

Biological effects of TGF- $\beta$ 1 are mediated via the six different receptors. The receptors can be subdivided into those which mediate an intracellular signal and those which store and/or present TGF- $\beta$ 1 to signaling receptors.<sup>9</sup>

Based on the accumulation of knowledge on TGF- $\beta$ 1 and its signaling, recent studies have suggested the bidirectional effect of TGF- $\beta$ 1 in immune response.<sup>23</sup>

The signal of TGF- $\beta$ 1 proceeds via a series of SMAD peptides. SMAD is a term derived from the fusion of "Sma" (Small) in *C. elegans* and "Mad" (Mothers against decapentaplegic) in *Drosophila*. The SMAD peptides play key roles in intracellular signaling. Activation of the TGF- $\beta$ /SMAD signaling cascade can result in both inhibition and stimulation.<sup>26</sup> The proinflammatory and fibrogenic effects of TGF- $\beta$ 1 enhances wound strength and stimulates epithelial cell growth in vivo, in contrast with the inhibitory effect seen in vitro, and promotes healing.<sup>27</sup> Thus, recent data suggest TGF- $\beta$ 1 can stimulate as well as inhibit immune responses.<sup>23</sup>

In migraine, neurogenic inflammations<sup>3</sup> and an allergic mechanism have been hypothesized. Although its actual role in migraine pathophysiology still remains unclear, we found significant increase of plasma TGF- $\beta$  in migraine patients during headache-free periods. Although the elevated TGF- $\beta$ 1 might be a result of the repeated migraine attack, that is released from activated platelets during migraine attack, there are some possibilities that elevated TGF- $\beta$ 1 involve and influence the pathophysiology of migraine. Further studies of TGF in migraine are needed.

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## Association of the insertion/deletion polymorphism of the angiotensin I-converting enzyme gene in patients of migraine with aura

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### Abstract

Recently, several angiotensin I-converting enzyme (ACE) inhibitors and an angiotensin II receptor blocker were demonstrated to have a clinically important prophylactic effect in migraine. ACE is one of the key enzymes in the rennin–angiotensin–aldosterone system, which modulates vascular tension and blood pressure. In humans, serum ACE levels are strongly genetically determined. Individuals who were homozygous for the deletion (D) allele showed increased ACE activity levels. To investigate the role of ACE polymorphism in headache, we analyzed the ACE insertion (I)/deletion (D) genotypes of 54 patients suffering from migraine with aura (MwA), 122 from migraine without aura, 78 from tension-type headache (TH), and 248 non-headache healthy controls. The ACE D allele were significantly more frequent in the MwA than controls ( $p < 0.01$ ). The incidence of the D/D genotype in MwA (25.9%) was significantly higher than that in controls (12.5%;  $p < 0.01$ ; odds ratio = 5.26, 95% confidence interval: 1.69–16.34, adjusted for age and gender). No differences in the remaining groups were found. Our results support the conclusion that the D allele and the D/D genotype in the ACE gene is a genetic risk factor for Japanese MwA. There seems to be a possible relationship between ACE activity and the pathogenesis of migraine.

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**Keywords:** Angiotensin-converting enzyme (ACE); Substance P; Migraine; Headache; Polymorphism; Association

The pathophysiology of migraine is not yet fully understood but may involve painful vasodilatation of cerebral blood vessels and/or the release of vasoactive neurotransmitters from the perivascular axons in the dura mater after activation of the trigeminovascular system [7]. Moskowitz [7] proposed the “trigemino-vascular theory” of migraine headache, which claims that neurogenic inflammations of meningeal blood vessels are evoked by excitation of trigeminovascular fibers. Angiotensin I-converting enzyme (ACE) is one of the key enzymes in the rennin–angiotensin–aldosterone system, which modulates vascular tension and blood pressure. In humans, serum ACE levels are strongly genetically determined [3].

It has been reported that insertion (I)/deletion (D) polymorphism in the ACE gene was related to serum ACE levels. ACE levels in the subjects of D/D genotype may be higher than I/I genotype and ACE in the subjects of I/D genotype may be intermediate levels [11,18]. ACE D/D genotype has been frequently, though controversially, linked to cerebrovascular disorders [6,15]. Migraine is in part associated with cerebral circulation. In this present study we have investigated the possible contribution of this polymorphism in Japanese patients with migraine and tension-type headache (TH).

This study consisted of 54 patients suffering from migraine with aura (MwA), 122 from migraine without aura (MoA), and 78 from chronic TH (Table 1). The diagnosis of headache was made following the International Headache Society (IHS) criteria [5]. Two hundred forty-eight normal

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Table 1  
Profile of subjects

	Cases	Males/females	Average age years $\pm$ S.D.
Controls	248	76/172	67.3 $\pm$ 11.7
MwA	54	17/37	33.1 $\pm$ 10.3
MoA	122	19/103	35.9 $\pm$ 13.4
TH	78	19/59	48.8 $\pm$ 18.0

healthy volunteers composed the control group. Control subjects have not suffered from migraine or tension-type headache in one's life. All the subjects were Japanese and gave their informed consent to the study.

A polymerase chain reaction (PCR) was performed on the genomic DNA samples with a GeneAmp PCR kit (Perkin-Elmer/Cetus) and primers as previously reported [12]. The PCR product is a 190-bp fragment in the absence of the insertion (D allele) and a 490-bp fragment in the presence of the insertion (I allele). In order to prevent from mistyping of the I/D genotype as D/D, we performed additional PCR using an insertion-specific primer pair with 5% dimethyl sulfoxide (DMSO) and confirmed ACE genotypes as previously reported [8]. The PCR fragments were electrophoresed in 2% agarose gels and stained with ethidium bromide. The differences in the frequency of ACE alleles and genotypes between groups were evaluated by the gene-counting method and comparison of groups by the  $\chi^2$  test. The level of significance was set at  $p < 0.05$ . The odds ratios associated with each genotype of ACE and their 95% confidence intervals were determined by using unconditional logistic regression. Statistical analyses were performed using SPSS version 11.0 for Windows (SPSS Inc., Chicago, IL, USA).

ACE I/D allele and genotype frequencies are given in Tables 2 and 3. The distribution of ACE genotypes in patients and controls did not deviate significantly from Hardy–Weinberg equilibrium. The ACE D allele was significantly more frequent in the MwA than controls. We detected that the incidence of the D/D homozygous genotype in MwA was significantly higher than that in controls. No differences in the remaining groups were found.

