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男性の全身性エリテマトーデス：臨床症状における性差

The Feature of the Male Patients of Systemic Lupus
Erythematosus: Sex Difference in a Clinical Symptom

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はじめに

　全身性エリテマトーデス（Systemic Lupus Erythematosus：SLE）は自己免疫疾患の代表であり，1972年に特定疾患治療研究事業の対象疾患として医療費公費負担制度が適用されて以来，病態や治療法，受給者数などが明らかにされてきた。2003年度の医療受給者数は地域保健老人保健事業報告[1]によれば5万1,865人（男性5,261人，女性4万6,604人：男性／女性＝0.11）と潰瘍性大腸炎，パーキンソン病関連疾患に次いで多く，中年女性に好発する疾患としてよく知られている。SLEの病因としては，遺伝的要因，リンパ球のアポトーシスの障害，性ホルモンなどが挙げられているが，いまだに明らかになっていない。このように女性に多い疾患であると認識されているSLEにおいても，女性受給者に対する男性受給者の比が年度を追うごとに徐々に高くなり，男性SLEの医療受給者が増加していることがこれまで報告されてきた[2,3]。男性受給者数増加の原因として，男性における有病率，罹患率の上昇の可能性があるが，医療受給者数の変化の理由を検討するためには，社会保障制度の変化や特定疾患医療費公費負担制度に関する知識の普及など，病気であってもこれまで受給しなかった者が受給するようになったこと，また感度の高い検査法の開発や普及，診断基準の整備など，これまで診断されなかった者が診断されるようになったことなど，広い意味での社会的な要因によるものについての配慮が必要である。男性SLE受給者数増加について原因解明が待たれるところである。

臨床症状，検査所見による診断基準

　SLEの診断については米国リウマチ協会の分類基準（表1）が標準的に用いられており，わが国でも一般的

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に使用されている。臨床経過中，経時的あるいは同時に11項目中4項目以上を満たす場合，SLEと診断可能であるとされており，病初期にはこの分類基準11項目中4項目を同時に満たすことは多くないことも臨床的にはよく知られている。また，発病初期に重篤な症状を呈する場合もあるため，蝶型紅斑，円板状紅斑，日光過敏症などの特異的な症状や，抗二本鎖DNA（ds-DNA）抗体，抗Sm抗体などの特異的抗体陽性を1つ以上呈する場合には，分類基準にはない腎生検や皮膚生検所見を参考に総合的に判断するのが一般的である[4]。

さて，特定疾患治療研究事業対象疾患については2003年度より，特定疾患の医療受給の申請時に提出される臨床調査個人票が電子入力されるようになった。臨床調査個人票は，受給者の性，年齢，推定発病年齢，受療状況，ADL，要介護度，身体障害者手帳交付の有無のほかに，各疾患ごとに臨床症状，検査所見，治療方法，合併症等の情報が含まれている。これまでは，これらの情報が，系統的に集計解析されることがなかったが，都道府県によって電子入力されることになったため，これが可能になった。2003年度に電子入力された臨床調査個人票は，受給者全体の50%弱であるが，入力状況に性，年齢別に大きな偏りが見られないため，疾患ごとの臨床症状についての検討が可能である[5]。そこでこのデータを用いて，わが国のSLEの受給者（男性2,297人，女性2万1,009人）の臨床症状を明らかにする。特に発病後1年未満の受給者の臨床症状の性差に注目し，男性SLEの初診時の臨床症状の特徴について概説する。

SLEの医療受給者の性差

受給者数の性差

医療受給者数は，男性では30歳代と50歳代，女性では40～50歳代に多く（図1），発病から現在までの期間は男性9.5年，女性13.2年と，女性の方が長い。最近1年以内に発病した受給者に限ってみると，年齢分布は男女ともに2峰性を示し，女性では30歳代，50歳代，男性では25～34歳と65～74歳で多くなっている（図2）。

表1　SLE分類のための1997年改定基準（米国リウマチ学会）

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1）顔面（頬部）紅斑
2）円板状皮疹（ディスコイド診）
3）光線過敏症
4）口腔潰瘍（無痛性で口腔あるいは鼻咽喉に出現）
5）非びらん性関節炎（2関節以上）
6）漿膜炎
        a）胸膜炎　または
        b）心膜炎
7）腎障害
        a）0.5g/day以上または＋＋＋以上の持続性
          蛋白尿　または
        b）細胞性円柱
8）神経障害
        a）痙攣　または
        b）精神障害
9）血液異常
        a）溶血性貧血
        b）白血球減少症（＜4,000／μL）
        c）リンパ球減少症（＜1,500／μL）または
        d）血小板減少症（＜100,000／μL）
10）免疫異常
        a）抗二本鎖DNA抗体陽性
        b）抗Sm抗体陽性　または
        c）抗リン脂質抗体陽性
          ①IgGまたはIgM抗カルジオリピン抗体の
            異常値
          ②ループス抗凝固因子陽性
          ③梅毒血清反応生物学的偽陽性
            のいずれかによる
11）抗核抗体陽性
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臨床経過中，経時的あるいは同時に上記11項目中4項目以上を満たす場合，全身性エリテマトーデスと診断可能である。

臨床症状の性差

女性では，顔面紅斑，光線過敏症，血液学的異常，関節炎，免疫学的異常を持つ者が多く，それに対して男性では円板状皮疹，血小板減少が多い。年齢が高くなると所見を持つ者が減るのは，顔面紅斑，血液学的異常，免疫学的異常であり，逆に年齢とともに増えるのは，関節炎，漿膜炎である。円板状皮疹を持つ者の割合は，女性では年齢が高くなると低下するが，男性では10歳未満と50歳代で多くなっており，性差がみられる（図3）。

