Michio Hashimoto, Yoko Tanabe, Yoshimi Fujii, Toshihiko Kikuta and Hitoshi Shibata	Chronic Administration of Docosahexaenoic Acid Ameliorates the Impairment of Spatial Cognition Learning Ability in Amyloid β-Infused Rats	J Nutr	135(3)	549-555	2005
Yoko Tanabe, Michio Hashimoto, Kozu Sugioka, Megumi Maruyama, Yoshimi Fujii, Rika Hagiwara, Toshiko Hara, Shahdat Md Hossain and Osamu Shido	Improvement of spatial cognition with dietary docosahexaenoic acid is associated with an increase in fos expression in rat CA1 hippocampus	Clinical and Experimental Pharmacology and Psysiology	31	700-703	2004

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Akira Ueki
Mieko Otsuka

Life style risks of Parkinson's disease: Association between decreased water intake and constipation

Abstract Gastrointestinal dysfunction, especially constipation, is one of the major problems in the daily life of patients with Parkinson's disease (PD). About 60 to 80 % of PD patients suffer from constipation. Several studies have proven that constipation appears about 10 to 20 years prior to motor symptoms. More recently, Abbott et al. have found from a large scale prospective study that lower frequency bowel movements predict the future risk of PD. Furthermore, Braak et al. have found that Lewy neuritis and Lewy bodies, the hallmarks of PD pathology, appear in the dorsal nucleus of vagus in the earliest stage of the disease and then extend upward through the brain stem to reach the substantia nigra in the third stage. They also hypothesize that some yet undefined toxins break through the mucosal barrier of the intestine and are incorporated into the axon terminal of the vagus nerve and transported in a retrograde manner to the vagus nucleus. In this study, we assessed bowel movements and nutritional status in Japanese patients with PD. We found that intake of water was significantly decreased in PD patients from early life and associated with their constipation.

Ninety four patients with PD (M 50, F 44) were enrolled. Nutritional status was assessed using the Self-administered Diet History Questionnaire (DHQ). Total water intake was calculated from the consumption of coffee, green tea, and tea. We also questioned the behavior of water drinking from the early stage of life. The questionnaire for bowel movements concerned the frequency of defecation, age of onset of constipation, and age of onset of motor dysfunction. Less than one bowel movement in 3 days was defined as constipation.

The nutritional status of PD patients did not differ significantly from those of controls though several studies have shown excess intake of animal fats or reduced consumption of coffee are risks in PD. In contrast, water intake was significantly lower in PD patients than controls (604.0 ± 377.2 ml/d vs 909.5 ± 531.6 ml/d; $P < 0.0001$). Interestingly, PD patients tended not to feel thirsty and thus they had no desire to drink water throughout their life. Seventy four patients out of 94 (78.7 %) complained of constipation. Mean bowel frequency was once per 3.3 ± 1.1 days and 71.1 % of patients were defined as having constipation. Women suffered from constipation more frequently than men (82.4 % vs 61.9 %). In 33 patients out of 74 (44.6 %), onset of constipation preceded motor disturbance by an average time of 18.1 ± 18.8 years. Furthermore, the amount of water intake correlated inversely with the severity of constipation and the depletion of water intake preceded constipation in most cases.

The present results support previous findings that constipation precedes the onset of motor dysfunction in PD. To our knowledge, this is the first report to point out latent water depletion in PD patients. It is not certain at present whether coffee or caffeine themselves are the protective factor for PD or alternatively the amount of water in coffee drinking is more essential. Prospective studies on a large scale are necessary to elucidate the real meaning of water depletion in PD.

Key words Parkinson's disease · constipation · water deficiency · nutritional factor · early diagnostic marker

Akira Ueki, MD (✉) · Mieko Otsuka
Department of Neurology
Jichi Medical School
Omiya Medical Center
1-847 Amanuma-cho, Omiya-ku
Saitama-City
Saitama 330-8503, Japan
Tel.: 048-647-2111
Fax: 048-648-5188
E-Mail: uekia@omiya.jichi.ac.jp

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Introduction

Research on the cause of Parkinson's disease (PD) points to both genetic and acquired factors. Over 10 genes causing familial PD have already been identified, but no genetic polymorphism has been confirmed for a majority of sporadic Parkinson's disease patients. Acquired factors are divided into environmental and lifestyle factors. Since the discovery of MPTP, there has been increased interest in environmental toxins, and the relationship between PD and exposure to insecticides with chemical structures similar to MPTP is being investigated, although there have as yet been no reports confirming a connection. Lifestyle factors include nutrition, exercise and rest, as well as alcohol consumption and smoking. Recently, there have also been reports of numerous prospective studies indicating that the lower the degree of coffee consumption, the higher the risk of developing PD [1, 2], drawing attention to the defensive effect of caffeine.

It has also been pointed out that there is a high incidence rate of constipation associated with PD, and that constipation appears 10 or more years prior to motor symptoms. Furthermore, it was recently reported that a large-scale prospective study conducted in Hawaii clearly showed that the lower the stool frequency at the beginning of the study, the higher the risk of developing PD in the future, confirming that constipation clearly precedes motor dysfunction in PD [3]. A series of pathological trials conducted by Braak et al. [4, 5] showed that Lewy neurites and Lewy bodies, the hallmarks of PD pathology, appear in the dorsal nucleus of vagus in the earliest stage of the disease. The lesions then extend upwards through the brain stem to eventually cause disturbance in the substantia nigra and the vagus nerve, resulting in reduced gastrointestinal movement, which is thought to explain the clinical findings that precede motor symptoms. Braak et al. also proposed the attractive hypothesis that an unidentified toxin passes through the mucosal barrier of the intestine and is transported in a retrograde manner by the vagus nerve axon, leading to vagus nerve neuron damage [6].

In light of this information, we conducted a study of constipation and nutritional status in PD patients, and sampled characteristic nutritional factors in PD while investigating whether constipation is related to nutrients, and whether there is a temporal relationship between constipation and nutrients and the appearance of motor symptoms. The results indicated that, in PD, constipation precedes the onset of motor dysfunction by roughly 20 years, and is accompanied by the dietary factor of insufficient uptake of water, pointing to a close relationship between constipation and insufficient water uptake.

Subjects

The subjects were 94 PD patients (M 50, F 44), in whom the onset age was 59.5 ± 10.4 years (M 58.4 ± 10.4, F 60.7 ± 10.3), and age at the time of the study was 68.1 ± 8.6 years (M 67.4 ± 9.6, F 69.1 ± 7.5). The control group consisted of 69 healthy adults of corresponding age not suffering from diabetes, hypertension, hyperlipidemia, or nervous disease.

Methods

Food and nutrient intake per energy intake of 1,000 kcal was calculated using the Self-administered Diet History Questionnaire (DHQ) from Dietary assessment: Sasaki et al. [7]. Strictly speaking, total water intake is calculated to include intake of green tea, coffee, tea, juice, hot water and other drinks, as well as metabolic water, but in this study, because the amount of metabolic water was less than 10% of the drinking water, only the amount of drinking water was calculated. In a survey of water intake, subjects were asked how much desire they had to drink water, including green tea, tea, coffee and other drinks, with answers classified as "Very little", "Little", "Normal", and "Much". They were also asked to state, as accurately as possible, when this drinking pattern first developed.

Constipation survey items

Subjects were asked how frequent their bowel movements were, and constipation was defined as less than one bowel movement in 3 days. They were also asked about the sequential relationship between when symptoms of constipation first appeared, when motor symptoms first appeared, and when their water intake behavior changed.