Recently, migraine has been shown to have a partly genetic basis. Point mutations in the voltage-dependent P/Q-type  $Ca^{2+}$  channel  $\alpha 1A$  subunit (CACNA1A) gene have been identified in familial hemiplegic migraine (FHM1), which is linked to chromosome 19p13 [9]. Another form of familial hemiplegic migraine (FHM2) is caused by mutation in the

Table 2  
The allele frequency of the ACE I/D polymorphism for headache sufferers

	Allele frequency		OR	95%CI	<i>p</i> value
	D	I			
Controls	176(35)	320(65)			
MwA	54(50)	54(50)	1.82	1.20–2.76	<0.01
MoA	98(40)	146(60)	1.22	0.89–1.67	0.22
TH	65(42)	91(58)	1.30	0.90–1.88	0.16

Figures in parentheses indicate percentages. D: deletion allele; I: insertion allele; OR: odds ratio; CI: confidence interval.

gene encoding the alpha-2 subunit of the sodium/potassium pump (ATP1A2), which is linked to chromosome 1q23 [4]. These specific migraines are rare forms and are caused by mutations in single genes. On the other hand, it is unlikely that “normal” migraine is caused by a single gene abnormality. Rather, it is probably caused by multifactorial genetic factors and environmental factors including foods and their life-style. Although non-genetic factors play a role in migraine, family and twin studies demonstrated that migraine, especially MwA, had a strong genetic component [13].

There was a report of the positive association with the D/D genotype and MoA in white subjects who were born in Sicily [10], but there was no data and comments with MwA. They also demonstrated a strong association between plasma ACE activity and the ACE I/D polymorphism [10]. Our data suggest that the D allele and the D/D genotype in the ACE gene is a genetic risk factor for Japanese MwA, but not for MoA. We have no data to clarify of this point, but several authors pointed out a significant ethnic differences in the frequency of the I/D polymorphism as well as the associated ACE activity. This is the first report that demonstrates a clear association of a common ACE mutation with Japanese migraineur.

ACE is also able to inactivate bradykinin and substance P, a potent vasodilator [16,17]. Substance P is suggested one of the neurotransmitters in the “trigemino-vascular theory”. Few studies have investigated the relationship between the ACE genotype and substance P. Arinami et al. [1] reported higher substance P levels in brain contents with the D/D genotype of ACE gene, and this is the opposite tendency, might be expected. The exact mechanism of the relationship between substance P and ACE genotype is still unknown. The alternation of ACE activity due to the I/D polymorphism would result in changed levels of the neurotransmitters and vulnerability to cranial vascular activity. These states appear to be analogous to those found during migraine headache or aura.

In addition, several ACE inhibitors and an angiotensin II receptor blocker were demonstrated to have a clinically important prophylactic effect in migraine. First, Bender [2] reported to have successfully treated with an ACE inhibitor for prophylaxis of migraine in a small group. Then, one of the ACE inhibitor, lisinopril, was demonstrated to have a clinically important prophylactic effect in migraine with a randomized, placebo controlled, crossover study [14]. Moreover, the angiotensin II receptor blocker, candesartan, also provided effective migraine prophylaxis with a randomized controlled trial [19]. These trials suggested that the rennin–angiotensin–aldosterone system must be concerned at least in part with the pathogenesis of migraine.

We conclude that the D allele and the D/D genotype of ACE gene are a genetic risk factor for MwA. In this study, ACE circulating levels in controls and headache subjects have not examined. Since our data was only designed to estimate the frequency of ACE genotype, we have no definite information on the etiology of difference between MwA and MoA. There seems to be a possible relationship between ACE activity and the pathogenesis of migraine, according to our results.

Table 3  
The ACE I/D genotype and odds ratios for headache sufferers

	Genotype	n	Not adjusted			Adjusted for age and gender		
			OR	95%CI	p trend	OR	95%CI	p trend
Controls	I/I	103(42)						
	I/D	114(46)						
	D/D	31(12)						
MwA	I/I	14(26)	1			1		
	I/D	26(48)	1.68	0.83–3.39	0.15	1.62	0.66–3.97	0.29
	D/D	14(26)	3.32	1.43–7.72	<0.01	5.26	1.69–16.34	<0.01
MoA	I/I	43(35)	1			1		
	I/D	60(49)	1.26	0.79–2.02	0.34	1.11	0.56–2.20	0.77
	D/D	19(16)	1.47	0.75–2.88	0.26	1.96	0.76–5.06	0.16
TH	I/I	26(33)	1			1		
	I/D	39(50)	1.36	0.77–2.38	0.29	1.03	0.55–1.93	0.92
	D/D	13(17)	1.66	0.76–3.61	0.20	1.67	0.70–3.98	0.25

Figures in parentheses indicate percentages. D: deletion allele; I: insertion allele; OR: odds ratio; CI: confidence interval.

Further studies with larger samples must be undertaken concerning the relationship between the ACE and headache.

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## Research Article

# Prevalence and clinical characteristics of restless legs syndrome in Japanese patients with Parkinson's disease

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## KEYWORDS

restless legs syndrome • Parkinson's disease • prevalence • Pittsburg Sleep Quality Index • iron

## ABSTRACT



To explore the clinical significance of restless legs syndrome (RLS) in Parkinson's disease (PD) and the causal relationship between these two disorders, we made a comparison of both the prevalence of RLS and the severity of sleep disturbance manifested on the Pittsburg Sleep Quality Index (PSQI) between patients with PD (n = 165) and age- and sex-matched control subjects (n = 131). The prevalence of RLS diagnosed by clinical interview was significantly higher in PD patients than in control subjects (12% vs. 2.3%). PSQI score was significantly higher in PD patients with RLS than in both patients without RLS and controls. However, PSQI score was not statistically different between the latter two groups. Among the PD patients with RLS, only 2 had a positive family history of RLS. Only 3 PD patients had requested treatment for the disorder. Our results emphasize the etiological link between RLS and PD in a Japanese cohort, and the existence of RLS is thought to be one of the most important factors aggravating sleep disturbance in PD, despite the low RLS severity. © 2005 Movement Disorder Society

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## ARTICLE TEXT

Restless legs syndrome (RLS) is characterized by unpleasant leg sensations and irresistible urges to move the lower extremities, mainly at night,<sup>[1]</sup> and may cause sleep disturbance. The reported prevalence rate of RLS varies from 0.1% to 15% among different ethnic populations.<sup>[2-6]</sup> The disorder is well-known to be familial<sup>[7]</sup> or secondary to other medical conditions, including iron-deficiency anemia, end-stage renal disease, neuropathy, pregnancy, and rheumatoid arthritis.<sup>[8-11]</sup> It has been widely accepted that dopaminergic drugs show therapeutic efficacy in RLS, and dopamine agonists now represent the first line of treatment for this disorder.<sup>[12]</sup> Ondo and colleagues<sup>[13]</sup> have suggested that Parkinson's disease (PD) and RLS may share a common pathogenesis. From this point of view, several studies have examined the possible etiological association between RLS and PD.<sup>[14]</sup> Previous studies in Caucasians, in which the prevalence of RLS has been estimated at 5 to 15% of the general population,<sup>[2-4]</sup> have indicated the high association of the two disorders.<sup>[13][15]</sup> However, a study of Chinese PD patients in Singapore, in which the reported prevalence of RLS in the general population was much lower than that in Western countries,<sup>[5]</sup> showed that none of the subjects satisfied diagnostic criteria of RLS.<sup>[16]</sup> This difference raises the question of whether there is a racial or ethnic difference between the prevalence of RLS not only in the general population but also in patients with PD. Moreover, the clinical significance of RLS secondary to PD remains unresolved. To clarify these issues, we investigated the prevalence and causal risk factors of RLS and its influence on sleep disturbance in Japanese patients with PD.