発病初期の臨床症状の性差

発病後1年未満の受給者の臨床症状をみると，顔面紅斑，光線過敏症，口腔内潰瘍，関節炎を持つ者の割合は，男性より女性で有意に高くなっており，円板状皮疹，漿膜炎，腎病変，血小板減少は有意に男性で高い
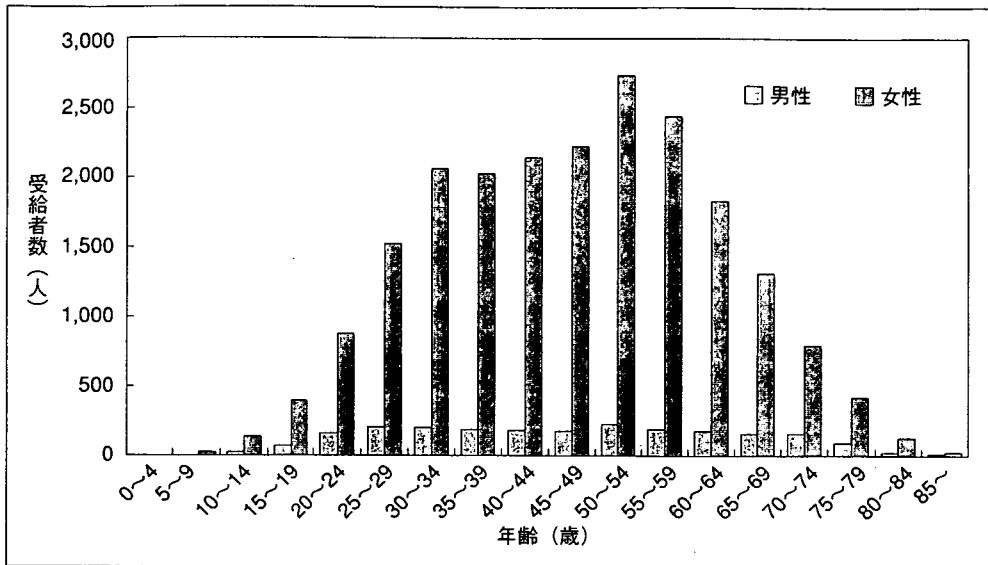
図1　性別年齢階級別受給者数
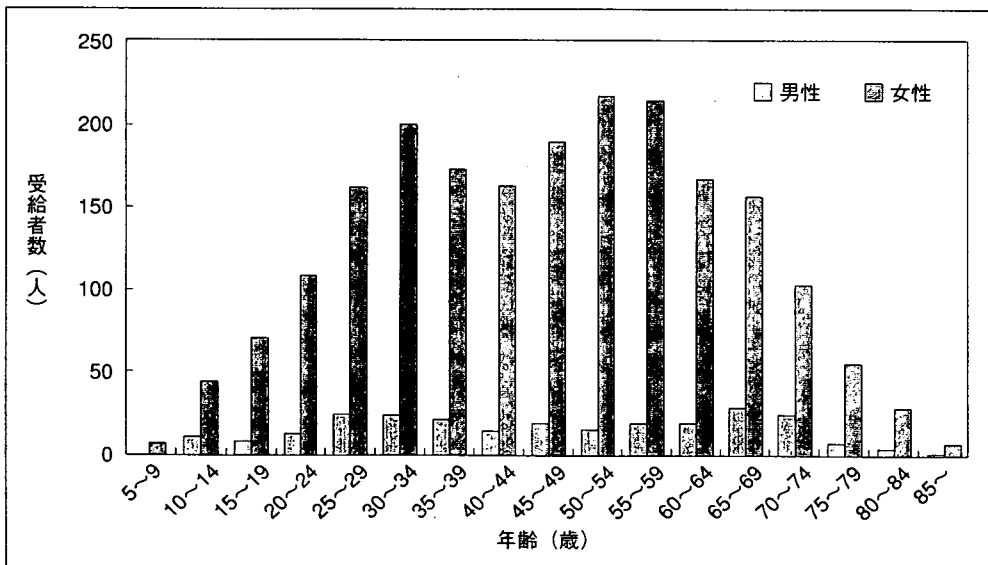
図2　性別年齢階級別発病後1年未満の受給者数

（図4）。女性に多いのは，従来SLEに特徴的とされている所見であり，男性で多いのは，SLEに特異的ではない所見であることが認められる。

まとめ

　SLEは，性比がもともと低く，女性に多い疾患としてよく知られており，これまで男性に着目した研究はあまりみられない。SLEのように皮膚症状など特異的な症状がよく知られている疾患では，より典型的，特異的な症状を有する場合には診断されやすく，そうでない場合には，診断されにくくなる。また，SLEは女性に多いことがよく知られている疾患であり，女性では医師がSLEを強く疑って詳細な検査を実施し診断するが，男性では医師が疑わないためにSLEの診断を受けにくいことがあるのではないかと考えられる。

