment for sex, age, region of residence, pack-years of smoking, years of education, intake of vitamin E, iron, and alcohol, and body mass index, the positive relationship was slightly strengthened: the adjusted OR for comparison of the highest with the lowest quartile was 2.09 (95% CI: 1.21–3.64, P for trend = 0.008). Cholesterol intake was also significantly positively associated with the risk of PD: the adjusted OR between extreme quartiles was 1.78 (95% CI: 1.04–3.05, P for trend = 0.01). Consumption of total fat, saturated fatty acids, monounsaturated fatty acids, n-3 polyunsaturated fatty acids, α-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid, n-6 polyunsaturated fatty acids, and linoleic acid and the ratio of n-3 to n-6 polyunsaturated fatty acid intake were not materially associated with the risk of PD.

When stratifying study subjects according to sex, positive associations of intake of arachidonic acid and cholesterol with the risk of PD were more evident in men than in women. However, only the positive association with arachidonic acid intake in men was statistically significant (Table 3). No significant interactions were observed in the association with the risk of PD between men and women ($P = 0.49$ and 0.55 for homogeneity of OR for intake of arachidonic acid and cholesterol in the highest quartile, respectively).

When cases were confined to patients (both men and women) having PD for a duration of less than 3 years ($n = 109$), positive exposure–response relationships between intake of arachidonic acid

Table 1
Characteristics of study population.

	n (%) or mean (SD)		
	Cases ($n=249$)	Controls ($n=368$)	*P*-value
Sex (%)			0.81
Male	93 (37.4)	141 (38.3)	
Female	156 (62.7)	227 (61.7)	
Age (y)	68.5 (8.6)	66.6 (8.5)	0.006
Region of residence (%)			0.13
Fukuoka	89 (35.7)	154 (41.9)	
Kinki	160 (64.3)	214 (58.2)	
Pack-years of smoking (%)			0.0004
None	185 (74.3)	222 (60.3)	
0.1−29.9	37 (14.9)	65 (17.7)	
≥30.0	27 (10.8)	81 (22.0)	
Education (%)			0.81
<10 y	51 (20.5)	77 (20.9)	
10−12 y	122 (49.0)	171 (46.5)	
≥13 y	76 (30.5)	120 (32.6)	
Body mass index (kg/m^2)	22.3 (3.3)	23.0 (3.4)	0.01
Daily intake[a]			
Total energy (kJ)	8435.4 (2636.8)	8348.8 (3067.5)	0.71
Total fat (g)	57.9 (13.7)	56.3 (17.2)	0.22
Saturated fatty acids (g)	15.6 (4.6)	15.2 (5.7)	0.31
Monounsaturated fatty acids (g)	19.9 (5.6)	19.3 (6.6)	0.21
n-3 Polyunsaturated fatty acids (g)	2.9 (1.1)	2.8 (1.2)	0.37
α-Linolenic acid (g)	1.6 (0.6)	1.6 (0.7)	0.87
Eicosapentaenoic acid (g)	0.37 (0.25)	0.35 (0.25)	0.30
Docosahexaenoic acid (g)	0.60 (0.38)	0.56 (0.39)	0.21
n-6 Polyunsaturated fatty acids (g)	10.5 (3.0)	10.4 (3.4)	0.85
Linoleic acid (g)	10.2 (3.0)	10.2 (3.4)	0.88
Arachidonic acid (g)	0.15 (0.05)	0.14 (0.06)	0.02
Cholesterol (mg)	331.3 (129.5)	300.9 (132.5)	0.005
Vitamin E (mg)	8.6 (2.4)	8.4 (2.9)	0.52
Iron (mg)	7.5 (1.9)	7.6 (2.2)	0.75
Alcohol (g)	5.5 (15.5)	10.0 (25.8)	0.008

[a] Nutrient intake was adjusted for total energy intake using the residual method.

and cholesterol and the risk of PD were statistically significant (*P* for trend = 0.01 and 0.01, respectively). The adjusted ORs from the lowest to the highest category of arachidonic acid intake by quartiles were 1.00, 1.32 (95% CI: 0.66−2.67), 1.51 (95% CI: 0.74−3.14), and 2.48 (95% CI: 1.22−5.20), respectively. The corresponding figures for cholesterol intake were 1.00, 0.99 (95% CI: 0.49−2.02), 1.33 (95% CI: 0.67−2.68), and 2.16 (95% CI: 1.08−4.42), respectively.