Statistical analysis

Data were analyzed using one-way analysis of variance (ANOVA) to determine the significance of differences among groups.

Results

Nutritional assessment

Apart from a significantly low intake of fish, alcohol and water, the nutritional status of the PD patients did not differ from that of the controls with respect to the 18 specified food groups (Table 1). The most striking difference was water intake, with the controls drinking 597.1 ± 402.5 ml per 1,000 kcal per day compared to the significantly lower amount of 341.3±209.0 ml for the PD patients ($P < 0.0001$). Even when comparing the absolute volume of water intake, the 604.0 ± 377.2 ml of the PD patients was significantly lower than the 909.5 ± 531 ml of the controls ($P < 0.0001$).

In terms of nutrients, the PD patients and controls showed little significant difference in intake of vitamin B_2, niacin, vitamin C and ethanol (Table 2). In terms of lipids, reflecting little intake of fish, the polyunsaturated fatty acid (PUFA) n-6/n-3 ratio was high (Table 3).

Table 1 Food groups (unit = g)

	PD (n = 80)	Control (n = 69)	P value
Grains	264.8±77.0	235.2±97.6	NS
Potatoes	21.7±18.1	20.9±15.1	NS
Sugar	4.4±2.7	5.9±4.6	NS
Snacks	14.5±11.7	15.3±12.5	NS
Beans	144.6±85.6	123.8±70.7	NS
Fish	44.3±22.5	55.8±29.5	0.008
Meat	22.5±14.5	19.7±15.2	NS
Eggs	13.3±9.5	12.8±11.4	NS
Milk	105.5±87.8	117.1±103.2	NS
Green vegetables	58.1±33.9	71.0±65.61	NS
Other vegetables	69.8±34.6	70.2±53.4	NS
Fruit	87.2±50.8	85.3±50.4	NS
Mushrooms	7.3±6.5	6.6±7.1	NS
Seaweeds	8.9±9.1	10.4±8.9	NS
Beverages	41.7±95.4	91.0±188.0	0.041
Water (tea, coffee, juice)	341.3±209.0	597.1±402.5	< 0.0001
Seasoning	41.3±41.2	38.0±45.8	NS

Table 2 Nutrients/1,000 kcal

		PD (n = 80)	Control (n = 69)	P value
T.protein	%E	15.0±2.5	15.6±3.5	NS
T.fat	%E	24.4±6.0	24.2±7.9	NS
T.carbohydrate	%E	57.7±7.7	55.2±9.7	NS
Na	mg	2893.2±735.2	2824.9±868.5	NS
K	mg	1386.3±378.8	1522.2±484.7	NS
Ca	mg	358.2±130.4	397.2±160.1	NS
P	mg	589.6±131.7	623.7±165.6	NS
Fe	mg	5.2±1.2	5.4±1.6	NS
Vit.A	IU	1403.3±791.4	1474.7±1008.4	NS
Vit.B_1	mg	0.5±0.1	0.5±0.1	NS
Vit.B_2	mg	0.8±0.2	0.9±0.3	0.003
Niacin	mg	7.6±2.1	8.4±2.4	0.043
Vit.C	mg	74.3±36.8	87.1±40.2	0.043
Carotene	μg	1384.2±942.6	1523.2±1172.1	NS
Alcohol	%E	2.0±4.2	3.9±7.1	0.048

Table 3 Nutrients2

Lipids		PD (n = 80)	Control (n = 69)	P value
Cholesterol	mg	141.2±53.6	148.1±70.5	NS
SFA	%E	7.1±2.3	7.1±3.0	NS
MUFA	%E	8.2±2.4	8.0±2.8	NS
PUFA	%E	6.3±1.7	6.3±2.1	NS
n-3 PUFA	%E	1.3±0.5	1.5±0.6	NS
n-6 PUFA	%E	5.1±1.3	4.9±1.5	NS
n-6/n-3 PUFA		4.0±0.9	3.5±1.0	0.002
Fibers	g	8.5±2.7	8.3±2.8	NS
water soluble	g	1.5±0.5	1.4±0.5	NS
insoluble	g	6.5±1.9	6.2±2.0	NS

SFA saturated fatty acid; *MUFA* monounsaturated fatty acid; *PUFA* polyunsaturated fatty acid

Degree of desire to drink water

Table 4 shows the results of the water drinking behavior survey. Of the 94 subjects, 44 (46.8 %) answered "Very little", and 20 (21.3 %) answered "Little". The water intake for each of these two groups was less than 300 ml and between 300 and 600 ml respectively. Of the remaining subjects, 27 (28.7 %) answered "Normal" (600 to 1,000 ml/day), and 3 (3.2 %) answered "Much" (over 1,000 ml/day). A majority of PD patient families, including spouses, are aware that the patient drinks very little, and many believe the amount drunk is insufficient.

Frequency of bowel movements

Mean bowel movement frequency was once every 3.3 ± 1.1 days, with a frequency of once every 3.3 ± 1.1 days for men and once every 3.3 ± 1.1 days for women, constipation being more severe among women. These results were obtained from 38 patients. Constipation was defined as less than one bowel movement in 3 days. Overall, 71.1 % of the patients were constipated, with 61.9 % of men and 82.4 % of women being constipated (Table 5).

Relation between constipation and motor symptoms

Table 6 shows the temporal relationship between constipation and the onset of motor symptoms. Among the 74

Table 4 Water drinking behavior in parkinsonian patients

Degree of desire to drink (ml/d)		Total n (%)	Men n (%)	Women n (%)
Very little	(300)	56 (46.7)	24 (38.7)	32 (55.2)
Little	(300–600)	31 (25.8)	16 (25.8)	15 (25.9)
Normal	(600–1,000)	27 (22.5)	8 (29.0)	9 (15.5)
Much	(> 1,000)	3 (2.5)	2 (3.2)	1 (1.7)
Unknown		3 (2.5)	2 (3.2)	1 (1.7)
Total		120 (100.0)	62 (100.0)	58 (100.0)

Table 5 Frequency of bowel movements

Interval for one defecation (days)	Total (n = 38)	Men (n = 21)	Women (n = 17)
1	5	2	3
2	6	6	0
3	12	5	7
4	7	4	3
5	4	3	1
6	2	1	1
> 3 days	27 (71.1%)	13 (61.9%)	14 (82.4%)

Table 6 Onset of constipation in relation to motor symptoms

Onset of Constipation	Total n (%)	Men n (%)	Women n (%)
Before PD	49 (50.5)	23 (43.4)	26 (59.1)
After PD	14 (14.4)	11 (20.8)	3 (6.8)
Unknown	34 (35.1)	19 (35.8)	15 (34.1)
Total	97 (100.0)	53 (100.0)	44 (100.0)

patients who responded, 33 (44.6%) suffered from constipation before the onset of motor symptoms, 14 (18.9%) became constipated following the onset of motor symptoms, and for 27 patients (36.5%) the relationship was unclear, indicating that the percentage of patients with constipation before the onset of motor symptoms was high.

Among patients who had constipation before onset of PD, the mean age at which constipation began was 39.9 ± 22.0 (45.8 ± 19.2 for men, 33.1 ± 23.6 for women). Constipation began a mean 18.7 ± 18.8 years before the appearance of motor symptoms, the figure being 12.6 ± 16.4 years earlier for men and 25.5 ± 19.9 years for women. Cases of patients who had constipation from childhood and university were also accurately recorded.