## SUBJECTS AND METHODS



The ethics committees of Tottori University and the Neuropsychiatric Research Institute approved this study, and all subjects gave their informed consent to take part in this investigation. This study investigated 165 consecutive PD patients (67 men, 98 women; mean age  $68.8 \pm 10.3$  (SD) years) who visited the outpatient clinic of either the Department of Neurology, Tottori University Hospital, or the Department of Neurology, Fuchu Hospital from 1 May 2003 to 31 October 2003, and 131 controls (50 men, 81 women; mean age  $68.3 \pm 5.8$  years), most of whom accompanied the outpatients at the Department of Neurology and were taking care of patients with neurological disorders. They did not report subjective sleep problems. Among the PD patients and controls described above, no subjects reported having conditions that might cause RLS such as pregnancy, diabetes mellitus, iron-deficiency anemia, rheumatoid arthritis, or renal failure. None of the subjects reported taking either antipsychotics or antidepressants at the time of the investigation. Diagnosis of PD was made based on standardized clinical criteria.<sup>[17]</sup> There was no significant difference in gender distribution or mean age between the two groups. The Pittsburg Sleep Quality Index (PSQI)<sup>[18]</sup> was measured for each subject to investigate the existence of sleep problems, and the presence of RLS was clinically evaluated by sleep disorder specialists experienced with RLS. Despite the difficulty in discriminating akathisia from RLS, we carefully excluded akathisia by investigating whether patients were medicated with antipsychotics and whether patients showed clear aggravation of symptoms at night, as well as whether symptoms were clearly relieved by movement.

After tremor, dyskinesia, painful neuropathy, and akathisia were carefully excluded, the diagnosis of RLS was made using four major symptoms of RLS developed by the International Restless Legs Syndrome Study Group (IRLSSG): (1) an urge to move the legs, usually accompanied or caused by uncomfortable sensation in the legs; (2) the beginning or worsening of symptoms

during periods of rest or inactivity; (3) the partial or total relief of symptoms by movement; and (4) the symptoms being worse in the evening or night than during the day or only occurring in the evening or night. A positive diagnosis of RLS was made when a subject had all of the four symptoms described above.[19] Additional input from spouses or caregivers was specifically allowed in some PD cases for which the patients could not competently answer all the questions.

After making a diagnosis of RLS, the PD patients were divided into two groups: those affected with RLS (PD with RLS) and those without RLS (PD without RLS). To investigate the causal factors for RLS in PD, clinical background data such as age; gender; both course and possible positive family history of RLS; duration of PD morbidity; severity of PD (Hoehn and Yahr grade); the amount of drugs used for the treatment of PD, including levodopa, dopaminergic agonists, droxydopa, amantadine, and anticholinergics such as trihexylphenidyl; and the number of patients who showed a reduction in symptoms in response to dopaminergic treatment were compared between the two groups described above. For ease of comparison, doses of dopaminergic agonists were converted into bromocriptine equivalents, such that 1 mg of pergolide was considered equivalent to 10 mg of bromocriptine, 1 mg of cabergoline to 5 mg of bromocriptine, and 1 mg of talipexole to 3.75 mg of bromocriptine.[20] Serum values of both iron and ferritin at the investigation were also compared between the two groups. In addition, the severity of RLS was evaluated using the Japanese version of the IRLSSG rating scale (IRLS).[21]

Comparisons of continuous variables between each group were made using both analyses of covariance followed by a post hoc test and a Mann-Whitney *U* test when appropriate. A  $\chi^2$  test was used to compare the categorical variables. Data are presented as mean  $\pm$  SE unless otherwise indicated. Statistical significance was considered to exist at  $P < 0.05$  (SPSS v. 11.5J, 2002; SPSS, Tokyo, Japan).

## RESULTS



A total of 20 (M:F = 8:12) of the 165 PD patients (12%) and 3 (M:F = 0:3) of the 131 controls (2.3%) were diagnosed to have RLS; the prevalence rate of the disorder was significantly higher in the PD patient group compared with the control group ( $P < 0.01$ ,  $\chi^2$  test). Among the 20 PD subjects with RLS, possible family history was reported by 2 patients (10%). The age at onset of RLS was  $56.2 \pm 2.7$  (SE) years old, and length of RLS morbidity was  $6.6 \pm 1.8$  years. All but 1 PD patient with a positive diagnosis of RLS reported that RLS symptoms clearly appeared after the onset of PD, and the mean period between the onset of the two disorders was  $6.5 \pm 1.8$  years. The exceptional patient reported to suffer from RLS 2 years before the onset of PD. Except for this single case, previous diagnosis of RLS had not been made in the PD group with RLS, because they had not reported RLS symptoms before the investigation. They also reported to have thought that the RLS symptoms were part of their PD symptom complex. Of 20 PD patients with RLS, 7 (35%) reported asymmetrical appearance of RLS symptoms; however, none of them reported any correlation between the predominantly affected side of RLS and that of PD. The IRLS score was  $19.7 \pm 1.5$ . Of 20 PD patients with RLS, 11 (55%) reported that the symptoms of RLS appeared almost every day, but only 3 patients requested treatment for the disorder at the interviews.

When the PSQI scores were compared (Fig. 1), a group difference was observed between the values found for PD with RLS ( $11.4 \pm 4.8$ ), PD without RLS ( $7.0 \pm 3.5$ ), and the controls ( $6.0 \pm 4.0$ ;  $F_{2,295} = 12.29$ ,  $P < 0.0005$ ). Post hoc tests revealed that PD patients with RLS showed a higher PSQI score than both PD patients without RLS ( $P < 0.0005$ ) and control subjects ( $P < 0.0005$ ). The PSQI score for PD patients without RLS was not statistically different from that of the controls.

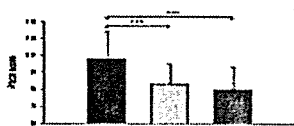
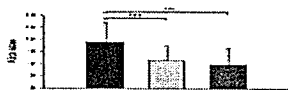


Figure 1. Pittsburgh Sleep Quality Index (PSQI) scores in Parkinson's disease (PD) with restless legs syndrome (RLS), PD without RLS, and controls.





Comparisons were by analysis of covariance with a post hoc test ( $F_{2,295} = 12.29$ ,  $***P < 0.0005$ ). Scores are means  $\pm$  SE.