　臨床調査個人票の解析から，蝶型紅斑，光線過敏症，
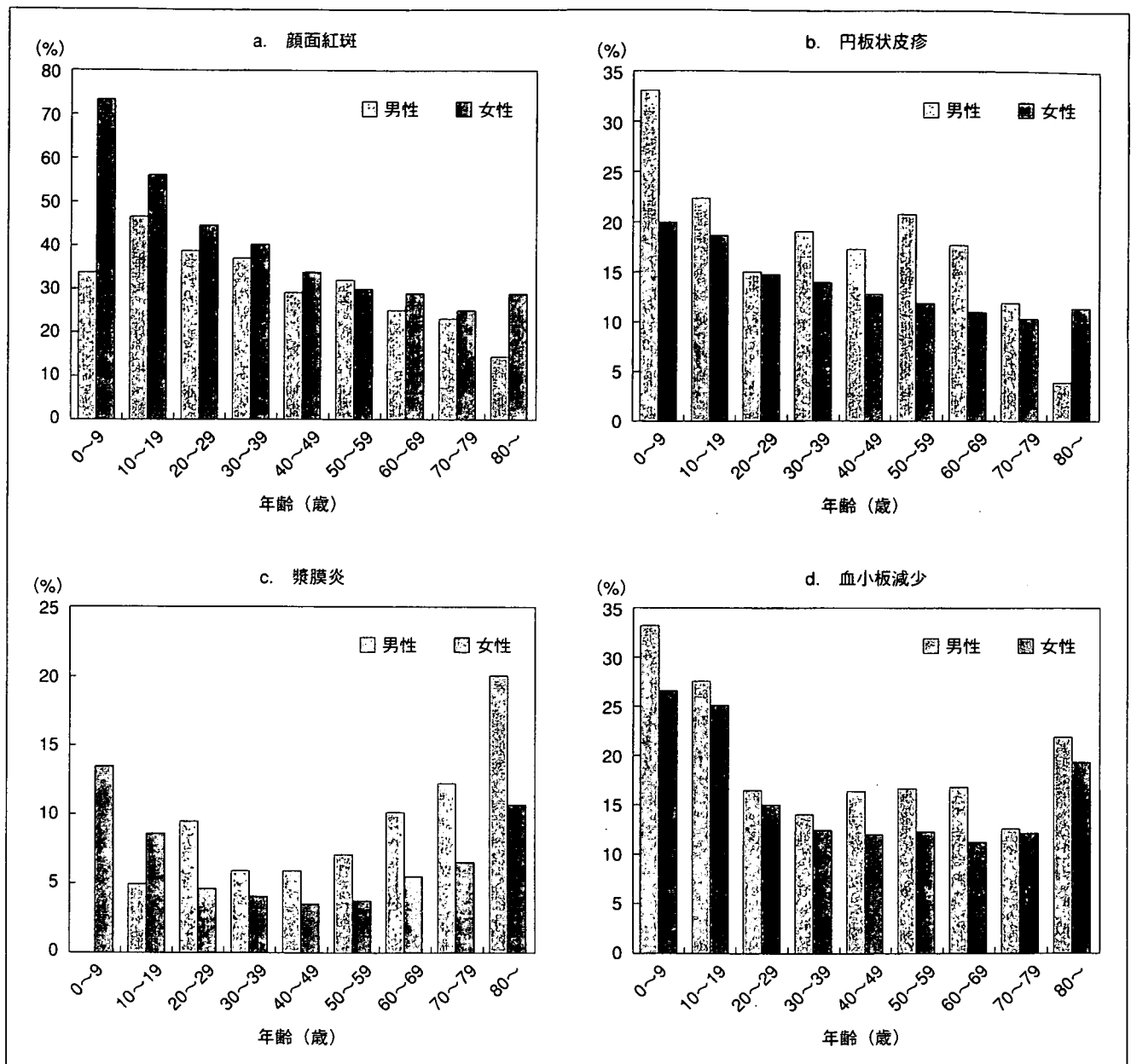
図3　性別年齢階級別症状・所見のある者の割合

口腔内潰瘍，関節炎の症状を持つ割合が女性で高く，男性では漿膜炎，腎病変といった内部臓器病変を持つ割合が高い結果が得られた。男性のSLEは，臨床症状が比較的非典型的な例が多いため臨床症状だけで診断されにくく，他の疾患の除外や詳細な検査をして初めて診断される者が多く含まれているのではないかと考えられた。最近の検査技術の進歩，普及，保険適応の拡大などによ

り，免疫検査等の特殊検査が比較的受けやすくなってきた。SLEについても特殊な検査を行うことによって臨床症状が非典型的な症例の診断がされやすくなった可能性があり，これら検査技術の進歩が男性SLE患者の増加に影響しているのではないかと考えられた。また，男性のSLEでは発病後1年未満の受給者の年齢が女性と比べて高く，発病後期間は男性で短いといった性差があること