4. Discussion

The current case-control study found significant positive exposure–response associations of intake of arachidonic acid and cholesterol with the risk of PD. No evident relationships were observed between the risk of PD and intake of the other types of fatty acids under investigation, especially docosahexaenoic acid. A prospective study in the Netherlands showed that consumption of total fat, unsaturated cis-fatty acids, monounsaturated fatty acids, n-3 polyunsaturated fatty acids, and α-linolenic acid was significantly related to a reduced risk of PD whereas there were no relationships between intake of saturated fatty acids, cholesterol, unsaturated trans-fatty acids, eicosapentaenoic acid, docosahexaenoic acid, n-6 polyunsaturated fatty acids, linoleic acid, and arachidonic acid and the risk of PD [21]. In a pooled analysis from the Health Professionals Follow-up Study and the Nurses' Health Study, intake of total fat, saturated fatty acids, major types of unsaturated fatty acids, and cholesterol was not associated with the risk of PD although only arachidonic acid intake was significantly inversely related to the risk of PD [22]. These findings regarding arachidonic acid and cholesterol intake are at variance with our results whereas findings in relation to a lack of association with docosahexaenoic acid consumption are in line with the present results. These discrepancies may be explained by differences in the study population and design. In particular, dietary habits had been assessed before the onset of PD in the previous prospective cohort studies in the Netherlands and the US [21,22] whereas in the present case-control study dietary habits had been assessed after the onset of PD.

A prospective cohort study in Singapore showed no associations between the intake of total fat, saturated fatty acids, n-3 polyunsaturated fatty acids, marine origin n-3 polyunsaturated fatty acids, and n-6 polyunsaturated fatty acids and the risk of PD whereas an inverse exposure–response relationship between monounsaturated fatty acid intake and PD was significant [19]. In a US case-control study, positive relationships between the intake of total fat and cholesterol and the risk of PD were observed but the intake of saturated fats, oleic acid, and linoleic acid was not significantly associated with the risk of PD after adjustment for body mass index, but not total energy [24]. A nested case-control study of males of Japanese ancestry in Hawaii reported a null association between animal fat intake and the risk of PD [28]. These observations are in partial agreement with our results. The present results are not consistent with findings of a case-control study that found marginally significant inverse exposure–response relationships between the intake of saturated fatty acids and total fat and the risk of PD [23] and those of two case-control studies showing a positive association between animal fat intake and PD [25,26].

Isofurans, derived from arachidonic acid, are chemically and metabolically stable oxidation products [15]. A post-mortem human tissue study demonstrated that levels of isofurans in the substantia nigra of patients with PD were significantly higher than those of controls [35]. High arachidonic acid intake might cause PD by stimulating oxidative stress. Moreover, in a rat model of acute neuroinflammation, a 6-day intracerebral ventricular infusion of bacterial lipopolysaccharide increased brain concentrations of linoleic acid and arachidonic acid and of prostaglandins E2 and D2 derived from arachidonic acid [36]. High arachidonic acid consumption could increase the risk of PD via an inflammatory process.

The underlying mechanisms for the observed positive relationship between cholesterol intake and the risk of PD are not clear. A prospective cohort study of Finnish men and women found a significant positive relationship between serum total cholesterol levels and the risk of PD [37]. This finding is partially consistent with our results regarding cholesterol intake, but incompatible with the current results with respect to saturated fatty acids, which are hypercholesterolemic, and unsaturated fatty acids, which elicit a hypocholesterolemic effect. The present positive relationship with cholesterol intake may be ascribed to some extent to elevated levels of serum total cholesterol although data on serum lipids and lipoproteins were not available in the current study. On the other hand, a significant inverse association between serum total cholesterol levels and PD risk was observed in two cohort studies: the Rotterdam Study [38] and pooled data from the Health Professionals Follow-up Study and the Nurses' Health Study [39]. The Honolulu Heart Program also showed that elevated levels of low density lipoprotein cholesterol were significantly associated with a decreased risk of PD [40].

Two prospective studies in the Netherlands and USA showed a null relationship between docosahexaenoic acid intake and the risk of PD [21,22]. According to the study in the Netherlands, median daily intake of docosahexaenoic acid was 0.05 g [21]. The corresponding figure in our controls was 0.52 g. Therefore, the lack of association between docosahexaenoic acid intake and the risk of PD in the present study is not likely to be attributable to the fact that consumption of marine origin n-3 polyunsaturated fatty acids in Japan is much higher than in Western countries. A beneficial association between docosahexaenoic acid intake and the risk of PD might not be detected irrespective of the amount of fish intake in different populations. The products of lipid peroxidation derived from docosahexaenoic acid such as neuroprostanes might have counteracted the advantage of intake of docosahexaenoic acid in protection against PD.

Table 2
Odds ratios (ORs) and 95% confidence intervals (CIs) for Parkinson's disease by quartiles of intake of specific types of dietary fat.