[Normal View 11K | Magnified View 31K]

Of the background variables (Table 1), neither gender distribution nor length of PD morbidity was statistically different between the PD groups with and without RLS. However, as a group, PD patients with RLS were younger, both at the time of investigation and at the onset of PD, than PD patients without RLS. When the number of patients with young-onset PD in which symptoms of PD occurred under 40 years of age were compared between the two groups, the value was significantly higher for PD with RLS ( $n = 6$ , 30%) compared with PD without RLS ( $n = 8$ , 5.5%;  $P < 0.01$ ,  $\chi^2$  test). Neither Hoehn and Yahr grade nor the amounts of the drugs used for the treatment of PD differed between the two PD groups; nor did the number of patients showing symptoms of reduced dopaminergic drug effectiveness differ between the two groups. Moreover, judging from the clinical interviews, RLS symptoms in PD patients did not appear to correlate with the symptoms of reduced dopaminergic drug effectiveness in all the PD patients with RLS. Serum iron and ferritin values did not differ between the PD groups with and without RLS. Only 1 PD patient with RLS (5%) showed a serum ferritin level lower than the recommended cutoff value of 50 ng/ml, under which iron replacement therapy for RLS is recommended.[22]

Table 1. Comparison of clinical background variables between PD with RLS and without RLS

	PD with RLS (n = 20)	PD without RLS (n = 145)	P
Age at investigation (yr)	59.7 $\pm$ 2.7	70.1 $\pm$ 0.8	0.0001
Gender (M/F)	8/12	59/86	n.s.
Length of PD morbidity (yr)	10.1 $\pm$ 1.8	10.3 $\pm$ 0.6	n.s.
Age at onset of PD (yr)	49.7 $\pm$ 3.7	59.2 $\pm$ 0.9	0.05
Young-onset PD (+/-)	6/14	8/138	0.005
Hoehn and Yahr grade	2.6 $\pm$ 0.2	2.9 $\pm$ 0.1	n.s.
Amount of drugs for the treatment of PD			
Levodopa (mg/day)	510 $\pm$ 151	337 $\pm$ 11	n.s.
Dopamine agonist (mg/day) <sup>a</sup>	4.7 $\pm$ 1.0	6.0 $\pm$ 0.5	n.s.
Trihexyphenidyl (mg/day)	0.5 $\pm$ 0.3	0.7 $\pm$ 0.1	n.s.
Droxydopa (mg/day)	90 $\pm$ 39	63 $\pm$ 15	n.s.
Amantadine (mg/day)	30 $\pm$ 14	33.7 $\pm$ 5.3	n.s.
Selegiline (mg/day)	2.25 $\pm$ 0.6	2.19 $\pm$ 0.2	n.s.
Serum ferritin (ng/ml)	79.0 $\pm$ 7.7	76.9 $\pm$ 3.9	n.s.
Serum Fe ( $\mu$ g/dl)	69.9 $\pm$ 6.0	70.4 $\pm$ 1.7	n.s.

<sup>a</sup> The amount of dopaminergic agonists was converted into bromocriptine equivalents.

Values are expressed as mean  $\pm$  SE.

RLS, restless legs syndrome; PD, Parkinson's disease; n.s., not significant.

## DISCUSSION



Through detailed interviews and examinations, the prevalence of RLS in our control subjects (2.3%) was estimated to be much lower than in reports on the general Caucasian population.[2-4] This finding corroborates the finding that RLS was less frequent in a southeast Asian population.[5] However, the prevalence of RLS in our PD patients was much higher than that in healthy controls, despite its being slightly smaller than the value for prevalence in the United States, where 20.3% of the PD patients had RLS symptoms.[13] Our results support an etiological link between RLS and PD beyond any gender or ethnic difference. Although the cause of the difference between the results of our study and the study in Singapore[16] is unknown, differences in culture as well as both social and educational conditions should be taken into consideration.

Although some previous reports indicated that sleep disturbance is significantly more frequent in PD patients than in the healthy population,[23][24] PSQI score was not statistically different between PD without RLS and controls in our results. The reason for this finding is unclear. However, our control subjects consisted mostly of family members taking care of patients with neurological disorders, and sleep disturbance had been reported to be more prevalent in this population than in the general population.[23][24] One possible explanation for the PSQI finding described above is that sample bias might mask the difference in the prevalence of sleep disturbance between controls and PD patients without RLS.

Our most striking finding was that PD patients with RLS showed a significantly higher PSQI score than PD patients without RLS. This finding is consistent with that reported by Krishnan et al.,[15] who found that 90% of PD patients with RLS showed delayed sleep onset. These findings suggest that sleep disturbance becomes prominent when a PD patient is affected with RLS. We speculate that sleep disturbance is more likely to become pronounced after the occurrence of RLS in PD patients who have potential sleep disturbance, such as decreased sleep efficiency, increased waking time after sleep onset, and an increased number of nocturnal awakenings.[25]

Of 20 PD patients with RLS, 7 reported an asymmetrical appearance of RLS symptoms. However, also consistent with the report by Krishnan and associates,[15] laterality of RLS symptoms had no correlation with that of PD symptoms. PD patients with RLS thought their RLS symptoms were sensory and motor symptoms associated with PD. These symptoms were first attributed to RLS by the investigators.

Moreover, only three patients requested treatment for RLS at the interviews. This finding emphasizes the mild RLS severity in PD and corroborates the report of RLS symptoms in PD being often transient and irregular.[13] However, at the time of investigation, all the PD patients with RLS were already medicated with dopaminergic drugs, which are well known to suppress RLS.[12] This bias should be taken into consideration when analyzing the severity of RLS in PD patients, and future study on drug naive PD patients associated with RLS is required to draw a conclusion.

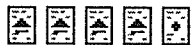
The percentage of PD patients with RLS who reported having a positive family history of RLS was smaller than the previously reported percentage in idiopathic RLS.[13] This finding is consistent with previous reports,[15] suggesting that RLS in PD patients does not occur on a genetic basis.

The findings of previous studies raised the possibility that a low level of serum ferritin could be related with the occurrence of RLS in PD.[13][15] Considering that iron has a role in both biosynthesis and transmission of monoamines, particularly dopamine,[26] this hypothesis appears reasonable. However, in our study, there was no difference in the value of serum iron between PD patients with and without RLS, suggesting that dysfunction of the central dopaminergic system

itself due to PD, rather than iron deficiency, might be responsible for the occurrence of RLS in this patient group. Moreover, consistent with a report by Ondo and coworkers,[13] our results did not reveal a difference in either the symptomatic characteristics of PD or the amount of drugs used for the treatment of the two PD groups. However, the number of young-onset PD patients was significantly higher in the PD group with RLS than in the PD group without RLS. This finding may explain the finding that age, both at the investigation and at the onset of PD, was younger in PD with RLS than PD without RLS. Although no pathological relationship between young-onset PD and RLS is known, our findings are quite different from the previous reports in which PD patients affected with RLS showed an older age at investigation,[15] suggesting that the prevalence of RLS secondary to PD did not seem to relate to advancing age as it does in late-onset RLS cases in the general population. Future study on a larger sample is necessary to confirm this finding.

Our study suffers from certain limitations. Referral bias might exist in this study, and our results, therefore, may not represent the true prevalence of RLS in the general population. A large part of the clinical information was based on interview of patients included in the study, perhaps leading to recall bias with regard to RLS symptoms. However, our results do indicate that the frequency of RLS is higher in PD patients than in controls in Japan. This study emphasizes the importance of diagnosing RLS in patients with PD to aid the management of sleep disturbance.