(%)
80
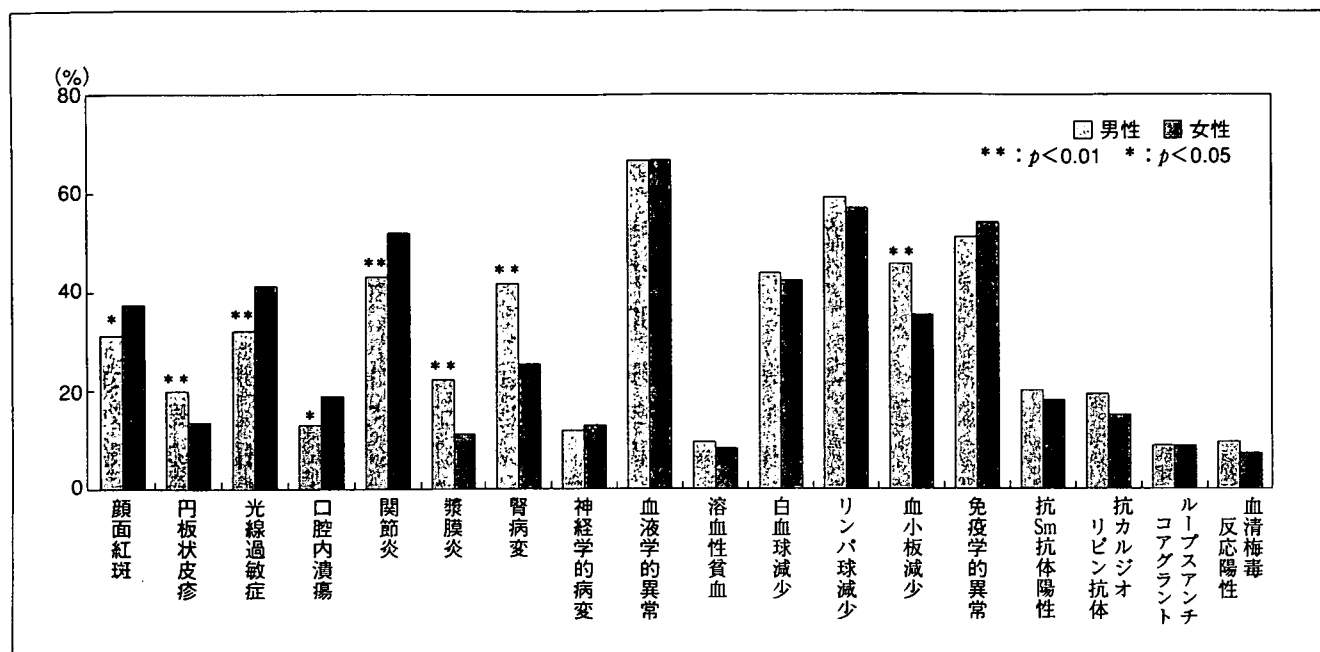
図4　性別臨床症状・所見のある者の割合

も明らかになった。

　SLEの臨床症状の性差を中心に男性SLEの特徴を概説した。男性では女性と比較して非特異的な症状を持つSLEが多いことを念頭に置いて日常の診療にあたる必要がある。また，男性SLEについては，機序，重症度，予後などまだ解明されていない点が多く，今後男性SLE患者の重症度，予後などの特徴を明らかにし，女性のSLEとの性差を明らかにするのと同時に，ホルモンや環境の変化，喫煙などの生活習慣との関連について明らかにする必要がある。SLEをひとまとめにすると全国の受給者数は5万人を越えるが，男性SLEは全国の受給者数が6,000人に満たない疾患であり，これらを検討するには，単一の医療機関で研究を進めることは難しいことが予想される。今後男性SLEの発病と関連する要因，特に環境要因についての多施設共同での疫学研究や基礎的研究が期待される。

　本稿は平成16年度厚生労働省科学研究費補助金難治性疾患

克服研究事業特定疾患の疫学に関する研究班による「電子入力された臨床調査個人票に基づく特定疾患治療研究医療受給者調査報告書」[5] の一部をまとめたものである。

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ORIGINAL ARTICLE

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Smoking, drinking, sleeping habits, and other lifestyle factors and the risk of systemic lupus erythematosus in Japanese females: findings from the KYSS study

Abstract Many risk factors have been proposed for systemic lupus erythematosus (SLE). However, there is little information about the relationship between lifestyles and SLE in Japan. Two case control studies were conducted in Kyushu, southern Japan, and in Hokkaido, northern Japan, to examine the relationship between lifestyles and development of SLE in females. The participants were 78 patients and 329 controls in Kyushu and 35 patients and 188 controls in Hokkaido. Smoking was associated with an increased risk of SLE after adjusting for age in both regions. However, in Hokkaido, this association between smoking and SLE did not reach statistical significance after adjusting for alcohol drinking. The present study suggests that smoking may increase the risk of SLE among Japanese females.

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Introduction

The Japanese Ministry of Health and Welfare designated systemic lupus erythematosus (SLE) as an intractable disease because there is no established way to cure or prevent it.[1] It is a serious, chronic inflammatory autoimmune disease that affects many tissues and organs.[2–4] The frequency is 8–10 per 100000 in the general Japanese population,[4] and females are 9–10 times more likely to suffer from SLE than males.[4] Serdula and Rhoads[5] reported that the age-adjusted prevalence of SLE was greater in Japanese (18.2 per 100000) than Caucasians (5.8 per 100000) in Hawaii, but

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they could find no reason for the high prevalence of SLE in Japanese ancestry.

The etiology of SLE has not yet been elucidated in detail, although genetic factors as well as environmental factors are thought to play a role in its development.[2-4] Several studies have demonstrated that smoking is a risk factor for SLE,[6-10] while it has been suggested that drinking alcohol decreases the risk.[6,7,10] Several investigators reported the following as risk factors for SLE among the Japanese population: smoking,[6] family histories of asthma[6] and collagen disease,[6] medical histories of operation[11] and blood transfusions,[11] working in a cold environment,[11] skin sensitivity to sunlight,[11] first menstrual period occurred at age 15 or later,[6] menstrual irregularity,[12] the frequent intake of meat;[12] while drinking alcohol[6] and milk[6] reduced the risk of SLE. However, there is little information about the relationship between lifestyles and SLE among the Japanese population.[6,11] In addition, these studies[6,11] showed only age- and sex-adjusted risk of SLE. Thus, the present study was conducted to investigate the influence of smoking, drinking, sleeping habits, and other lifestyle factors on the development of SLE in Japanese women.

Methods

Profile of Kyushu Sapporo SLE (KYSS) study

The Kyushu Sapporo SLE (KYSS) study was a case control study to evaluate risk factors for SLE. From 2002 to 2005, cases were recruited from outpatients of Kyushu University Hospital and Saga University Hospital and their collaborating hospitals in Kyushu while eligible cases were outpatients of Sapporo Medical University Hospital and its collaborating hospital in Hokkaido during the period from 2004 to 2005.

All patients fulfilled the American College of Rheumatology 1982 revised criteria for SLE.[13] Controls were recruited from nursing college students and care workers in nursing homes in Kyushu while in Hokkaido controls were recruited from participants of a health checkup in a local town.

Kyushu is located in the extreme southwestern edge of Japan and has a temperate climate (the world swimming championship series were held in Fukuoka). On the other hand, Hokkaido is the northernmost island of Japan and has a subarctic climate (the Winter Olympics were held in Sapporo).

A self-administered questionnaire was obtained from SLE patients and controls, along with written informed consent for cooperation in the study. A section of the participants also agreed to donate blood samples, which were stored until use for DNA extraction and genotyping of the candidate genes of SLE.

The present study was approved by the institutional review boards of Kyushu University Graduate School of Medical Sciences, Sapporo Medical University, and each of the other institutions involved.