Variable	Quartile				*P* for trend
	1 (lowest)	2	3	4 (highest)	
Total fat					
Intake (g/day)[a]	<49.5	49.5–<57.23	57.23–<64.98	≥64.98	
No. cases/controls	54/92	62/92	74/92	59/92	
Crude OR (95% CI)	1.00	1.15 (0.72–1.83)	1.37 (0.87–2.16)	1.09 (0.68–1.75)	0.59
Multivariate OR (95% CI)[b]	1.00	1.00 (0.59–1.67)	1.21 (0.72–2.05)	0.95 (0.52–1.72)	1.00
Saturated fatty acids					
Intake (g/day)[a]	<12.24	12.24–<15.04	15.04–<18.00	≥18.00	
No. cases/controls	46/92	70/92	76/92	57/92	
Crude OR (95% CI)	1.00	1.52 (0.95–2.45)	1.65 (1.04–2.65)	1.24 (0.76–2.02)	0.53
Multivariate OR (95% CI)[b]	1.00	1.36 (0.82–2.29)	1.50 (0.90–2.51)	1.05 (0.61–1.83)	0.92
Monounsaturated fatty acids					
Intake (g/day)[a]	<16.46	16.46–<19.32	19.32–<22.60	≥22.60	
No. cases/controls	63/92	60/92	58/92	68/92	
Crude OR (95% CI)	1.00	0.95 (0.60–1.50)	0.92 (0.58–1.46)	1.08 (0.69–1.69)	0.72
Multivariate OR (95% CI)[b]	1.00	0.84 (0.51–1.38)	0.78 (0.47–1.32)	1.01 (0.58–1.78)	0.90
n-3 Polyunsaturated fatty acids					
Intake (g/day)[a]	<2.258	2.258–<2.780	2.780–<3.248	≥3.248	
No. cases/controls	61/92	71/92	57/92	60/92	
Crude OR (95% CI)	1.00	1.16 (0.74–1.82)	0.93 (0.59–1.48)	0.98 (0.62–1.56)	0.74
Multivariate OR (95% CI)[b]	1.00	1.07 (0.66–1.75)	0.92 (0.55–1.56)	0.93 (0.52–1.65)	0.67
α-Linolenic acid					
Intake (g/day)[a]	<1.27839	1.27839–<1.5897	1.5897–<1.880	≥1.880	
No. cases/controls	66/92	64/92	49/92	70/92	
Crude OR (95% CI)	1.00	0.97 (0.62–1.52)	0.74 (0.46–1.19)	1.06 (0.68–1.65)	0.93
Multivariate OR (95% CI)[b]	1.00	0.84 (0.51–1.38)	0.66 (0.39–1.14)	1.01 (0.58–1.76)	0.95
Eicosapentaenoic acid					
Intake (g/day)[a]	<0.232	0.232–<0.3155	0.3155–<0.4708	≥0.4708	
No. cases/controls	64/92	59/92	67/92	59/92	
Crude OR (95% CI)	1.00	0.92 (0.58–1.46)	1.05 (0.67–1.64)	0.92 (0.58–1.46)	0.84
Multivariate OR (95% CI)[b]	1.00	0.79 (0.48–1.29)	0.92 (0.57–1.48)	0.89 (0.53–1.50)	0.90
Docosahexaenoic acid					
Intake (g/day)[a]	<0.370	0.370–<0.522	0.522–<0.727	≥0.727	
No. cases/controls	56/92	66/92	62/92	65/92	
Crude OR (95% CI)	1.00	1.18 (0.75–1.87)	1.11 (0.70–1.76)	1.16 (0.73–1.84)	0.63
Multivariate OR (95% CI)[b]	1.00	1.02 (0.63–1.67)	1.00 (0.61–1.65)	1.14 (0.68–1.93)	0.62
n-6 Polyunsaturated fatty acids					
Intake (g/day)[a]	<8.78	8.78–<10.27	10.27–<12.25	≥12.25	
No. cases/controls	66/92	59/92	58/92	66/92	
Crude OR (95% CI)	1.00	0.89 (0.57–1.41)	0.88 (0.56–1.39)	1.00 (0.64–1.57)	1.00
Multivariate OR (95% CI)[b]	1.00	0.77 (0.46–1.27)	0.80 (0.47–1.36)	0.99 (0.56–1.74)	0.92
Linoleic acid					
Intake (g/day)[a]	<8.54	8.54–<10.04	10.04–<11.938	≥11.938	
No. cases/controls	65/92	63/92	54/92	67/92	
Crude OR (95% CI)	1.00	0.97 (0.62–1.52)	0.83 (0.52–1.32)	1.03 (0.66–1.61)	1.00
Multivariate OR (95% CI)[b]	1.00	0.84 (0.51–1.39)	0.77 (0.45–1.31)	1.04 (0.59–1.84)	0.86
Arachidonic acid					
Intake (g/day)[a]	<0.1063	0.1063–<0.136	0.136–<0.171	≥0.171	
No. cases/controls	44/92	62/92	64/92	79/92	
Crude OR (95% CI)	1.00	1.41 (0.87–2.29)	1.45 (0.90–2.36)	1.80 (1.13–2.88)	0.02
Multivariate OR (95% CI)[b]	1.00	1.36 (0.82–2.29)	1.48 (0.87–2.53)	2.09 (1.21–3.64)	0.008
n-3/n-6 Polyunsaturated fatty acid ratio					
Intake[a]	<0.2139	0.2139–<0.250	0.250–<0.306	≥0.306	
No. cases/controls	60/92	49/92	78/92	62/92	
Crude OR (95% CI)	1.00	0.82 (0.51–1.31)	1.30 (0.84–2.03)	1.03 (0.65–1.63)	0.48
Multivariate OR (95% CI)[b]	1.00	0.75 (0.45–1.24)	1.26 (0.78–2.04)	1.01 (0.62–1.65)	0.51
Cholesterol					
Intake (mg/day)[a]	<227.8	227.8–<290.0	290.0–<374.0	≥374.0	
No. cases/controls	48/92	51/92	70/92	80/92	
Crude OR (95% CI)	1.00	1.06 (0.65–1.73)	1.46 (0.92–2.34)	1.67 (1.06–2.65)	0.01
Multivariate OR (95% CI)[b]	1.00	0.99 (0.59–1.68)	1.42 (0.85–2.37)	1.78 (1.04–3.05)	0.01