Relation between constipation and adipsia

Among the 74 patients suffering from constipation, when asked how much water they drank, 35 (47.3%) answered "None", 17 (23%) answered "Hardly any", 21 (28.4%) answered "Normal amount", and 1 (1.4%) answered "A large amount", indicating that 70.3% of the patients drank none or very little water. Among the 10 patients without constipation, 4 (40%) answered "None", 0 (0%) answered "Hardly any", 4 (40%) answered 'Normal amount", and 2 (20%) answered "A large amount", but since the number of cases in this group was small, this did not indicate any significant statistical difference. A tendency for motor symptoms to be lighter in patients who drank large amounts of water was also observed, but no precise relationship between water intake and symptom severity could be ascertained in this study.

Sequence of adipsia, constipation and motor symptoms

Responses were received from 43 patients concerning the temporal relationship between insufficient water intake, constipation and motor symptoms (Table 7). In 31 (72.1%) cases, the majority, adipsia occurred first followed by constipation and then motor dysfunction, while there were only 3 (6.9%) cases in which constipation and motor dysfunction occurred before adipsia. The following case concerns a doctor who kept a detailed record of his daily life from childhood.

Table 7 Sequence of adipsia, constipation, and motor symptoms

Adipsias → Constipation/Motor	31 (72.1%)
Constipation/Motor → Adipsia	3 (6.9%)
Undefined	9 (21%)
Total	43 (100%)

Typical case

A 75-year old man. He had never felt the desire to drink water since adolescence. In his junior high school days, he used to give all of his water to his friends when on excursions or during athletic training. Constipation started when he was a university student, and he began using laxatives 3 to 5 times per month. After becoming 70 years old, the severity of his constipation increased to the point where his bowel movements were limited to once every 6 days. Parkinson's disease occurred at the age of 73.

Discussion

Parkinson's disease and dietary factors

There have been a wide range of reports on PD and dietary factors, such as those focusing on excessive intake of animal lipids [8–11], insufficient intake of nicotinic acid (niacin) [12–14], and insufficient intake of antioxidants [20]. A study in Seattle by Anderson et al. [11] with 4 groups of subjects consuming different amounts of animal lipids indicated that the risk of PD increased as animal lipid intake increased, with an odds ratio of 3.30 for those in the group consuming the largest amount. The authors of the report proposed that this could be due to the large effect of oxidative stress caused by animal lipid intake. In a cross-sectional study in Rotterdam focusing on the relationship between antioxidant intake and PD [15], the results indicated that is was harder for subjects in a group taking 10 mg of vitamin E per day to develop PD (OR 0.5, 95% confidence interval; 0.2–0.9). Due to problems with the studies, however, the relationship between PD and dietary factors has as yet not been confirmed.

Coffee consumption and the risk of Parkinson's disease

Recently, extremely interesting reports of various prospective studies [1,2] indicate that intake of coffee or

caffeine is a preventive factor for PD. In the Boston study [2], subjects were divided into 5 groups receiving varying amounts of caffeine. Compared to the group with the lowest intake of caffeine, the group with the largest intake had an OR of 0.42 for PD. It made no difference whether caffeine intake was via coffee or tea. A study in Hawaii [1] showed that compared to a group drinking only 4 ounces (120 ml) of coffee per day, the OR for a group drinking 28 ounces (840 ml) was reduced by roughly 1/5. The same results were obtained with tea and other caffeinated drinks, indicating that the higher the intake of caffeine, the lower the risk of developing PD.

Parkinson's disease and adipsia

The intake of green tea and other caffeinated drinks by patients in our nutritional survey was certainly significantly small. The small water intake, however, was more statistically significant, and taking into consideration the lack of desire to drink water from a young age, it indicates that insufficient water intake is a more important factor. In the report from Hawaii, intake of 4 ounces (120 ml) and 28 ounces (840 ml) of coffee are statistically compared, but although the difference can be seen to be due to different coffee intake, it could also be interpreted as a reflection of different water intake. In this report, however, water intake was not measured. Adipsia is closely related to constipation, and there are cases of a lack of desire to drink water preceding the appearance of motor dysfunction by up to 50 years, which suggests that adipsia is of primary importance in the appearance of PD. The reason why the lack of desire develops from around the time of childhood is unknown.

It is easy to understand that latent dehydration in PD patients would provide an ideal background for the easy development of chronic symptoms during very hot summers.

Parkinson's disease and constipation

Constipation, which is not a rare condition, is something that increases with age. In the case of PD patients, however, the frequency of constipation is high [16], with reports of the results of many studies showing an onset rate of 28 % to 61 % [17–19], which is significantly higher than the 6 % to 33 % of controls. There has also been a report of a high onset rate of 80 % [20], which agrees with our results.

Many factors play a role in the mechanism of constipation in PD patients, such as reduced contraction of smooth muscle due to gastrointestinal neuron dysfunction, insufficient exercise, antiparkinson agents, diet and water intake.

The primary mechanism for the onset of constipation in PD is defecation disorder due to the disease itself, which in turn consists of peripheral and central disorders. The most important peripheral mechanisms are the loss of dopaminergic cells in the large intestine [21], and the degeneration of myoenteric plexus and the appearance of Lewy bodies resulting in reduction and loss of large intestine peristalsis [16]. A lack of synergy between the pelvic floor skeletal muscle, which regulates defecation, and the anal sphincter has been indicated as a central mechanism [22]. Other factors that contribute to a worsening of constipation in PD include insufficient exercise, the effects of antiparkinson agents (levodopa, anticholinergics), antidepressants and other drugs, swallowing dysfunction, diet and water intake [1].

Constipation precedes motor symptoms

Our study indicates that constipation appears roughly 20 years before motor symptoms (12.6 ± 16.4 years before in men, 25.5 ± 19.9 years in women). Although this study relies on data from previous studies, constipation is attracting a great deal of attention, and since there are many cases where the time of onset is accurately recorded, it is probable that the data are reliable. In the same way as our results, many reports clearly indicate that constipation precedes motor symptoms in PD. In a cross-sectional study by Ashraf et al. [23], 10 of 12 PD patients developed constipation an average of 16 years prior to the appearance of motor symptoms. Abbot et al. [3] conducted a prospective study for the Honolulu Heart Program. The subjects of the study, which spanned a period of 24 years, were 6,790 American men of Japanese descent aged 51 to 75, 96 of whom developed PD. It was reported that the lower the frequency of bowel movements at the start of the study, the higher the future risk of PD, with the risk for less than 1 bowel movement per day being 2.7 times that for 1 per day, 4.1 times that for 2 per day, and 4.5 times that for 3 per day. This study indicated that constipation appeared a mean 10 years (5 months to 19 years) before motor symptoms. Abbot et al. could not say that constipation is a cause of PD, but did suggest that the presence or absence of constipation could be useful to define individuals with a high risk of developing PD in the future.

Pathological studies conducted by Braak et al. [4, 5] indicate that Lewy neurites and Lewy bodies, both PD hallmarks, first appear in the dorsal nucleus of vagus. Following pathological changes, they then move up to the brain stem and appear in the raphe nucleus, nucleus giganto cullularis reticularis and substantia nigra, eventually leading to disturbance of the cerebral cortex. It has been reported that the dorsal nucleus of vagus, which regulates gastrointestinal functions, is damaged first, adding support to the idea that constipation precedes motor dysfunction. Braak et al. proposed the hy-

pothesis that the reason why the dorsal nucleus of vagus is damaged first is because an as yet unidentified toxin passes through the mucosal barrier of the intestine, and in a retrograde manner is transported up by VIP neurons as far as the vagus nerve [6]. Further research is required to ascertain whether constipation is simply a pathological phenomenon of PD, or whether it has a specific meaning regarding the cause of PD.