Subjects and methods in this study

In Kyushu, 180 out of 332 SLE patients (54.2%) agreed to participate in this study while 71 out of 145 SLE patients (49.0%) agreed in Hokkaido. On the other hand, 340 volunteers (262 nursing college students and 78 care workers in nursing homes) agreed to participate in this study as controls in Kyushu while 188 female participants of a health checkup in a local town agreed to take part in this study as controls in Hokkaido. Thus, a self-administered questionnaire was obtained from 180 SLE patients and 340 controls and 71 SLE patients and 188 controls in Kyushu and Hokkaido, respectively. Cases were asked to complete the self-administered questionnaire about lifestyles before the diagnosis of SLE. From among the Kyushu subjects, 11 patients and 11 controls were excluded because they were males, and 91 patients treated for SLE for more than 10 years were excluded because we were afraid that they might have been confused about when various lifestyle habits were followed, i.e., before or after the diagnosis of SLE. Thus, in the Kyushu study cases were 78 female patients and controls were 329 female volunteers (251 nursing college students and 78 care workers in nursing homes). From among the Hokkaido subjects, 7 patients were excluded because they did not fit the criteria for the ages of participants of a health checkup (i.e., between 20 and 69 years), and 29 others, who had been treated for SLE for more than 10 years, were excluded in order not to include inaccurate information about lifestyles before the diagnosis of SLE. Thus, in Hokkaido cases were 35 female patients and controls were 188 female volunteers (participants of a health checkup in a local town).

Since the number of cases was small in the present study, we could not exclude the patients treated for SLE for 5–9 years in the first analysis. To obtain accurate information before the diagnosis of SLE, however, we conducted a case control study with the patients treated for SLE for less than 5 years as well. Thus, we used two types of case: (1) patients treated for SLE for less than 10 years and (2) patients treated for SLE for less than 5 years.

Tables 1 and 2 display the age distributions of the two patient groups (age at the diagnosis of SLE) and the control group (age at the time of the survey), respectively.

Statistical analysis

A conditional logistic model was applied to evaluate the odds ratios (ORs) and their 95% confidence intervals (CIs) for SLE. Because smoking is suggested as a risk factor for SLE[6-10] and drinking is suggested as a factor that decreases the risk of SLE,[6,7,10] we used age, smoking, and drinking as other risk factors for SLE to estimate adjusted ORs in relation to lifestyle factors. Age was treated as a continuous variable, and indicator variables were used for smoking and alcohol drinking. We treated current and former smokers as smoking positive while those who drank 1 day/week or more were defined as having a drinking habit. Ages at the time of the survey were used for controls whereas the ages

Table 1. Number of patients and controls in Kyushu, southern Japan, stratified by age

Age (years)	Case A ($n = 78$)	Case B ($n = 38$)	Control K ($n = 329$)
10–19	15 (19.2)	8 (21.1)	73 (22.2)
20–29	33 (42.3)	12 (31.6)	188 (57.1)
30–39	15 (19.2)	10 (26.3)	17 (5.2)
40–49	9 (11.5)	4 (10.5)	27 (8.2)
50–59	3 (3.9)	3 (7.9)	20 (6.1)
60–69	3 (3.9)	1 (2.6)	4 (1.2)
Mean (SD)	30 (12)	31 (13)	26 (11)

Values are expressed as number (%) or mean (SD)
Case A: patients treated for SLE for less than 10 years: Case B: patients treated for SLE for less than 5 years; Control K: nursing college students and care workers in nursing homes

Table 2. Number of patients and controls in Hokkaido, northern Japan, stratified by age

Age (years)	Case C ($n = 35$)	Case D ($n = 24$)	Control H ($n = 188$)
20–29	16 (45.7)	10 (41.7)	1 (0.5)
30–39	9 (25.7)	6 (25.0)	42 (22.3)
40–49	6 (17.1)	5 (20.8)	51 (27.1)
50–59	2 (5.7)	1 (4.2)	93 (49.5)
60–69	2 (5.7)	2 (8.3)	1 (0.5)
Mean (SD)	34 (12)	35 (13)	47 (8)

Values are expressed as number (%) or mean (SD)
Case C: patients treated for SLE for less than 10 years; Case D: patients treated for SLE for less than 5 years; Control H: participants of a health checkup in a local town

at diagnosis were used for the SLE patients. All statistical analyses were conducted by use of a statistical analysis system package (SAS Institute, Cary, NC, USA). In this paper, we present the results for Kyushu and Hokkaido separately because the characteristics of controls were different between the two regions. In addition to age-adjusted ORs, we also report ORs adjusted for age, smoking, and drinking.

Results

Analyses of the patients treated for SLE in Kyushu, southern Japan

Tables 3 and 4 summarize the ORs for SLE and 95% CIs in relation to lifestyle factors (i.e., sleeping habits, leisure-time physical exercise, and smoking and alcohol drinking) in Kyushu, southern Japan.

As shown in Table 3, the analyses of all the patients treated within 10 years (case A) revealed that sufficient sleep was associated with a 55% reduced risk of SLE even after adjusting for age, smoking and alcohol drinking (OR = 0.45, 95% CI = 0.22 – 0.88). In contrast, after adjusting for age, smoking and alcohol drinking, walking showed a two-fold increased risk (30 min/day or more vs less than 30 min/day: OR = 2.07, 95% CI = 1.14 – 3.76) while leisure-time physical exercise showed a 66% increased risk (OR = 1.66, 95% CI = 0.94 – 2.91), but its 95% CI was rather wide.

Smoking increased the risk of SLE (current and former smokers vs never smokers: OR = 1.94, 95% CI = 1.09 – 3.45) even after adjusting for age and alcohol drinking. Current

smokers (OR = 1.97, 95% CI = 1.06 – 3.65) as well as former smokers (OR = 1.85, 95% CI = 0.62 – 5.50) showed an increased age- and drinking-adjusted OR compared with never smokers, but the 95% CI for former smokers was rather wide. High-frequency drinkers (4–5 days/week or more vs less than 1 day/week: OR = 4.49, 95% CI = 1.43 – 14.08) showed an increased risk compared with never or seldom drinkers even after adjusting for age and smoking.