[a] Quartiles were based on intake in g/day (except for cholesterol: mg/day) adjusted for energy intake using the residual method, except for quartiles for the ratio of n-3 to n-6 polyunsaturated fatty acids, which were based on crude intake in g/day.
[b] Adjusted for sex, age, region of residence, pack-years of smoking, years of education, intake of vitamin E, iron, and alcohol, and body mass index.

A strength of our study is that cases were identified according to strict diagnostic criteria: the possibility of misclassification of PD is negligible. Weaknesses of the present study should be clarified. The dietary intake under study was estimated using a self-administered semi-quantitative dietary assessment questionnaire. Our DHQ could only approximate consumption although this questionnaire had been validated [30,31]. Because such exposure misclassification was non-differential, the consequence would bias the estimates of the observed association toward the null.

Our DHQ was designed to assess recent dietary intake, i.e. for 1 month prior to completing the questionnaire. Thus, pre-symptomatic and/or post-symptomatic PD could influence dietary habits in some cases, which led to misclassification of their true long-term dietary exposure. The results of a sensitivity analysis confined to cases

Table 3
Odds ratios (ORs) and 95% confidence intervals (CIs) for Parkinson's disease by quartiles of intake of arachidonic acid and cholesterol in men and women.

Variable	Adjusted OR (95% CI)[a]				*P* for trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Arachidonic acid					
Men	1.00	1.81 (0.80–4.14)	1.44 (0.58–3.61)	2.97 (1.18–7.73)	0.03
Women	1.00	1.10 (0.56–2.18)	1.37 (0.70–2.72)	1.76 (0.88–3.60)	0.08
Cholesterol					
Men	1.00	1.48 (0.64–3.45)	2.09 (0.91–4.86)	2.30 (0.97–5.53)	0.06
Women	1.00	0.74 (0.37–1.48)	1.02 (0.52–2.03)	1.43 (0.71–2.94)	0.10

[a] Adjusted for age, region of residence, pack-years of smoking, years of education, intake of vitamin E, iron, and alcohol, and body mass index.

less than 3 years from onset ($n=109$) were similar to those in the overall analysis. However, dopamine depletion in PD patients might affect their food choices in the preclinical stage [41]. Moreover, some of the non-motor symptoms such as constipation and hyposmia might precede the onset of overt motor signs [42,43]. Such symptoms might also affect food preferences. Given that such symptoms were associated with a higher intake of eggs, our results might be ascribed to the preclinical symptoms because eggs are one of the sources of arachidonic acid and cholesterol. In fact, a positive exposure–response association between egg intake and PD was of borderline significance in our data (P for trend $=0.09$). Thus, we cannot rule out the possibility that the observed positive associations are a consequence of PD.

Because our control subjects were selected from 3 of the 11 collaborating hospitals at which cases were recruited, controls were not representative of the population from which our cases arose. However, in a sensitivity analysis restricted to cases who were recruited from three hospitals associated with control recruitment ($n=153$), the positive associations with intake of arachidonic acid and cholesterol were strengthened (P for trend $=0.005$ and 0.008, respectively).

This is the first epidemiological study of the relationship between dietary intake of individual fatty acids and the risk of PD in Japan. Further epidemiological investigation of the effects of dietary fat on PD is required.