Limitation of the study

Since our study is a cross-sectional study, there are concerns about recall bias. For example, nutritional surveys are influenced if subjects drink more water, consume large quantities of vegetable fiber or make other changes to their eating and drinking habits to alleviate constipation, resulting in reverse cause. There are also cases of constipation appearing after subjects were administered antiparkinson agents, but it is difficult to confirm whether this is due to an adverse drug reaction or the course of the disease itself. Nevertheless, there are numerous patients who have suffered from constipation for many years, and since in most cases the time of onset is precisely recorded, our results can be considered reliable. Although there are few ordinary patients who can be subjective about their water intake, many spouses and other family members were aware of the patient's low water intake long before motor symptoms appeared. Strictly speaking, however, there is a need for prospective studies to clarify the cause and effect relationship.

From the viewpoint of life style factors, this study offers valuable suggestions for studies of the pathology and cause of sporadic nerve degeneration diseases.

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No genetic association between tumour necrosis factor receptor II 196R polymorphism and Japanese sporadic Alzheimer's disease

Nobuto Shibata[a], Tohru Ohnuma[a], Tadashi Takahashi[a], Yoichiro Matsubara[a], Akira Ueki[b], Masatsugu Nagao[c] and Heii Arai[a]

Recent studies have reported that acute effects of tumour necrosis factor (TNF), a pro-inflammatory cytokine, are limited by binding to a soluble receptor, TNF receptor II, and the G allele at position 196 in exon 6 of the TNF receptor II gene (TNFRII 196R) has been associated with auto-immune diseases. Since complex interactions among cytokines have been suggested around senile plaques in Alzheimer's disease, TNF might be associated with ageing and the pathophysiology of Alzheimer's disease. We examined the TNFRII 196R polymorphism in 243 Japanese sporadic Alzheimer's disease cases and 106 control cases using a polymerase chain reaction-restriction fragment length polymorphism method. Allelic frequencies with TNFRII 196R T/G polymorphism were 28.3% and 27.4% in the control and Alzheimer's disease groups, respectively. The results showed no genetic association between TNFRII 196R polymorphism and Alzheimer's disease. The TNFRII 196R G allele does not appear to be associated with Alzheimer's disease susceptibility in a Japanese population. *Psychiatr Genet* 14:53–55 © 2004 Lippincott Williams & Wilkins.

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[a]Department of Psychiatry, Juntendo University School of Medicine, Tokyo, Japan, [b]Department of Neurology, Omiya Medical Center, Jichi Medical School, Saitama, Japan and [c]Department of Psychiatry, Nagao Hospital, Hiroshima, Japan.

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Correspondence and requests for reprints to Nobuto Shibata, MD, Department of Psychiatry, Juntendo Koshigaya Hospital, 560 Fukuroyama, Koshigaya-shi, Saitama 343-0032, Japan.
Tel: +81 489 750321; fax: +81 489 787821;
e-mail: nobuto.shibata@nifty.ne.jp

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Introduction

Recently, several genetic polymorphisms of inflammatory cytokines including interleukin-6 were reported to be associated with Alzheimer's disease (Papassotiropoulos *et al.*, 1999). It has been reported that chronic low-grade inflammation in ageing promotes an atherogenic profile and is related to age-associated disorders including Alzheimer's disease (Viel *et al.*, 2001). Additionally, a local inflammatory process has been studied as Alzheimer's disease-related neurodegeneration (Blacker *et al.*, 1998; Bruunsgaard *et al.*, 2001), because some epidemiological studies have shown that anti-inflammatory drugs delayed onset of or slowed progression of Alzheimer's disease (Breitner, 1989; McGeer *et al.*, 1990; Breitner *et al.*, 1994; Breitner, 1996; Aisen, 1997).

Tumour necrosis factor (TNF) is one of the pro-inflammatory cytokines and might be involved in inflammatory changes surrounding senile plaques (Collins *et al.*, 2000). It has been confirmed that high levels of TNF together with amyloid β are toxic to neurons in old rats (Viel *et al.*, 2001). It should be noted that one of the TNF polymorphisms, TNFa2, which had been functionally associated with a high TNF production, was recently reported to genetically associate with Alzheimer's disease (Collins *et al.*, 2000). Therefore, since TNF acts via binding to TNF receptors I and II (TNFRI and TNFRII) (Al-Ansari *et al.*, 2000; Barton *et al.*, 2001), it is of interest to identify whether the TNFRII polymorphism is a risk factor for sporadic Alzheimer's disease.

The gene of TNFRII is mapped on chromosome 1p36. The TNFRII T/G polymorphism at position 196 in exon 6 (TNFRII 196R), which results in an amino acid substitution (methionine to arginine), was reported to be associated with familial rheumatoid arthritis (Barton *et al.*, 2001). In the present study, therefore, we investigated the polymorphism in Japanese sporadic Alzheimer's disease.

Materials and methods

All genomic DNA (gDNA) samples of sporadic Japanese Alzheimer's disease cases ($n = 243$, male: female = 106:137) were obtained from inpatients/outpatients of the hospitals where the authors worked. The mean ± standard deviation age of the Alzheimer's disease group (69.4 ± 9.9 years, range 38–90 years) was not significantly different from that of the control group

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Table 1 Genotype and allelic distribution of the tumour necrosis factor receptor II 196R (TNFRII 196R) polymorphism

	Genotype			Allele	
	T/T	G/T	G/G	T allele	G allele
Alzheimer's disease	133 (54.7%)	87 (35.8%)	23 (9.5%)	353 (72.6%)	133 (27.4%)
Control	56 (52.8%)	40 (37.7%)	10 (9.4%)	152 (71.7%)	60 (28.3%)

(70.3 ± 9.0 years, range 51–93 years). All Alzheimer's disease cases were diagnosed according to the National Institute for Neurological Disease and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. None had a familial history of Alzheimer's disease. The control cases ($n = 106$, male:female = 54:52) were obtained from healthy volunteers with no history of dementia or other neuropsychiatric diseases. The purpose and significance of this study were explained in detail to each patient and his/her family, and all subjects provided their informed consent. Study protocol was approved by the Ethics committee of Juntendo University School of Medicine.

All gDNA were extracted from white blood cells using a standard method with the Nucleon II kit (Scotlab, UK). The TNFRII 196R genotype was studied by the polymerase chain reaction-restriction fragment length polymorphism analysis method as previously reported (Al-Ansari *et al.*, 2000). The genotypes and allelic distribution between the Alzheimer's disease and control groups were compared using chi-square tests.

Results

The distribution of the TNFRII 196R polymorphism is presented in Table 1. No significant difference was observed in the TNFRII 196R genotype frequencies between the Alzheimer's disease and control groups ($\chi^2 = 0.13$, degrees of freedom = 2, $P = 0.94$). The frequency of the TNFRII 196R G allele was 27.7% in total subjects. There was no significant difference in the frequency of the TNFRII 196R G allele between the Alzheimer's disease group and the control group ($\chi^2 = 0.06$, degrees of freedom = 1, $P = 0.80$). The genotype distribution of the TNFRII 196R was expected under Hardy–Weinberg equilibrium in the Alzheimer's disease and control groups.