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## 食事・栄養

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おおつかみえこ

- 孤発性アルツハイマー病発症には遺伝因子以外に、栄養・運動などの生活習慣要因（ライフスタイル）が関連している。
- 生活習慣の中では特に食事因子が重要で、抗酸化ビタミン不足、n-3系多価不飽和脂肪酸不足がアルツハイマー病の発症に関連する。
- 総エネルギー摂取過剰や運動不足による肥満はインスリン抵抗性を引き起こし、アルツハイマー病の発症につながる。
- アルツハイマー病患者への抗酸化ビタミン、n-3系多価不飽和脂肪酸の摂取を推奨した栄養介入により30ヵ月認知機能の低下を抑制することが可能であった。

**Key Words** アルツハイマー病, 食事因子, 抗酸化ビタミン, n-3系 PUFA, インスリン抵抗性

### はじめに

アルツハイマー病 (Alzheimer disease : AD) のうち約95%は孤発性であり、その発症には複数の遺伝的素因、加齢、頭部外傷、教育歴、ライフスタイル (運動、栄養、休養、飲酒、喫煙)、精神的ストレスなどが関連している。また、ADにも高血圧、インスリン抵抗性、糖尿病、高脂血症など血管系の危険因子が存在し、脳血管性痴呆との類似点が次第に明らかにされてきた。なかでも食習慣を中心としたライフスタイルの改善は可能でありADの予防として期待されている。本稿では、AD発症と食習慣などのライフスタイル、ADと血管因子との関係、さらに栄養介入効果の実際についても述べる。

### □ ADの栄養学的問題点

ADと栄養の問題は現在のところ次の3点に絞られてきている。第1に野菜・果物の摂取はADを予防することで、ビタミンE、ビタミンCなどの抗酸化ビタミンやビタミンB群、葉酸の摂取に関するもの。第2に魚の摂取はADを予防し、魚油に含まれるドコサヘキサエン酸 (DHA) やエイコサペンタエン酸 (EPA) などのn-3系多価不飽和脂肪酸 (PUFA) の役割。第3は糖・エネルギー代謝に関連するものであり、総カロリーおよび脂質、糖の摂取過剰、肥満、糖尿病、インスリン抵

抗性、高脂血症との関連である。これらは酸化ストレス、慢性炎症、血管因子などADの病的過程を悪化させる因子に対しても何らかの作用を持っていると考えられる。

### □ AD患者の栄養調査

調査に際しては患者および介護者より同意を得たうえで、Sasakiらの開発した自記式食事暦法調査票 (self-administered diet history questionnaire : DHQ) を用いてAD患者と健常対照者の食事栄養調査を行い比較検討した<sup>1,2)</sup>。表1はAD患者の摂取食品の特徴である。この調査はすでに認知症を発症している場合での横断的研究であり、厳密な意味では認知症と食事との因果関係を証明するものではないが、AD患者の若い頃からの食習慣をかなりの程度抽出することが可能である。健常対照者に比べて魚、緑黄色野菜、淡色野菜、キノコ類、海藻の摂取量が少ないことが明らかにされた。栄養素ではビタミンB<sub>12</sub>、ビタミンB<sub>6</sub>、葉酸、ビタミンC、ビタミンE、β-カロテンなどの摂取が少なくなっていた。高齢の一般住民でも認知機能が低下している群ではこれらの栄養素が低下していることがすでに報告されている<sup>3,4)</sup>。脂質ではコレステロールの摂取に差はなく魚に含まれるEPAやDHAなどのn-3系PUFAの摂取が少なく、肉や植物油に多く含まれるリノール酸やア

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表1 食品の比較 (単位=g)

食品群	AD (n=64)	対照 (n=80)	P 値
穀類	261.9±105.8	231.9±94.1	NS
芋類	16.7±12.2	22.6±16.7	NS
砂糖	6.1±15.1	5.4±3.8	NS
菓子類	16.1±16.0	16.5±13.4	NS
豆類	119.5±86.9	127.8±69.2	NS
魚	40.5±24.4	58.3±28.2	0.0001
肉	25.1±15.4	21.0±16.3	0.13
卵	16.0±15.4	13.5±11.0	NS
牛乳	77.2±77.8	117.5±99.9	0.01
緑色野菜	45.7±31.7	68.9±59.8	0.01
他の野菜	55.9±32.2	70.6±46.4	0.03
果物	78.9±60.1	89.4±54.2	NS
キノコ類	4.4±4.4	7.6±7.7	0.004
海藻	6.3±7.3	10.7±8.3	0.001
アルコール	65.1±164.4	75.5±177.2	NS
飲み物	399.7±320.0	559.8±381.5	NS
調味料	18.9±23.1	39.4±47.3	NS
水分	18.9±23.1	20.4±28.1	NS

(NS:有意差なし)

ラキドン酸などの n-6 系 PUFA の摂取が多く、その摂取バランスを示す n-6/n-3 比が有意に高かった。

#### □ 野菜・果物の摂取不足

AD と抗酸化物との関連は古くから研究されており<sup>5)</sup>、抗酸化物を含む食品の予防効果に関心が寄せられていた。ロツテルダムからの大規模な調査報告<sup>6)</sup>では抗酸化物をβカロテン、フラボノイド、ビタミンC、ビタミンEの4つに分けて検討している。調査は55歳以上の5395人を平均6年追跡した。この期間中に197人が認知症となり、うち146人がADであった。栄養調査は食品摂取頻度調査にて行い、ビタミンC、ビタミンE、マルチビタミンなどのサプリメントの使用状況(種類と量)、栄養指導の有無を加えた。教育歴、体格指数(body mass index: BMI)などの交絡因子を調整したところ、抗酸化物の最大量摂取群は最小量摂取群に比して、ADに罹患する危険率はビタミンCの場合には0.66、ビタミンEの場合は0.57と有意に低かった。サプリメント使用者は最大量摂取群に含めたが、サプリメント使用者を除外しても結果は同じであった。また、シカゴのMorrisら<sup>7)</sup>の報告では1993年から2000年まで平均3.9年間追跡調査し、65歳以上の815人のうちこの期間に131人が認知症になった。サプリメント使用者はビタミ

ンC 16.1%、ビタミンE 17.3%、βカロテン 4.3%であった。抗酸化物を食品のみから摂取した場合と、食品とサプリメントの両者から摂取した場合に分け、摂取量を5分割して解析した。ビタミンEを食品のみから摂取した場合にのみ抑制効果が認められ、食品とサプリメントの両者から摂取した場合には抑制効果がなくなった。

これらの疫学調査が示すように、抗酸化物を含む野菜・果物の摂取は認知症予防に有効だが、サプリメントのみでなく食品として摂ることと食事パターン全体の改善が重要である。