In Kyushu, current and former smokers were more likely to be drinkers than never smokers in both SLE patients (48.3% vs 12.5%, $P < 0.01$) and controls (26.6% vs 9.7%, $P < 0.01$) while current and former smokers were less likely to keep regular hours than never smokers only in SLE patients (41.4% vs 68.8%, $P = 0.02$) (not shown in the table).

In a mirror image, drinkers were more likely to have smoking experience than nondrinkers in both SLE patients (40.5% vs 16.7%, $P < 0.01$) and controls (70.0% vs 26.3%, $P < 0.01$). (not shown in the table). On the other hand, compared with nondrinkers, drinkers were less likely to practice leisure-time physical exercise 3 days/week or more in SLE patients (10.0% vs 43.9%, $P < 0.01$) but more likely to do so in controls (34.9% vs 20.4%, $P = 0.03$). Drinkers were more likely to feel psychological stress than nondrinkers only in controls (88.4% vs 73.9, $P = 0.04$).

The analyses of the patients treated for SLE for less than 5 years (case B) are presented in Table 4. After adjusting for age, smoking and drinking, sufficient sleep showed a decreased OR (OR = 0.47, 95% CI = 0.18 – 1.22) while walking (OR = 1.85, 95% CI = 0.82 – 4.17) and leisure-time physical exercise (OR = 1.56, 95% CI = 0.72 – 3.36) showed

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for SLE according to lifestyle factors among the patients treated for SLE for Less than 10 years in Kyushu (case A)

Lifestyle factors	Case no.	Control no.	Age-adjusted OR (95% CI)	Multivariate-adjusted OR (95% CI)
Sleeping hours				
Less than 7 h/day	53	242	Reference	Reference
7 h/day or more	25	87	1.01 (0.58–1.79)	1.01 (0.56–1.81)
Kept regular hours				
No	32	170	Reference	Reference
Yes	46	159	1.40 (0.84–2.34)	1.61 (0.94–2.75)
Had sufficient sleep				
No	16	37	Reference	Reference
Yes	62	292	0.45 (0.23–0.87)	0.45 (0.22–0.88)
Felt psychological stress				
No	13	79	Reference	Reference
Yes	65	250	1.74 (0.88–3.41)	1.54 (0.78–3.04)
Walked				
Less than 30 min/day	20	155	Reference	Reference
30 min/day or more	58	174	2.00 (1.13–3.56)	2.07 (1.14–3.76)
Leisure-time physical exercise				
Less than 3 days/week	51	256	Reference	Reference
3 days/week or more	27	73	1.64 (0.94–2.84)	1.66 (0.94–2.91)
Smoking habit				
Never smokers	48	261	Reference	Reference
Current and former smokers	29	64	2.24 (1.29–3.88)	1.94 (1.09–3.45)
Never smokers	48	261	Reference	Reference
Current smokers	24	49	2.27 (1.25–4.13)	1.97 (1.06–3.65)
Former smokers	5	15	2.11 (0.72–6.16)	1.85 (0.62–5.50)
Drinking habit				
Less than 1 day/week	57	284	Reference	Reference
1 day/week or more	20	43	2.18 (1.17–4.04)	1.80 (0.94–3.44)
Less than 1 day/week	57	284	Reference	Reference
1–3 days/week	11	37	1.43 (0.67–3.03)	1.29 (0.60–2.77)
4–5 days/week or more	9	6	6.22 (2.10–18.44)	4.49 (1.43–14.08)

Multivariate-adjusted OR: adjusted for age, smoking and drinking

increased ORs, but none of these three factors reach the point of significance. In contrast, even after adjusting for age and alcohol drinking, current and former smokers (OR = 2.24, 95% CI = 1.04 – 4.81) and current smokers (OR = 2.45, 95% CI = 1.10 – 5.49) showed an increased OR compared with never smokers. On the other hand, those with a drinking habit (drinking 1 day/week or more) showed an increased age and smoking adjusted OR (OR = 3.20, 95% CI = 1.45 – 7.07). High-frequency of drinking was a strong risk factor for SLE (4–5 days/week or more vs less than 1 day/week: OR = 8.22, 95% CI = 2.21 – 30.50) even after controlling for age and smoking.

Analyses of the patients treated for SLE in Hokkaido, northern Japan

Tables 5 and 6 illustrate the ORs for SLE and 95% CIs in relation to lifestyles (i.e., sleeping habits, leisure-time physical exercise, and smoking and alcohol drinking) in the patients treated for SLE in Hokkaido.

Table 5 shows the result of analyses of all the patients treated for SLE for less than 10 years (case C). Smoking

(current and former smokers) showed a significantly increased age-adjusted OR (vs never smokers: OR = 2.41, 95% CI = 1.01 – 5.74) but the 95% CI for smoking became rather wide after adjusting for alcohol drinking (OR = 2.44, 95% CI = 0.98 – 6.03). On the other hand, after adjusting for age and alcohol drinking, former smokers (OR = 9.07, 95% CI = 1.11 – 74.74) showed a significantly increased risk of SLE compared with never smokers while current smokers (vs never smokers: OR = 2.19, 95% CI = 0.87 – 5.76) showed a marginally increased risk. In contrast, after adjusting for age and smoking, both low frequency of drinking (1–3 days/week) and high frequency of drinking (4–5 days/week or more) failed to show any meaningful association with the development of SLE.