Discussion

The present study clearly shows that the allelic and genotype frequencies of the TNFRII gene in Japanese healthy controls are similar to those in a Caucasian population (Al-Ansari *et al.*, 2000; Barton *et al.*, 2001). The results suggest that the inter-ethnic differences in this polymorphism might be few, if any. It was also disclosed that Japanese sporadic Alzheimer's disease cases are unlikely to be genetically associated with the TNFRII 196R G allele.

There have been several studies that have focused on the association between TNF and the pathophysiology of Alzheimer's disease. It is of interest that positive studies on the association between TNF and Alzheimer's disease (Collins *et al.*, 2000; Viel *et al.*, 2001) have been reported, but no difference of serum TNF between Alzheimer's disease and control groups has been reported (Solerte *et al.*, 2000). Another study has indicated that increased intrathecal production of TNF in AD is preferentially controlled by environmental factors (Tarkowski *et al.*, 2000). Although there might be a complex interaction between TNF and the TNFR affecting the inflammatory process of Alzheimer's disease, our results failed to demonstrate a genetic association between the receptor-site polymorphism and Japanese sporadic Alzheimer's disease. It is still interesting to study the interaction among the genotypes and the several phenotypes (serum, cerebrospinal fluid and brain tissue) of the TNF gene.

Inflammation should modulate the risk for Alzheimer's disease with the abnormality of cytokines (Singh, 1994; Rogers *et al.*, 1996; Singh and Guthikonda, 1997). Further genetic studies of cytokines will be needed to clarify the pathophysiology of Alzheimer's disease.

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Final Program & Abstracts

Methods: All subjects and their accompanying caregivers, who came to our geriatric psychiatric clinic, were assessed using the GDS and SPMSQ (Short Portable Mental Status Questionnaire). Caregivers completed the GDS adapted for evaluation of patients, i.e., one in which the questions and answers are in the third person. Somatic complaints, number of physical illnesses, and activities of daily living (PADL and IADL) were assessed in both the patient and caregiver group following procedures performed as GDS administration. In patients with GDS score ≥(self-assessment) and SPMSQ corresponding to normal function (both patient and caregiver), interviews were applied to establish diagnosis according to DSM IV, and severity of depressive symptoms was assessed using the Hamilton Depression Rating Scale (HDRS).X2 test was used to analyze categorical variables, and one-way ANOVA was used for continuous variables. Regression analysis was conducted to assess the contribution of the main variables to the prediction of HDRS and GDS scores. Agreement between item scores was determined by). X2 test and λ value. $P < 0.05$ (two-tailed) was chosen for statistical significance.

Results: Women who were older and had more physical illnesses and disabilities in ADL were thought to be more depressed on the basis of GDS caregiver ratings. HDRS severity correlated with both patients' and caregivers' GDS ratings, patients' IADL ratings, and caregivers' ratings of the number of somatic complaints. The patients' self-assessment and caregivers' assessment of 19 of the GDS items (item 1- 4, 7-8, 10, 11, 14-18, 22, 25-28, and 30) were significantly correlated, and 9 of these showed the highest degree of agreement (1, 7-8, 10, 15, 17, 22, and 26- 27). The resulting GDS (administered by the caregiver to the patient) alpha values were 0.88 for the 30-item, 0.82 for the 19-item, and 0.79 for the 9-item GDS questionnaire. Among of GDS caregiver-based ratings, 5 items could be the major determinants of the total scores obtained by patient self-assessment (1, 13, 16, and 22-23; $R2=0.419$, $F=15.588$, $P < 0.0005$).

Conclusion: The results of this study suggest that the caregivers of younger elderly men with fewer physical illnesses and greater independent activity consider them to be less depressed. Use of a brief screening instrument modified from the GDS can improve caregiver case identification and lead to appropriate management of geriatric depression.

P063 Relationships between Depression and Dietary Variety in Elderly People Living in a Community

K. Yamashita, Shimane Nursing College, *Japan*; *Y. Sakamura*, Hiroshima International University, *Japan*.

Objective: To investigate and measure the relationship between clinical depression and dietary variety in a population of elderly people (65 years or older) living in a rural town.

Materials and Methods: The study used survey methods to question every resident (n = 609, 295 male, mean age 73.0 years old, 314 female, mean age 73.7 years old) 65 years or older living in a rural town in Shimane prefecture. The Zung Self-Rating Depression Scale (SDS) was used to assess the depression. For assessing dietary variety, we used the dietary variety score (DVS), counting the number of 10 food groups consumed daily, indicated on food frequency questionnaires: meat, fish and shellfish, eggs, milk, soybean products, potatoes, green yellow vegetables, fruits, seaweed, fat and oil. The DVS ranged from 0 to 10 with higher scores indicating a broader dietary variety.

Results: The average DVS was 3.2 points for men and 3.5 points for women. The SDS however, was significantly higher for women than for men ($p<0.0005$). In subjects with a depression (high SDS score) 20.5% had low DVS scores and 11.6% had high DVS scores. In addition to these findings, there were significant differences in the food group distribution (fish and shellfish, eggs, milk, green yellow vegetables and fruits) between the depression group and the normal group.

Conclusion: A higher dietary variety is associated with a reduced risk of depression in community elderly.

P064 Prevalence and Correlates of Depressive Disorders among the Elderly in Korea

S.U. Kim, psychiatry, Eulji University School of Medicine, *Republic of Korea*; ***G.H. Suh***, Hallym University College of Medicine, *Republic of Korea*; ***J.P. Hong***, Ulsan University College of Medicine, *Republic of Korea*; ***T. Suh***, Korea Institute of Health and Social Affairs, *Republic of Korea*; ***B.J. Hahm***, Seoul National University College of Medicine, *Republic of Korea*; ***J.Y. Lee***, Seoul National University College of Medicine, *Republic of Korea*; ***E.J. Joo***, Eulji University School of Medicine, *Republic of Korea*; ***M.J. Cho***, Seoul National University College of Medicine, *Republic of Korea*.

Objective: There is no community study generate the rate of depressive disorder in the Korean elderly by clinical diagnosis through direct interview by psychiatrists.

Design: A two-phase community survey

Materials and Methods: A multi-stage, cluster sampling method was used for the selection of subjects from one rural and one urban community, respectively. A two-phase community survey, screening and diagnostic interview, was conducted.

Results: 1,760 elderly people aged 65 and over completed the interview. The current prevalence rates for major depressive disorder and other depressive disorder were found to be 6.7% (95% CI: 5.5 - 7.3) and 3.1% (95% CI: 2.3 - 3.5), respectively. Four statistically significant correlates associated with depressive disorder were female gender, low economic status, low family APGAR scores, and CAGE score greater than or equal to 2.

Conclusion: Depressive disorder in the Korean elderly was as common as Western European countries and the prevalence rates were much higher than those reported in a number of earlier East Asian studies except for those performed in Taiwan. The authors suggest that the rapid corruption of traditional Confucian ideology and rapid growth of the elderly population influenced on the relatively high prevalence rates.

P065 Prevalence of Depression in Singapore - Results ofthe National Mental Health Survey of the Elderly in Singapore

P.C. Chiam, Department of Geriatric Psychiatry, Institute of Mental Health, *Singapore*; ***T.P. Ng***, Department of Psychological Medicine, University of Singapore, *Singapore*; ***P.S. Ong***, Department of Geriatric Psychiatry, Institute of Mental Health, *Singapore*; ***L.L. Tan***, Department of Geriatric Psychiatry, Institute of Mental Health, *Singapore*; ***A. Ang***, Department of Geriatric Psychiatry, Institute of Mental Health, *Singapore*; ***L.Y. Kong***, Department of Medical Social Work, Institute of Mental Health, *Singapore*; ***E.H. Kua***, Department of Psychological Medicine, National University of Singapore, *Singapore*.