#### □ 魚の摂取不足

ロツテルダムの調査<sup>8)</sup>では、痴呆のない55歳以上の住民5386人を2.1年間追跡したところ、総脂質と飽和脂肪酸の摂取過剰が血管障害をともなう痴呆の危険因子であったが、純粋なADに関しては魚の摂取は防御因子であり、魚を1日3g以下しか摂取しない群に比して18.5g以上摂取した群は有意に危険率が低かった(オッズ比0.3)。

ボルドーの調査<sup>9)</sup>では、68歳以上の認知機能の正常な高齢者1674人のうち1416人を7年間追跡した。この期間中に170人が痴呆になり、そのうち135人はADであった。その結果魚を少なくとも1日1回摂取する場合を基準にすると、少なくとも週に1回食べる場合のAD発症の危険率は1.64、2週に1回では2.24、まったく食べない場合は5.29であった。肉を少なくとも1日に1回食べる場合は1.75であったが、肉をまったく食べないと6.23と高くなることより、やはり肉も必要であることを示している。

さらにシカゴの調査結果<sup>10)</sup>でも同じだった。815人を平均3.9年追跡し、この間に131人がADに罹患したが魚を週に1回以上食べる群はそれ以下の群に比してAD発症の危険率は0.4であった。また、総n-3系PUFAの摂取量を5分割すると、最大量摂取群は最小量摂取群に比して危険率は0.4であった。心筋梗塞や脳梗塞の既往によって食事を肉食から魚食に変更した例を除くと、魚の防御効果はさらに明らかになった。

#### □ 魚油の役割

魚油に含まれるn-3系PUFAは抗炎症作用、抗不整脈作用、抗血小板凝集能亢進作用、抗動脈硬化作用を通じて心血管系に良好に作用する。また、魚と野菜の摂取は血清コレステロールと中性脂肪

を下げ、HDL コレステロールを上げる。AD にも動脈硬化が関与するとの知見が増加してきているが、魚油はこの点でも有利に働くものと考えられる。また、AD には慢性炎症が関係するという仮説があり、予防や治療として非ステロイド系抗炎症薬 (NSAIDs) の投与が試みられている<sup>11)</sup>。NSAIDs はアラキドン酸エイコサノイドを産生するシクロオキシゲナーゼ (COX1 と COX2) を阻害するが、NSAIDs を服用することと魚油を摂取することとは同等の作用を持つと考えられる。さらに最近の知見では、アミロイド  $\beta$  蛋白を脳から消去し血液へ移行させるアミロイド結合蛋白として注目されている蛋白にトランスサイレチンがあるが、n-3 PUFA を多く含む餌を老齢ラットに与えると、海馬のトランスサイレチンの発現が 10 倍にも増加することが見いだされた<sup>12)</sup>。一方、n-6 系 PUFA は肉や植物油に多く含まれ、n-3 系 PUFA 由来と n-6 系 PUFA 由来のエイコサノイド (プロスタグランジン、トロンボキサン、ロイコトリエン) の生物活性は互いに拮抗関係にあるため n-6 系 PUFA 由来のエイコサノイドが多くなるほど炎症、動脈硬化、血栓形成に傾く。肉は良質なタンパク質源であり、ビタミン B<sub>12</sub> も豊富な食品である。摂取に際しては極端な偏りは避けバランスを保つこと、つまり n-6/n-3 比を極端に上昇させないことが必要である。

#### □ カロリー摂取過剰、肥満、インスリン抵抗性

最近、肥満が AD の危険因子であることがスウェーデンの 18 年間の前向き調査で明らかにされた<sup>13)</sup>。79~88 歳で AD になった群の 70~79 歳での BMI は 28.2~29.6 であり、痴呆にならなかった群の 25.0~25.7 に比して有意に高かった。この結果は女性にだけあてはまり、男性では患者数が少なく有意差はなかった。また脳血管性痴呆にもあてはまらなかった。われわれは肥満による動脈硬化、高血圧、高脂血症、糖尿病が血管性因子と強い関連を示し、AD のリスクになると推定している。

AD 患者では空腹時のインスリン値が高く、インスリン抵抗性を示す報告が多い。われわれの調査でも 60 歳以上の AD 患者では高インスリン血症を示す例が 78.3% (47/60) と高率であった。

規則的な運動が AD を予防するとされているが、運動するほどインスリン感受性が高くなり、空腹時のインスリン値が低下することと関連して

いる可能性がある。Craft ら<sup>14)</sup>の報告では、AD では髄液のインスリン値が対照よりも低く、インスリンの髄液/血清比は有意に低い。さらに Watson ら<sup>15)</sup>はインスリンを点滴すると髄液中のアミロイド  $\beta$  蛋白 ( $A\beta_{42}$ ) が一過性に増加することを示し、この傾向は特に高齢者に著しいとしている。さらに、海馬の CA1 および CA3 領域にはインスリン受容体の密度が高いことより記憶との関連に興味を持たれている。最近、インスリン分解酵素 (insulin degrading enzyme: IDE) が  $A\beta$  蛋白をも基質とすることが明らかにされ<sup>16)</sup>、しかも、IDE は  $A\beta$  蛋白よりもインスリンのほうにはるかに親和性が高いため、高インスリン血症があると相対的に  $A\beta$  蛋白の分解が抑制されるという。高インスリン血症は血管内皮細胞の機能障害を起こすことが知られているため、インスリン自体が脳最小動脈の内皮細胞障害を起こしている可能性がある。

#### □ AD 患者への栄養学的介入

AD 患者に対して食事による治療への応用はまだほとんど行われていない。AD 患者の栄養調査結果をもとに患者および介護者より同意を得たうえで、われわれは食行動全体の改善をめざす行動修正療法を試みている。魚を 1 日 1 回、緑黄色野菜 1 日 2 回、果物を 1 日 1 回摂取することを推奨している。この食事で栄養素を計算すると、ビタミンやミネラルの必要量を満たし、n-6/n-3 比は 3.0 程度となる。全 AD 患者でみると 30 ヶ月では介入群は非介入群より有意に高得点を示した (図 1)。ミニメンタルテスト (MMSE) で 20~23 点の軽度の AD 患者では認知機能を維持することが可能で 30 ヶ月の段階では非介入群と比べて平均 6.6 点高かった (図 2)。しかし 10~19 点の重症 AD 患者では効果はなく、早期介入が重要と考えられた。栄養