Acknowledgments

This study was supported by Health and Labour Sciences Research Grants, Research on Intractable Diseases, Research Committee on Epidemiology of Intractable Diseases from the Ministry of Health, Labour, and Welfare, Japan.

Appendix

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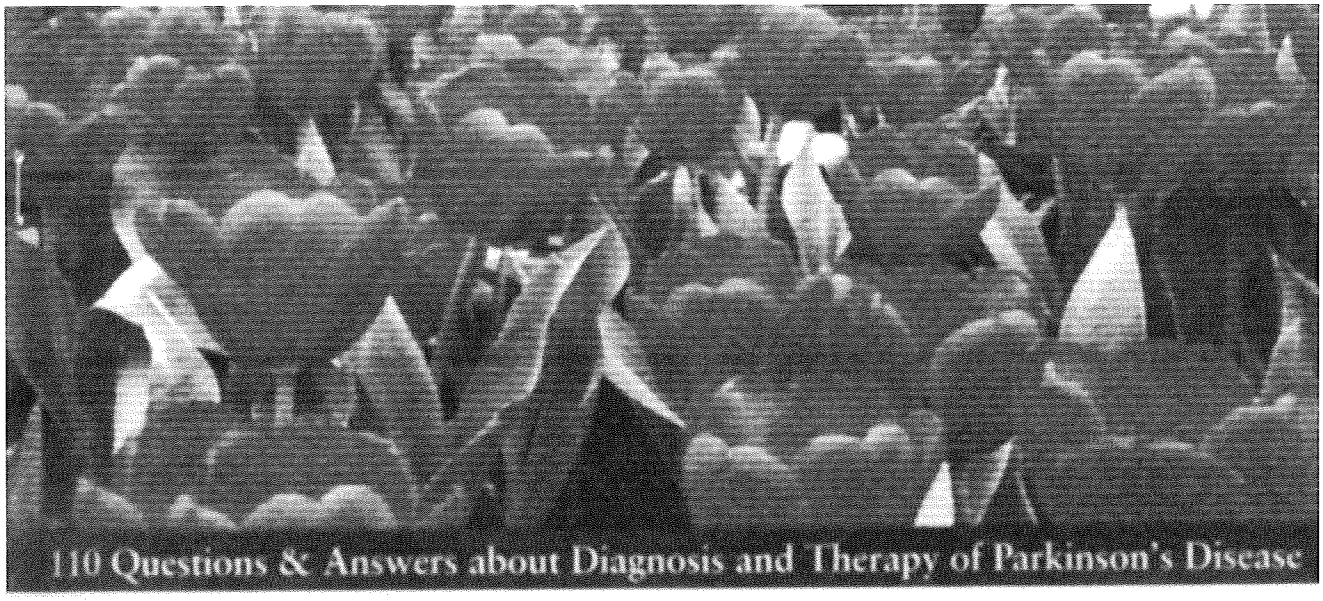

パーキンソン病診療 Q&A 110

水野美邦◉編集
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6. その他

105 パーキンソン病のQOLを計るいろいろな評価スケールについて説明してください.

quality of life（QOL，生活の質）は，WHOQOL Groupによると“an individual's perception of his/her position in life in the context of the culture and value systems in which he/she lives and in relation to his/her goals, expectations, standards and concerns”と定義されている[1,2]．これは，個人が生活する文化や価値観のなかで，自分の状況を，個人の目標や期待，基準や関心などに照らし合わせ，どのように認識しているかということと解釈される．QOLとして，健康と直接関連のあるQOL（health-related QOL），健康とは直接関連のないnon-health related QOL，さらに疾患特異的なQOL，疾患非特異的な包括的QOLなどが分類される．

パーキンソン病のQOLを計るスケールで，疾患特異的な尺度として，Parkinson's disease questionnaire-39 items（PDQ-39）[3]，Parkinson's disease questionnaire-8 items（PDQ-8）[3]，Parkinson's Disease Quality-of-Life questionnaire（PDQL）[4]，Parkinson impact scale（PIMS）[5]などがあげられる．包括的な健康関連QOLスケールとして，Nottingham health profile（NHP）[6]，Nottingham Adjustment Scale（NAS）[7]，Nottingham Adjustment Scale-Japanese Version（NAS-J）[8]，Sickness impact profile（SIP）[9]，Medical Outcomes Study 36-Item Short Form Health Survey（SF-36）[10-13]，EuroQOL（EQ-5D）[14]などがある．また，対象者の身体機能に直接影響されない心理的内面の満足度を重視したQOL評価スケールとしてWorld Health Organization Quality of Life assessment instrument-BREF（WHOQOL-BREF）[15]，the Schedule for Evaluation of Individual Quality of Life Direct Weighting（SEIQoL-DW）[16,17]，SEIQoL-DW日本語版[18,19]などがあげられる（表6-3）．