特集2 痴呆性高齢者への薬物療法
—行動障害への薬物を理解する！—

抗痴呆薬の効果と今後の展開

群馬県こころの健康センター 所長 宮永和夫

はじめに

抗痴呆薬は，痴呆の中核症状（記憶，見当識，判断力の障害）を改善するか，進行を遅延する薬物と定義できる。

今までの治療の流れを見ると，脳血流改善薬ないし脳代謝改善薬の一群を抗痴呆薬の第一世代と考えることができるが，厚生労働省による再評価の結果，これらの大部分が中核症状に効果を認めないとして中止になってしまった。そのため，一時期抗痴呆薬の概念は消失したように思われたが，タクリンの登場で再度日の目を見ることになった。現在は，この流れを受けてコリン作動薬やモノアミン作動薬などの神経伝達物質を調整する薬物が主流になっているが，これは第二世代と位置づけることができよう。さらに，現在開発中の薬物は，アルツハイマー型痴呆（AD）の病態に直結するアミロイドβ蛋白（Aβ）の蓄積防止や神経成長因子などを標的とするものであり，第三世代として扱うことができると思われる。

現在の日本では，使用可能でかつ有効な抗痴呆薬はドネペジルに限られるため，最初にこの薬物について述べた後，今後登場する予定の第二世代と第三世代の薬物の話をしたい。

1．現在使用可能な抗痴呆薬

ドネペジル（アリセプト）

日本の製薬メーカーによって作られた薬剤※1であったが，アメリカ，ヨーロッパの販売が先となり，日本では1999（平成11）年に承認された。

薬理作用は，中枢神経系のアセチルコリンエステラーゼ（AChE）※2の働きを阻害する作用が中心で，末梢性コリン系への作用は軽微であるため，副作用が少ない。また，作用時間（半減期は89時間±36時間）が長いため，1日1回の投与で十分である。

ドネペジルの有効率は2分の1から3分の2といわれるが，投与前には効果の有無

※1 薬剤：承認された薬物を意味する。
※2 AChE：神経シナプス間隙に存在する，アセチルコリン分解酵素

は予測できず，実際の投与後の変化から判断しなければならない。また有効な場合でも，改善した知的機能レベルは再度低下し，個人差は大きいが，平均2年程度で投与時の知的機能レベルにまで戻るといわれている。

副作用の頻度は，1,291例中142例で約11％と，プラセボ7％と比較して多くみられるため，投与ができない例もある（副作用がひどい場合は，減量して1日3mgにとどめたり，隔日で1.5～2.5mgを投与したりすることもある）。主な副作用は，消化器症状（食欲低下，悪心，嘔吐，下痢，腹痛），精神症状（不眠，興奮，攻撃性，せん妄），自律神経症状（頭痛，めまい，動悸，血圧変動）などで，投与開始から1週間以内に見られる。ただし，いずれの症状もブチルスコポラミンで改善することから，末梢のAChE阻害による薬理作用と考えられる。

2．抗痴呆薬の今後の展開

1）AChE阻害薬（第二世代）

（1）ガランタミン（レミニール）

薬理作用は，AChE阻害と併せてニコチン性アセチルコリン（nACh）受容体結合能を増加させる作用を持つ。現在，アメリカ，ヨーロッパで承認されているが，日本ではヤンセンが治験を行っており，早ければ2年後に承認される予定である。ドネペジルより有効率が高いといわれている。

（2）リバスチグミン（エクセロン）

薬理作用は，AChE阻害のみである。アメリカ，ヨーロッパで承認されている。日本でもノバルティスが治験中である。

（3）タクリン（コグネックス）

AChE阻害薬として最初に承認され，現在，アメリカ，ヨーロッパで使用されている。肝障害などの副作用が強く，日本では今後とも承認される見通しはない。

（4）今後承認される可能性のある，AChE阻害作用を持つ薬物

①ヒュペルジンA

コケ植物（ヒカゲノカズラ）の抽出液。AChE阻害作用がある。現在でも通信販売で入手可能である。

②ルバミン酸誘導体（フェネチルアミン，ヒドロキシアミノインダン）

AChE阻害作用とMAO阻害作用がある。Herzigらが報告したが，現在治験が実施されているかは不明である。

③TAK-147（ザナペジル）

AChE阻害作用を持つ。現在，フェーズⅢにある。

（5）すでに発売されているが，抗痴呆薬の適応がない薬物

①セビメリン（エポザック）

口腔乾燥改善薬として使用されている。ムスカリン性アセチルコリン受容体（M3）に高い親和性があり，イノシトールリン酸の代謝回転を促進する作用を持つ。

②セレギリン（エフピー）

抗パーキンソン剤として発売されている。MAO-B阻害作用が中心だが，抗酸化作用およびAChE阻害作用も持っている。

③銀杏葉抽出液（EGb761）

イチョウの緑葉と小枝のエキスである。健康食品としても入手可能だが，自分でも簡単に作ることができる。抗酸化作用とアセチルコリン系の賦活作用がある。

④当帰芍薬散

漢方薬として承認されている。エストロゲンの分泌亢進，nAChの増加および抗酸化作用※3がある。

2）グルタミンレセプター阻害薬（第二世代）

グルタミン酸受容体は，グルタミンレセプター（NMDA）受容体と，非NMDA受容体（カイニン酸〈KA〉受容体とグルタミンに反応するキスカル酸受容体〈AMPA〉）に区分され，さらに，NMDA受容体はグリシン結合部位とグルタミン酸結合部位を持っている。

（1）メマンチン（ナメンダ）

NMDA受容体の拮抗薬としてアメリカで承認され，アリセプトと併用してアルツハイマー型痴呆に使用できるようになった。現在でも通信販売で入手可能である。

（2）サイクロセリン（サイクロセリン）

NMDA受容体グリシン結合部位作動薬。すでに抗結核薬として日本でも発売されている。頭部外傷後遺症の患者や動物（ネズミ）実験では記憶障害に有効との報告があるが，抗痴呆薬としての承認はされていない。

3）抗炎症薬（第三世代に準じる薬物）

抗炎症薬によるアルツハイマー型痴呆の進行防止作用は，COX-2阻害と考えられている。これは，ミクログリアの活性を抑制し，フリーラジカルやサイトカインの放出を抑えるものである（図1）。

さらに，抗炎症薬にはAβx-42産生を直接抑制する作用が見つかり，γ-セクレターゼへの作用と考えられている。なお，この作用が見られる抗炎症薬には，イブプロフェン（イブプロフェン），インドメタシン（インダシン），フルルビプロフェン（ロピオン），スリンダク（クリノリル）などが報告されている。しかし，Aβ産生の抑制はない抗炎症薬も存在する。具体的には，ジクロフェナク（ソファリン，ボルタレン），ナプロキセン（ナイキサン），セレコキシブ（未発売），メロキシカム（モービック）などであるが，前者との違いは不明である。