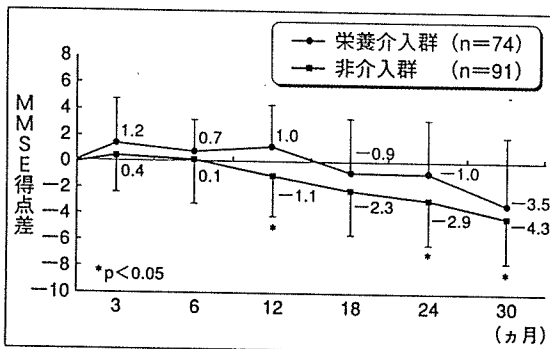


図 1 MMSE の推移 全 AD

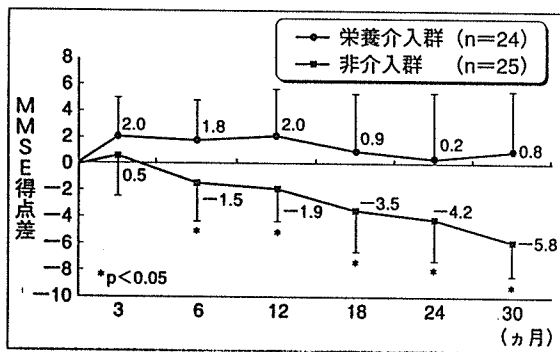


図2 MMSEの推移 AD (20~23点)

介入は介護者の協力なくしては成り立たないため、患者だけでなく食事担当者や同居者で食事摂取状況の把握が可能な観察者の同席が必要で、栄養士から直接指導を受けてもらうことが重要である。

#### まとめ

メタボリックシンドローム発症の上流には過食・運動不足からくる肥満、次に引き起こされるインスリン抵抗性があり、その後高血圧、高脂血症、血管障害がもたらされ脳血管障害、虚血性心疾患、認知症などを発症すると考えられ、認知症は今やメタボリックシンドロームの一疾患と位置づけされる。したがって、食事療法や運動療法はインスリン抵抗性を改善し、認知症発症予防のみならずメタボリックシンドローム発症の予防にもつながる普遍的な手段と考えられる。しかし、ADの発症には遺伝的素因が大きいと考えられる患者がいることも事実であり食事だけではすべてを説明できないことも明らかである。食事栄養の意味づけをより明確にするためにはADの本態の解明を待たなければならない。

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# 女性の認知症・アルツハイマー病と生活習慣

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## abstract

孤発性アルツハイマー病発症には遺伝因子以外に、栄養・運動などの生活習慣要因（ライフスタイル）が関連している。生活習慣のなかでは特に食事因子が重要で、抗酸化ビタミン不足、n-3系多価不飽和脂肪酸不足がアルツハイマー病の発症に関連する。また、総エネルギー摂取過剰や運動不足による肥満はインスリン抵抗性を引き起こし、アルツハイマー病の発症につながることもわかってきた。一方、アルツハイマー病の発症頻度は女性のほうが高いが、女性ホルモンとの因果関係をはじめ、その原因は解明されていない。われわれの調査によると、女性のアルツハイマー病患者では野菜、魚の絶対的摂取不足を示す例が男性より多かった。また、BMI 25以上の肥満の割合は少なく、耐糖能障害はないがインスリン高値を示す割合が男性の場合より高かった。社会心理学的な面でも心身のストレスに脆弱な性格行動パターンを示す例が有意に多く、発症との関連が示唆された。

## I はじめに

アルツハイマー病（AD）は老人斑と神経原線維変化を特徴とする変性疾患で、このうち約95%は孤発性である。その発症には複数の遺伝的素因に加えて食事や運動などの生活習慣、精神的ストレスなどが関連している。また、AD発症と高脂血症、高インスリン血症、糖尿病など血管系の危険因子が存在し、脳血管性痴呆との類似点が次第に明らかにされてきた。ADの発症頻度は女性のほうが高いがその真の原因はよくわかっていない。本稿では、女性のADについて食習慣の特徴や運動などの影響、ストレスとの関係をわれわれの調査結果を中心に述べる。

## II AD発症と女性ホルモン

ADの発症の性差を説明する仮説の一つとして閉

経後の女性ホルモンの減少が考えられてきた。実際、エストロゲンは脳に対する広範な作用を有し、アセチルコリン濃度の増加、神経細胞死の抑制、神経終末の側芽形成促進作用、樹状突起形成作用、脳血流量改善作用と脳虚血防止作用、コレステロール低下作用などが動物実験のレベルで明らかにされている。ヒトにおいても、認知機能に対する女性ホルモン補充療法（HRT）の効果が多方面から検討され、なかでもThe Women's Health Initiative（WHI）はHRTに関する最大規模の二重盲検無作為割付臨床試験であり、その副調査として認知機能に関するThe Women's Health Initiative Memory Study（WHIMS）が行われた<sup>1), 2)</sup>。

WHIでは介入群は大腸癌と骨粗鬆症による骨折には有益だったが、心筋梗塞、脳血栓、肺塞栓、乳癌の比率が高かったため5.6年の段階で中止された。また4,532人を平均4.05年追跡したWHIMSの結果では、実薬群のほうがプラセボ群よりもAD発症の危

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険率が2.05倍高く、さらには、実業群のほうが脳血栓を起こしやすかった。ADの発症に血管因子、特に細小動脈の潜在性微小脳梗塞の関与が重視されてきているが、女性ホルモンがどのような機序で潜在性微小脳梗塞を起こすのかは不明である。

以上のように、現段階ではHRTが確実に閉経後の女性の認知機能に対して有益な効果をもたらすという結論は得られておらず、ADの発症と女性ホルモンとの因果関係はいまだに不明である。

### III AD患者の栄養学的問題点

ADと栄養の問題は現在のところ次の三点に絞られてきている。第一に野菜・果物の摂取はアルツハイマー病を予防することで、ビタミンE、ビタミンCなどの抗酸化ビタミンやビタミンB群、葉酸の摂取に関するもの。第二に魚の摂取はADを予防し、魚油に含まれるドコサヘキサエン酸 (DHA) やエイコサペンタエン酸 (EPA) などのn-3系多価不飽和脂肪酸 (PUFA) が有用であること。第三は糖・エネルギー代謝に関連するものであり、総カロリーおよび脂質、糖の摂取過剰、糖尿病、インスリン抵抗性、高脂血症との関連である。これらは酸化ストレス、慢性炎症、血管因子などADの病的過程を悪化させる因子に対してもなんらかの作用をもってい

ると考えられる。

表1は男性と女性AD患者の摂取食品および栄養素のまとめである。調査に際しては患者および介護者より同意を得たうえで、Sasakiらの開発した自記式食事暦法質問票 (self-administered diet history questionnaire: DHQ) を用いてAD患者と健常対照者の食事栄養調査を行い比較検討した<sup>3), 4)</sup>。女性AD患者の特徴として健常対照者に比べて魚、緑黄色野菜、海藻の摂取量が、また栄養素ではカルシウム、カリウム、ビタミンB<sub>2</sub>などの摂取量が有意に少なかった。男性AD患者で示された総エネルギーや脂質、炭水化物、肉類の摂取過多は女性AD患者には少なく、男性は食べ過ぎ、女性は食べなさすぎの傾向があった。脂質について、女性AD患者ではコレステロールの摂取と魚に含まれるEPAやDHAなどのn-3系PUFAの摂取が少なかった。一方男性AD患者では魚の摂取不足はなかったが、肉や植物油に多く含まれるn-6系PUFAの摂取が多く、男女ともその摂取バランスを示すn-6/n-3比が有意に高かった。