1 パーキンソン病に疾患特異的なQOL評価スケール

a. PDQ-39[3]

イギリスオックスフォード大学公衆衛生学部Health Services Research Unitでパーキンソン病患者のQOL測定のために開発されたスケールである．SF-36との平行性やパーキンソン病の臨床的評価スケールとの相関性など，疾患特異的QOLスケールとしての妥当性や再現性が示されている．さらに日本人への適応の妥当性が認められており，PDQ-39日本語版（version 1.1）[20,21]として頻用されている．表6-4にPDQ-39日本語版（version 1.1）の質問項目を引用し示した．

これは8つの構成要素 domain，39質問項目からなる．各構成要素は，運動能 mobility，日常生活活動 activity of daily living，情緒安定性 emotional well-being，烙印（疾患と関連した精神的負い目，stigma），コミュニケーション communication，身体的不具合 bodily discomfort，社会的支援 social support，認知 cognitionとなっている．それぞれの質問について，「全くなかった」から「いつもあった」まで5段階で頻度を回答する．PDQ-39の短縮版として各構成要素から質問項目を1つずつ取り出したPDQ-8が開発されており，PDQ-39との高い相関が示されている．

PDQ-39は，パーキンソン病に関する健康関連QOL評価スケールとして最も頻用されている尺度

表 6-3　パーキンソン病の QOL を計る種々の評価スケール

健康と直接関連のある QOL（health-related QOL）評価スケール	（文献）	（参照，連絡先など）
疾患特異的な QOL 評価スケール		
Parkinson's disease questionnaire-39 items（PDQ-39），PDQ-39 日本語版，PDQ-8	3, 20	表 6-4
Parkinson's Disease Quality-of-Life questionnaire（PDQL）	4	
Parkinson impact scale（PIMS）	5	
疾患非特異的な包括的 QOL 評価スケール		
Nottingham health profile（NHP）	6	
Nottingham Adjustment Scale（NAS），NAS-J, NAS-J-P	7,8, 25, 29	http://www.i-hope.jp/qol/
Sickness impact profile（SIP）	9	
Short form health survey-36 items（SF-36），SF-8	10, 11, 12	
SF-36v2™ 日本語版，アキュート版	13	表 6-5, http://www.sf-36.jp/
EuroQOL（EQ-5D）	14	
個別性を重視した QOL 評価スケール		
WHOQOL-BREF, WHO QOL26	15, 30, 31	
SEIQoL-DW, SEIQoL-DW 日本語版（暫定版）秋山美紀訳，大生定義，中島孝，監修	16, 17, 18, 19	SEIQoL-DW 事務局

である．疾患特有の QOL 上の問題点や QOL の阻害/向上要因の抽出，パーキンソン病の病型と関連した QOL の比較，さらに治療研究におけるアウトカム指標として広く使用されている．PDQ-36 とうつ尺度，パーキンソン病重症度（Hoehn-Yahr 重症度），統合パーキンソン病評価スケール（Unified Parkinson's Disease Rating Scale：UPDRS[22]），Mini Mental State Examination（MMSE）などを比較した検討において，うつ状態，運動機能障害，姿勢反射障害，認知機能障害などが QOL 低下に関与することが示された[23, 24]．また PDQ-39 と NAS-J，SF-36 など複数の健康関連尺度との比較において，パーキンソン病の重症度よりは疾病の受容[25]や医師からの説明に満足していること，病気に対する楽観的な心持ちが QOL に大きな影響を及ぼす[21]ことが明らかにされた．認知についての評価が含まれる点が本スケールの特徴であるが，1）経済的状況や sexual activity に関する項目が含まれない，2）個々の症例の経時的変化の追跡には，主観的評価の基準が動く（反応シフト現象），3）各項目についての頻度調査であり程度（質）は反映され難い，4）個人の内面的経験を評価するには必ずしも十分とはいえない[21, 26, 27]などが本スケールの問題点としてあげられている．本スケールの使用には登録が必要となる[20]．

b. PDQL[4]

37 項目の質問に 5 段階評価をする形式で，パーキンソン症状，全身症状，情緒機能，社会的機能の領域からなり，認知機能に関する項目を含むことが特徴である．PDQL は PDQ-39 と高い相関性が示されている[28]．

2 疾患非特異的な健康関連 QOL 評価スケール

a. The Nottingham Adjustment Scale 日本語版（NAS-J）[8]

オリジナル版は，視覚障害患者における心理的適応を判定するために開発されたスケールで，55 項目，7 領域からなる尺度である．日本語版 NAS-J v1.1 では，帰属スタイル（成功を外的な力では