※3　抗酸化作用：SOD活性の亢進，8-ヒドロキシ-2'-デオキシグアノシン：8-OHdG生成を抑制する作用。

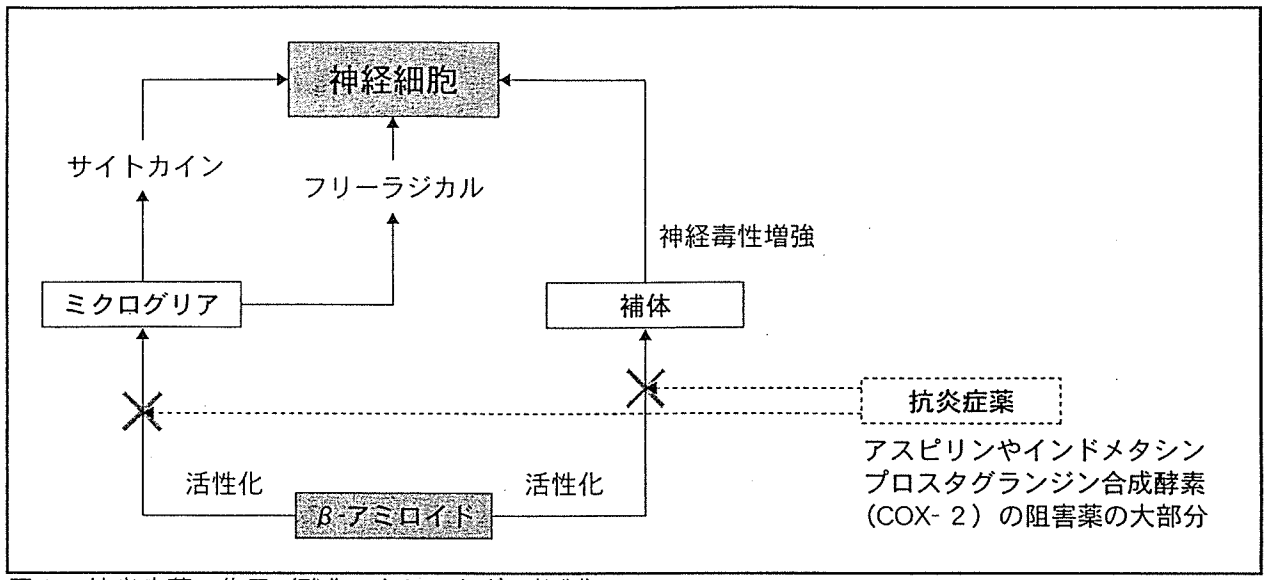

図1　抗炎症薬の作用（酸化ストレスなどの抑制）

4）コレステロール降下薬（第三世代に準じる薬物）

今まで，高コレステロール血症とアルツハイマー型痴呆に有意の相関があること，アポ蛋白（APO）E4が高コレステロール血症を生じることなどの報告はあった。その後，スタチンによるアルツハイマー病の発症率の低下の報告があり，以下のような機序が提案された。

すなわち，神経細胞膜には，グリコスフィンゴリピドやコレステロールの部分に対応した，界面活性剤に対する不溶性の膜部分があり，これはLipid raftsと呼ばれている。この部分には，アミロイド前駆体蛋白質（APP），Aβ，γ-セクレターゼ，β-セクレターゼ（BACE1）が存在し，Aββ分裂が起こるといわれる（ちなみに，α-セクレターゼはこの部分には存在しない）。そのため，総コレステロールを低下させると，コレステロールを含むLipid raftsの大きさが減少し，α-セクレターゼの活性を増強し，水溶性のα-APPを増加させ，逆に不溶性のβ-APP産生量を低下させることになる。

ただし，スタチンのなかで，ロバスタチン，プラバスタチン（メバロチン）にはアルツハイマー型痴呆発症抑制効果があるが，シンバスタチン（リポバス）には抑制作用がない。この機序の違いについては不明である。

5）女性ホルモン（エストロゲン：第三世代に準じる薬物）

エストロゲンがアルツハイマー型痴呆発症を抑制すると報告されているが，これはエストロゲンのα-セクレターゼ活性の亢進と抗酸化作用に基づく。閉経直後からのエ

ストロゲンの早期投与はアルツハイマー型痴呆の発症を減少させるが，高齢になってからの投与は効果が少ないといわれる。これは，エストロゲンに対する反応性の減弱が原因といわれる。ただし，エストロゲンによる治療トライアルは，乳がん発症率が高くなるという理由で，アメリカにおいては中止された。現在日本では，合成の17α-エストラジオール派生物（J-861）の治験が行われている。

6）ワクチン療法（第三世代）

研究の発端は，変異型ヒトアミロイド前駆体蛋白質（APP）発現マウスにAβ-42の注射で抗Aβ-42抗体作成を試みていたところ，アミロイドの新規沈着防止と，沈着したアミロイドの除去が認められたことに始まる。

マウスへの有効性が確認された後，ヒトに対して合成Aβ-42（AN-1792/Betabloc）による臨床治験が開始されたが，2002（平成14）年フェーズⅡ段階で脳炎と髄膜炎患者が15名ほど発生したため，中止になった。しかし，脳炎患者の剖検例でアミロイド沈着の防止が確認されたことなどもあり，現在は接種方法や抗原が変更されて，新たな臨床治験が開始されている。具体的には，Aβ-42のN（1－11）部位のペプチドによるワクチン療法（注射，経口）であるが，今後は作成された抗体の投与（受動免疫）も考えられている。

3．痴呆治療および予防のための戦略

65歳以上に限れば，痴呆と診断される疾患の種類は大きく2つに分けられる。1つは血管の変化に基づくもの，もう1つは異常蛋白の蓄積に基づくものである。前者は，脳血管性痴呆（VD）としてまとめられ，後者はアルツハイマー型痴呆や前頭側頭型痴呆（FTD）に代表される変性疾患にまとめられる。なお，有病率でいえば，脳血管性痴呆3％，アルツハイマー型痴呆（Aβとタウの蓄積）3％，前頭側頭型痴呆（タウの蓄積）1％，レビー小体病（α-シヌクレインの蓄積）0.1％である。ここでは，これらのうち脳血管性痴呆とアルツハイマー型痴呆について述べる。

1）血管性痴呆の治療と予防

脳血管性痴呆の発生原因は，脳血管障害（脳梗塞や脳出血）によって血流が停止し，神経細胞が酸素欠乏や栄養不足に陥って死滅することにある。脳血管性痴呆は，障害される血管の部位や分布により種々に分類されるが，脳血管の障害に統一される。脳血管性痴呆の治療は，脳梗塞や脳出血の再発を防止することにある。これらに有効なものは，血管拡張を目的とした薬剤（脳血管拡張薬），血流の凝固を阻害する薬剤（抗凝固薬）および血管の狭窄を防止する

薬剤（コレステロール降下薬）である。

すなわち，予防ないし治療は戦略１（図２）を用いることになるが，脳血管障害の原因となる各種の生活習慣病（高血圧，糖尿病，高脂血症，肥満）の治療や予防こそ，本来は脳血管性痴呆の予防に最も重要な因子である。

２）アルツハイマー型痴呆の治療と予防

アルツハイマー型痴呆の原因は，β-アミロイド蛋白による細胞毒性である。β-アミロイドの毒性を軽減するためには，活性酸素やインターロイキンを放出するミクログリアの反応性を低下させたり，補体の活性を低下させたりするような，抗炎症薬の投与がある（図１）。

また，根本的なアルツハイマー型痴呆の予防ないし治療は，β-アミロイドの蓄積の阻止と蓄積したものの除去にある。蓄積の阻止は，α-セクレターゼの活性を増強して可溶性βアミロイドを増加すること（M１，エストロゲンなど）と，β-セクレターゼの活性を減少させて，不溶性β-アミロイドの産生を低下すること（セクレターゼ阻害薬など）にある。また，蓄積物の除去には，β-アミロイドの分解と，ミクログリアによる呑食能の亢進，すなわちワクチン療法が有効であろう（図３）。