Among Hokkaido controls, current and former smokers were more likely to be drinkers than never smokers (43.4% vs 14.6%, P < 0.01) (not shown in the table). Current and former smokers were less likely to keep regular hours (45.3% vs 75.0%, P < 0.01), and to have sufficient sleep than never-smokers (32.1% vs 51.2%). Drinkers were more likely to have smoking experience than nondrinkers in controls (54.8% vs 21.3%, P < 0.01) while they were less likely to keep regular hours than their counterparts (40.5% vs

Table 4. Odds ratios (ORs) and 95% confidence intervals (CIs) for SLE according to lifestyle factors among the patients treated for SLE for less than 5 years in Kyushu (case B)

Lifestyle factors	Case no.	Control no.	Age-adjusted OR (95% CI)	Multivariate-adjusted OR (95% CI)
Sleeping hours				
Less than 7 h/day	28	242	Reference	Reference
7 h/day or more	10	87	0.75 (0.34–1.68)	0.74 (0.32–1.73)
Kept regular hours				
No	16	170	Reference	Reference
Yes	22	159	1.34 (0.68–2.69)	1.67 (0.80–3.48)
Had sufficient sleep				
No	7	37	Reference	Reference
Yes	31	292	0.51 (0.21–1.26)	0.47 (0.18–1.22)
Felt psychological stress				
No	7	79	Reference	Reference
Yes	31	250	1.56 (0.64–3.71)	1.13 (0.46–2.79)
Walked				
Less than 30 min/day	11	155	Reference	Reference
30 min/day or more	27	174	1.78 (0.83–3.82)	1.85 (0.82–4.17)
Leisure-time physical exercise				
Less than 3 days/week	25	256	Reference	Reference
3 days/week or more	13	73	1.57 (0.75–3.29)	1.56 (0.72–3.36)
Smoking habit				
Never smokers	20	261	Reference	Reference
Current and former smokers	17	64	3.17 (1.56–6.46)	2.24 (1.04–4.81)
Never smokers	20	261	Reference	Reference
Current smokers	15	49	3.51 (1.66–7.44)	2.45 (1.10–5.49)
Former smokers	2	15	1.92 (0.41–9.05)	1.42 (0.29–7.02)
Drinking habit				
Less than 1 day/week	22	284	Reference	Reference
1 day/week or more	15	43	4.17 (1.99–8.74)	3.20 (1.45–7.07)
Less than 1 day/week	22	284	Reference	Reference
1–3 days/week	8	37	2.65 (1.09–6.44)	2.33 (0.94–5.82)
4–5 days/week or more	7	6	12.75 (3.89–41.76)	8.22 (2.21–30.50)

Multivariate-adjusted OR: adjusted for age, smoking and drinking

73.6%, $P < 0.01$). There was no meaningful association between lifestyle-related factors among the Hokkaido SLE patients.

Analyses restricted to the patients treated for SLE for less than 5 years (case D) are shown in Table 6. Leisure-time physical exercise (3 times/week or more vs less than 3 times/week: OR = 2.81, 95% CI = 0.94 – 8.37) showed a marginally increased risk of SLE after adjusting for age, smoking and alcohol drinking. Compared with never smokers, current and former smokers (OR = 2.66, 95% CI = 0.93 – 7.57), and current smokers (OR = 2.50, 95% CI = 0.86 – 7.25) showed a nonsignificantly increased OR adjusted for age and drinking while either low frequency of drinking (1–3 days/week) or high frequency of drinking (4–5 days/week or more) showed no meaningful relation to the risk of SLE.

Discussion

Systemic lupus erythematosus is a chronic inflammatory autoimmune disease,[2-4] and subjective sleep quality is reported to influence immunity.[14] These findings suggest that good sleeping habits may reduce the risk of SLE. However, there is little information about the relationship between sleep hygiene and the risk of SLE except the study by Nagai et al.,[11] who reported that sleeping 8 h/day or more failed to reduce the risk of SLE. In the present study, neither the length of sleep nor keeping regular hours showed any meaningful relation to the development of SLE. In contrast, the case control study in Kyushu revealed that sufficient sleep decreased the risk of SLE although it failed to show any meaningful association with SLE in Hokkaido. The following possibilities may explain the different results in the two regions. Firstly, controls in Kyushu were not free from selection bias because the lifestyles of nursing college students and care workers may be different from those of the general population. Another explanation is that this result may be a chance phenomenon, because the number of SLE patients analyzed in both regions was small. An additional study is needed to clarify whether quality of sleep influences the development of SLE.

Physical activity is reported to reduce the risk of cancer[15,16] and coronary artery disease.[17] However, as with sleep hygiene, there is little information about leisure-time physical exercise and the risk of SLE. Nagai et al.[11] reported that

Table 5. Odds ratios (ORs) and 95% confidence intervals (CIs) for SLE according to lifestyle factors among the patients treated for SLE for less than 10 years in Hokkaido (case C)

Lifestyle factors	Case no.	Control no.	Age-adjusted OR (95% CI)	Multivariate-adjusted OR (95% CI)
Sleeping hours				
Less than 7 h/day	4	8	Reference	Reference
7 h/day or more	31	180	0.60 (0.14–2.69)	0.58 (0.13–2.52)
Kept regular hours				
No	19	63	Reference	Reference
Yes	16	125	1.07 (0.44–2.57)	1.34 (0.53–3.37)
Had sufficient sleep				
No	20	100	Reference	Reference
Yes	15	88	1.33 (0.57–3.12)	1.43 (0.60–3.40)
Felt psychological stress				
No	6	53	Reference	Reference
Yes	29	135	1.49 (0.51–4.33)	1.49 (0.50–4.46)
Walked				
Less than 30 min/day	13	57	Reference	Reference
30 min/day or more	22	131	1.03 (0.44–2.44)	1.13 (0.46–2.79)
Leisure-time physical exercise				
Less than 3 days/week	26	139	Reference	Reference
3 days/week or more	9	49	1.63 (0.62–4.28)	1.82 (0.67–4.95)
Smoking habit				
Never smokers	12	132	Reference	Reference
Current and former smokers	22	53	2.41 (1.01–5.74)	2.44 (0.98–6.03)
Never smokers	12	132	Reference	Reference
Current smokers	19	50	2.12 (0.86–5.18)	2.19 (0.87–5.56)
Former smokers	3	3	8.38 (1.10–63.79)	9.07 (1.11–74.41)
Drinking habit				
Less than 1 day/week	22	144	Reference	Reference
1 day/week or more	13	42	1.22 (0.51–2.94)	0.95 (0.37–2.43)
Less than 1 day/week	22	144	Reference	Reference
1–3 days/week	4	24	0.71 (0.20–2.51)	0.60 (0.16–2.22)
4–5 days/week or more	9	18	1.91 (0.65–5.65)	1.34 (0.44–4.34)