表 6-4　PDQ-39 日本語版（version 1.1）における質問項目[20)]

パーキンソン病が原因で，次のようなことを経験することはどのくらい頻繁にありましたか？　この 1 カ月についてお答え下さい．（それぞれの質問について，一番よくあてはまる 1 つの□にレをつけて下さい．）

□全くなかった，□たまにあった，□時々あった，□よくあった，□いつもあった（もしくは全くできない）

問 1　やりたい余暇の活動を行うのが困難でしたか．
問 2　家のことをするのが困難でしたか，例えば日曜大工，家事，料理など
問 3　買い物の荷物を持ち運ぶのが困難でしたか
問 4　1 キロメートルを歩くのに支障がありましたか
問 5　100 メートルを歩くのに支障がありましたか
問 6　好きなように家の中を歩くのに支障を感じましたか
問 7　街の中など人前を歩くのが困難でしたか
問 8　外出の際に付き添いが必要でしたか
問 9　人前で倒れるのではないかと恐ろしくなったり，心配になりましたか
問 10　望む以上に家に引きこもらなければなりませんでしたか
問 11　自分の身体を洗うのが困難でしたか
問 12　着替えをするのが困難でしたか
問 13　ボタン掛けや靴ひもを結ぶのに支障がありましたか
問 14　字をはっきりと書くのに支障がありましたか
問 15　食べ物を箸やナイフで一口サイズに切るのが困難でしたか
問 16　飲み物をこぼさないように持つのが困難でしたか
問 17　気分が落ち込みましたか
問 18　疎外感，孤独を感じましたか
問 19　涙ぐんだり，涙もろくなったりしましたか
問 20　いらいらしたり，悲しくなったりしましたか
問 21　何となく心配（不安）になりましたか
問 22　自分の将来が心配になりましたか
問 23　自分がパーキンソン病であることを人に隠さなければならないと感じましたか
問 24　人前で食べたり飲んだりするような状況を避けましたか
問 25　パーキンソン病であるために人前で恥ずかしい思いをしましたか
問 26　他の人の自分に対する反応を心配しましたか
問 27　親しい人間関係に支障がありましたか
問 28　妻／夫や同居者からの助けや支えが不十分だということがありましたか
問 29　家族や親しい友人からの助けや支えが不十分だということがありましたか
問 30　日中予期せぬうちに眠ってしまったことがありましたか
問 31　例えば読書やテレビを見ている時などに，集中できないということがありましたか
問 32　記憶力が悪いと感じましたか
問 33　いやな夢や幻覚を見ましたか
問 34　話をするのが困難でしたか
問 35　適切に人と意思の疎通ができないと感じましたか
問 36　人から無視されたと感じましたか
問 37　苦痛を伴う筋肉のひきつけやけいれんがありましたか
問 38　関節や体に疼きや痛みを感じましたか
問 39　不快な暑さや寒さを感じましたか

なおこの評価表を使用するには登録が必要となる．

なく自分の力によるものであると考える程度）の領域を除き，27項目6領域に整理された．下位尺度は不安・うつ，自尊感情，視覚障害者への態度，ローカスオブコントロール（リハビリテーションの成否がどの程度自分の行動によって決まると感じている程度），障害の受容，自己効力感となっている．障害者の心理的適応を多面的に測定する尺度とされ，パーキンソン病（NAS-J-P）やその他8疾患・障害への使用可能性が確認されている．パーキンソン病患者のQOLは，身体機能の重症度に関連する[23,24]が，それ以上に心理的適応度が大きく影響すると報告されている[29]．本スケールの使用には登録が必要となる．

b. SF-36[10-12]

各種疾患を有する患者に加えて，一般健康人に対しても用いられる包括的な健康関連QOL評価スケールである．汎用性が高く標準値も報告されており，計量心理学的な特性をもつ．構成は，身体機能，日常役割機能（身体），体の痛み，全体的健康感，活力，社会生活機能，日常役割機能（精神），心の健康の8下位尺度について36項目の質問からなる．日本語版[13]の信頼性と妥当性が示され，国民標準値が算出されている．ただし，疾患の重症度や進行に関連した健康状態に影響されることから，重症疾患を有する患者の個別性を重視したQOLの測定には適さないとされる[26]．現在オリジナルのSF-36（日本語版はversion1.2）を改良したSF-36v2™が標準版として使用されている．SF-36v2™にはスタンダード版（振り返り期間が過去1カ月），アキュート版（過去1週間，表6-5）があり，各々自己記入式／面接式がある．また，SF-36の短縮版として，8項目の質問のみで構成さ