３）補助療法

第三世代ないし第三世代に準じる治療が可能になるまでの治療として，また当面補助的に用いて有用と思われる療法について述べる。これは，現在の治療法のアプローチを逆にしたもので，筆者が考えた視点である。

（１）神経細胞の機能保持

アルツハイマー病などの異常蛋白蓄積病について，蓄積した異常蛋白の面からでなく，それに曝される神経細胞の面からみる

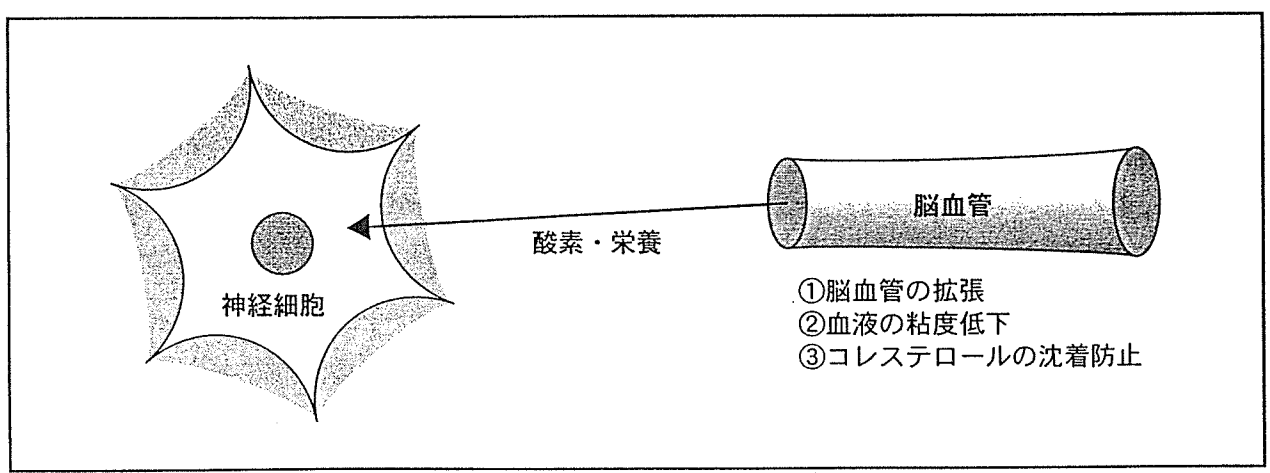

図２　戦略１：脳循環を正常に保ち，神経細胞への酸素と栄養の供給を図る

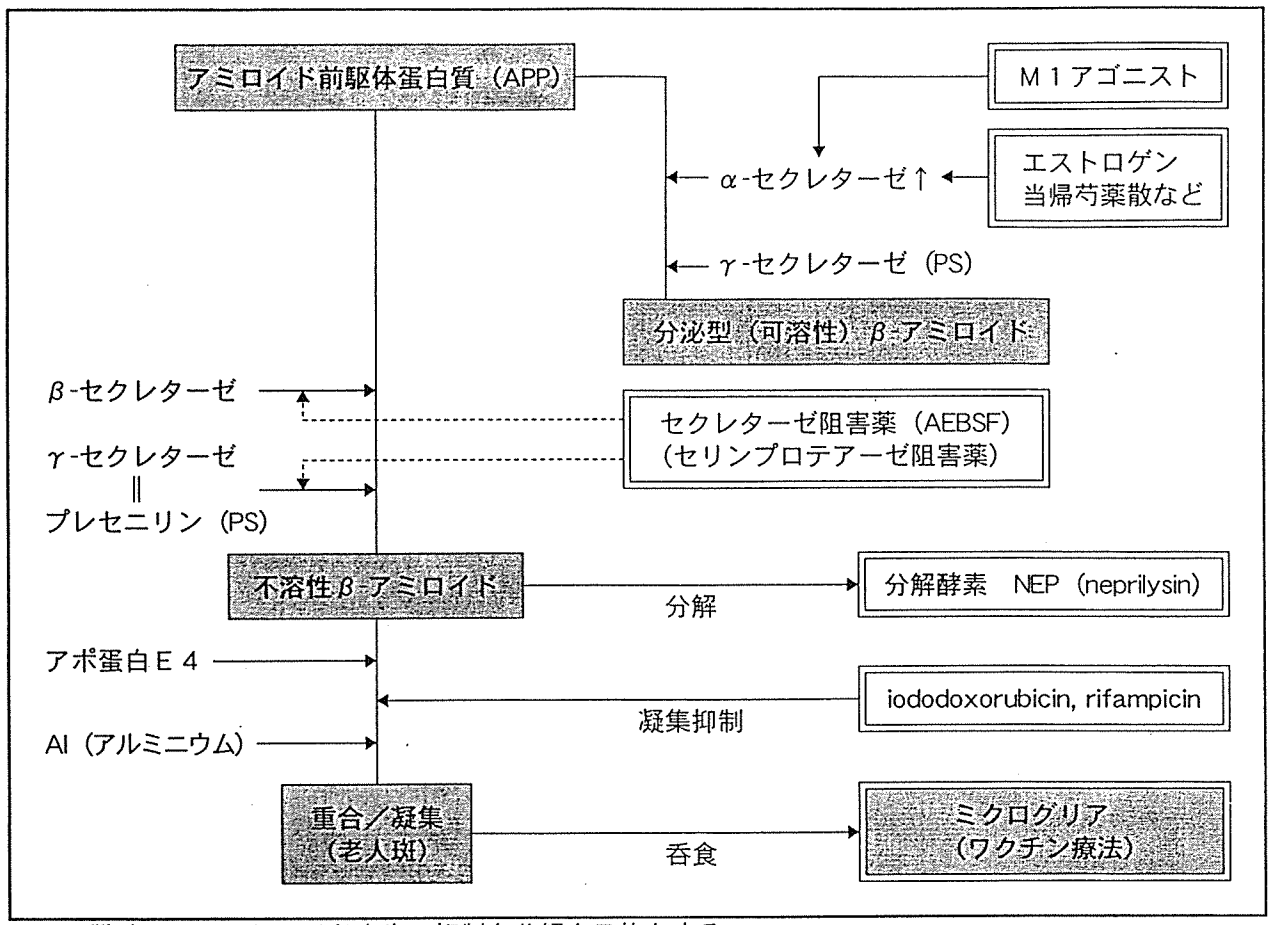

図３　戦略２：βアミロイド産生の抑制と分解を目的とする

と，別の戦略が考えられる。すなわち，神経細胞の変性や消失は，すでに述べたようにβ-アミロイドによるミクログリアの活性化によるフリーラジカルやインターロイキンなどのサイトカインの発生および凝集した老人斑以前のアミロスフェロイド（真球状物質Aβ-40，42）の細胞膜への付着が原因とされる。そのため，β-アミロイド除去を第一義とすべきだが，細胞膜の強化により毒性に対抗する形で，神経細胞の機能保持を図ることも可能ではないかと考えられる（図４）。

①膜成分の必須アミノ酸と
　必須脂肪酸の摂取

例えば，神経細胞膜上の脂質の25～30％を占めるDHA（Docosahexaeic acid）を含むｎ３系多価不飽和脂肪酸を適度に摂取し，膜の機能改善を目指す方法である。

②膜の酸化防止

ミクログリアの活性を抑えるというより，抗酸化物質（ビタミンA，C，E，ポリフェノール，フラボノイド）摂取により，ミクログリアから発生したフリーラジカルなどを除去して，細胞膜を保護する方法である。