### IV 野菜・果物および魚の摂取不足

野菜・果物に多く含まれる抗酸化ビタミン類とADとの関連は古くから研究されており<sup>5)</sup>、老化に

	Crude values		amount/day	
	AD (n=25)		N (n=26)	
総エネルギー (kcal/day)	1394.0 ± 439.3		1566.2 ± 480.7	
魚介類 (%)	65.1 ± 38.1 <sup>#</sup>		104.8 ± 49.3	
肉 (%)	32.9 ± 21.9		39.4 ± 40.6	
緑黄色野菜 (%)	64.6 ± 49.3 <sup>#</sup>		116.1 ± 117.5	
カルシウム (mg)	454.1 ± 210.8 <sup>#</sup>		670.5 ± 320.2	
カリウム (%)	793.4 ± 297.7 <sup>#</sup>		1063.2 ± 393.8	
ナトリウム (%)	1872.3 ± 858.3 <sup>#</sup>		2455.1 ± 897.3	
カロテン (%)	1618.4 ± 1178.3		2416.2 ± 1724.2	
ビタミンC (%)	114.9 ± 76.2		129.2 ± 60.5	
ビタミンB <sub>1</sub> (%)	0.8 ± 0.3		0.8 ± 0.4	
ビタミンB <sub>2</sub> (%)	1.1 ± 0.4 <sup>#</sup>		1.4 ± 0.7	
ナイアシン (%)	11.1 ± 4.7 <sup>#</sup>		14.1 ± 5.4	
コレステロール (mg)	198.0 ± 107.4 <sup>#</sup>		275.2 ± 131.8	
SFA (g)	10.8 ± 4.1		13.1 ± 7.3	
MUFA (%)	13.2 ± 5.8		15.2 ± 7.8	
n-6 PUFA (%)	8.2 ± 3.7		9.2 ± 3.9	
n-3 PUFA (%)	2.1 ± 1.0 <sup>#</sup>		3.0 ± 1.3	
n-6/n-3	4.3 ± 2.0 <sup>#</sup>		3.3 ± 1.1	

表1  
女性AD患者の摂取食品と栄養素  
SFA: saturated fatty acids  
MUFA: monounsaturated fatty acids  
PUFA: polyunsaturated fatty acids  
#: p<0.05

伴うフリーラジカルの増大は男女を問わずADの増悪因子であることは多くの基礎研究より証明されている。ロッテルダムの大規模な調査<sup>6)</sup>では抗酸化物をβカロテン、フラボノイド、ビタミンC、ビタミンEの四つに分けて検討し、抗酸化物の最大量摂取群は最小量摂取群に比して、ADに罹患する危険率はビタミンCの場合には0.66、ビタミンEの場合には0.57と有意に低かったとされている。また、シカゴのMorrisら<sup>7)</sup>の報告も同様であった。これらの疫学調査では、サプリメントでなく抗酸化物を含む野菜・果物の摂取が認知症予防に有効であると報告されている。

魚の摂取に関して、ロッテルダムの調査<sup>8)</sup>では、痴呆のない55歳以上の住民5,386人を2.1年間の追跡したところ、総脂質と飽和脂肪酸の摂取過剰が血管障害を伴う痴呆の危険因子であったが、純粋なADに関しては魚の摂取は防御因子であり、魚を1日3g以下しか摂取しない群に比して18.5g以上摂取した群は有意に危険率が低かった(オッズ比0.3)と報告されている。ボルドー<sup>9)</sup>やシカゴ<sup>10)</sup>からも魚を多く摂取すればするほどADが予防されるという疫学調査が出されている。魚油に含まれるn-3系PUFAは抗酸化作用、抗炎症作用<sup>11)</sup>、抗血栓作用、脂質改善作用など広範な作用がある。さらに最近では、マウスの実験でDHAを大量に与えると老人斑が抑制されるとの結果も出されている<sup>12)</sup>。

一方、n-6系PUFAは肉や植物油に多く含まれ、n-3系PUFA由来とn-6系PUFA由来のエイコサノイド(プロスタグランジン、トロンボキサンなど)の生物活性は互いに拮抗関係にあるためn-6系PUFA由来のエイコサノイドが多くなるほど炎症、動脈硬化、血栓形成に傾くためn-6/n-3比を極端に上昇させないことが必要である。われわれの調査では、魚の摂取不足は女性のAD患者で際立っていた。

### 脂質・糖代謝, 高インスリン血症

AD患者では空腹時のインスリン値が高く、インスリン抵抗性を示す報告が多い<sup>13)</sup>。われわれの調査でも60歳以上のAD患者では高インスリン血症を示す例が72.2% (70/97) と高率であった。特に、女

性AD患者では菓子など甘いものを多く摂取する傾向が強く耐糖能異常を示す例が男性よりやや多かった(65% [39/60] vs 60% [35/58])。また、耐糖能正常例でも高インスリン血症例は女性のほうが男性より多い傾向があった(81% [17/21] vs 66% [15/23])。規則的な運動がADを予防するとされ、運動するほどインスリン感受性が高くなるためと考えられる。

また、運動は血圧や脂質レベルを低下させ血小板の凝集を抑制したりあるいは脳代謝が増加することにより脳血流を維持していると報告されている<sup>14)</sup>。さらに、Laurinら<sup>15)</sup>は、運動は女性のほうが男性より有効があるのは運動とホルモン代謝になんらかの関連があるためではないかと述べているが、詳細は不明である。むしろ、女性のほうが男性より高インスリン血症が多いことと関連があるのかもしれない。

インスリンとアミロイドβ(Aβ)蛋白はインスリン分解酵素(insulin degrading enzyme: IDE)の共通の基質<sup>16)</sup>で、しかも、IDEはAβ蛋白よりもインスリンのほうにはるかに親和性が高い。そのため、高インスリン血症はAβ蛋白の分解を抑制しADを起しやすくなると考えられる。規則的な運動を日課とすることはAD発症の予防に繋がり、重要である。

### ストレスと性格

AD発症とストレスの関係を調査したところ、55例中36例(65.5%)で人間関係のトラブルなど精神的疲労を訴えていた。配偶者や家族との死別(36.4%)、介護疲れ(34.5%)なども多く、また複数のストレスを抱えている例もあった。性格特性に注目すると、女性AD患者ではこれらのストレスの影響を強く受けやすいC型<sup>17)</sup>が健常対照者に比較して有意に多かった(p=0.001)。一方、男性では有意な特徴はなかった。強いストレスによりコルチゾールが増加し認知機能が障害されやすくなる<sup>18)</sup>が、これはコルチゾール高値と海馬の萎縮に関連があることを示している<sup>19)</sup>。したがって、AD発症予防にはストレスを和らげるような対処行動を身につけることも必要である。

女性のAD発症に関して、栄養学的問題点は野菜・果物、魚摂取の重要性であり、男性の場合と基本的には同じである。また、インスリンがAD発症の男女差と本質的にどのようにかかわっているのかは今後の解明が待たれる。

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