表6-5　SF-36アキュート版の質問内容（質問票サンプルより引用．一部変更あり）

以下のそれぞれの質問について，一番よくあてはまるもの（□）にレ印をつけて下さい		
問1	あなたの健康状態は？	□[1]最高によい，□[2]とても良い，□[3]良い，□[4]あまり良くない，□[5]良くない
問2	一週間前に比べて，現在の健康状態はいかがですか．	□最高によい，□とても良い，□良い，□あまり良くない，□良くない
問3	以下の質問は，日常よく行われている活動です．あなたは健康上の理由で，こうした活動をすることがむずかしいと感じますか．難しいとすればどのくらいですか．	
	ア）激しい活動，例えば，一生けんめい走る，重い物を持ち上げる，激しいスポーツをするなど	□とてもむずかしい，□少しむずかしい，□ぜんぜんむずかしくない
	イ）適度の活動，例えば，家や庭の掃除をする，1～2時間散歩するなど	□とてもむずかしい，□少しむずかしい，□ぜんぜんむずかしくない
	ウ）少し重い物を持ち上げたり，運んだりする（例えば買い物袋など）	□とてもむずかしい，□少しむずかしい，□ぜんぜんむずかしくない
	エ）階段を数階上までのぼる	□とてもむずかしい，□少しむずかしい，□ぜんぜんむずかしくない
	オ）階段を1階上までのぼる	□とてもむずかしい，□少しむずかしい，□ぜんぜんむずかしくない
	カ）体を前に曲げる，ひざまずく，かがむ	□とてもむずかしい，□少しむずかしい，□ぜんぜんむずかしくない
	キ）1キロメートル以上歩く	□とてもむずかしい，□少しむずかしい，□ぜんぜんむずかしくない
	ク）数百メートルくらい歩く	□とてもむずかしい，□少しむずかしい，□ぜんぜんむずかしくない

	ケ）百メートルくらい歩く	□とてもむずかしい，□少しむずかしい，□ぜんぜんむずかしくない
	コ）自分でお風呂に入ったり，着がえたりする	□とてもむずかしい，□少しむずかしい，□ぜんぜんむずかしくない
問4	過去1週間に，仕事やふだんの活動（家事など）をするにあたって，身体的な理由で次のような問題がありましたか．	
	ア）仕事やふだんの活動をする時間を減らした	□いつも，□ほとんどいつも，□ときどき，□まれに，□ぜんぜんない
	イ）仕事やふだんの活動が思ったほど，できなかった	□いつも，□ほとんどいつも，□ときどき，□まれに，□ぜんぜんない
	ウ）仕事やふだんの活動の内容によっては，できないものがあった	□いつも，□ほとんどいつも，□ときどき，□まれに，□ぜんぜんない
	エ）仕事やふだんの活動をすることがむずかしかった（例えばいつもより努力を必要としたなど）	□いつも，□ほとんどいつも，□ときどき，□まれに，□ぜんぜんない
問5	過去1週間に，仕事やふだんの活動（家事など）をするにあたって，心理的な理由で（例えば，気分がおちこんだり不安を感じたりしたために）次のような問題がありましたか．	
	ア）仕事やふだんの活動をする時間を減らした	□いつも，□ほとんどいつも，□ときどき，□まれに，□ぜんぜんない
	イ）仕事やふだんの活動が思ったほど，できなかった	□いつも，□ほとんどいつも，□ときどき，□まれに，□ぜんぜんない
	ウ）仕事やふだんの活動がいつもほど，集中してできなかった	□いつも，□ほとんどいつも，□ときどき，□まれに，□ぜんぜんない
問6	過去1週間に，家族，友人，近所の人，その他の仲間とのふだんのつきあいが，身体的あるいは心理的な理由で，どのくらい妨げられましたか．	□全然妨げられなかった，□わずかに妨げられた，□少し，□かなり，□非常に
問7	過去1週間に，体の痛みをどのくらい感じましたか．	□全然なかった，□かすかな痛み，□軽い痛み，□中くらいの痛み，□強い痛み，□非常に激しい痛み
問8	過去1週間に，いつもの仕事（家事も含みます）が痛みのために，どのくらい妨げられましたか．	□全然妨げられなかった，□わずかに妨げられた，□少し，□かなり，□非常に
問9	次にあげるのは，過去1週間に，あなたがどのように感じたかについての質問です．	
	ア）元気いっぱいでしたか	□いつも，□ほとんどいつも，□ときどき，□まれに，□ぜんぜんない
	イ）かなり神経質でしたか	□いつも，□ほとんどいつも，□ときどき，□まれに，□ぜんぜんない
	ウ）どうにもならないくらい，気分がおちこんでいましたか	□いつも，□ほとんどいつも，□ときどき，□まれに，□ぜんぜんない
	エ）おちついていて，おだやかな気分でしたか	□いつも，□ほとんどいつも，□ときどき，□まれに，□ぜんぜんない