Multivariate-adjusted OR: adjusted for age, smoking and drinking

neither outdoor sports nor physical activity had any meaningful associated with SLE. In the present study, walking showed a significantly increased risk of SLE and leisure-time physical exercise showed a marginally increased risk while sufficient sleep was associated with a significantly decreased risk of SLE in Kyushu. On the other hand, in Hokkaido, neither walking nor sufficient sleep showed any meaningful association with SLE, although leisure-time physical exercise showed a marginally increased risk. Kyushu is located in the extreme southwestern part of Japan with a temperate climate, and summer sports are popular. On the other hand, Hokkaido is the northernmost island of Japan with a subarctic climate, where winter sports are popular. Because skin sensitivity to sunlight increases the risk of SLE,[10,11] walking, which was a significant risk factor only in southern Japan, may be a surrogate of staying outdoors under the sunlight. Further studies are needed to clarify this.

Several investigators[6-10] have suggested that smoking is a risk factor for SLE. Mongey and Hess[18] stated that tobacco smoke contained chemical risk factors for SLE (i.e., hydrazine and its derivatives). Ghaussy et al.[8] reported a significantly increased risk of SLE in both current and former smokers. In contrast, the studies by Nagata et al.[6] and Hardy et al.[7] showed that the increased risk of SLE existed only in current smokers. On the other hand, Sanchez-Guerrero et al.[19] and Cooper et al.[20] reported no association with smoking history (i.e., current, former, or never-smoker) and the risk of SLE. In the present study, compared with never smokers, current and former smokers showed an increased OR. However, only a marginally increased risk of SLE was seen in Hokkaido whereas in Kyushu a significantly increased risk was seen. These findings may be explained by the fact that the number of subjects was small in the present study.

Several reports suggested that alcohol drinking may prevent the development of SLE,[6-10] whereas others disclosed no association between alcohol drinking and risk of SLE.[9,11] In the present study, there was no meaningful association between alcohol drinking and risk of SLE in Hokkaido. However, in Kyushu, high frequency drinkers showed an increased risk. It is possible to partly explain these findings in the following ways. Firstly, these results may be a chance phenomenon, because the number of subjects was small in the present study. Another explanation is that high frequency drinkers may include heavy drinkers or binge drink-

Table 6. Odds ratios (ORs) and 95% confidence intervals (CIs) for SLE according to lifestyle factors among the patients treated for SLE for less than 5 years in Hokkaido (case D)

Lifestyle factors	Case no.	Control no.	Age-adjusted OR (95% CI)	Multivariate-adjusted OR (95% CI)
Sleeping hours				
Less than 7 h/day	3	8	Reference	Reference
7 h/day or more	21	180	0.50 (0.10–2.45)	0.52 (0.11–2.59)
Kept regular hours				
No	14	63	Reference	Reference
Yes	10	125	0.75 (0.28–2.01)	0.89 (0.32–2.45)
Had sufficient sleep				
No	15	100	Reference	Reference
Yes	9	88	0.97 (0.37–2.55)	0.98 (0.37–2.61)
Felt psychological stress				
No	4	53	Reference	Reference
Yes	20	135	1.39 (0.41–4.69)	1.46 (0.42–5.10)
Walked				
Less than 30 min/day	10	57	Reference	Reference
30 min/day or more	14	131	0.82 (0.32–2.13)	0.82 (0.30–2.20)
Leisure-time physical exercise				
Less than 3 days/week	16	139	Reference	Reference
3 days/week or more	8	49	2.38 (0.84–6.71)	2.81 (0.94–8.37)
Smoking habit				
Never smokers	8	132	Reference	Reference
Current and former smokers	16	53	2.56 (0.95–6.96)	2.66 (0.93–7.57)
Never smokers	8	132	Reference	Reference
Current smokers	14	50	2.38 (0.85–6.62)	2.50 (0.86–7.25)
Former smokers	2	3	5.31 (0.66–42.79)	5.87 (0.67–51.19)
Drinking habit				
Less than 1 day/week	15	144	Reference	Reference
1 day/week or more	9	42	1.20 (0.45–3.24)	0.88 (0.30–2.53)
Less than 1 day/week	15	144	Reference	Reference
1–3 days/week	3	24	0.73 (0.18–3.0)	0.60 (0.14–2.60)
4–5 days/week or more	6	18	1.80 (0.54–5.99)	1.20 (0.33–4.31)

Multivariate-adjusted OR: adjusted for age, smoking and drinking

ers. In the present study, drinkers were more likely to feel psychological stress than nondrinkers among controls in Kyushu, and psychological stress showed an increased OR in Kyushu although it failed to be a significant risk factor for SLE. Heavy drinkers and binge drinkers may have felt emotional stress, which is a risk factor for SLE.[21]

There are some limitations to our study. First, cases were not newly diagnosed SLE patients but patients treated for SLE for less than 10 years in both Kyushu and Hokkaido. The patients may have changed their lifestyles after the development of SLE. They may have quit smoking, drinking heavily, or participating in outdoor sports. On the other hand, their sleep quality may have become poorer because SLE female patients are more likely to suffer from poor sleep quality than healthy females.[22,23] Therefore, risk factors for SLE such as smoking, high frequency of drinking, and leisure-time physical exercise may have been underestimated, whereas preventive factors such as sleep sufficiency may have been overestimated. Second, our cases were not free from selection bias because half of eligible SLE patients did not agree to participate in this study. Some of them refused to participate in this study after we asked them to donate blood samples for DNA extraction and

genotyping of the candidate genes of SLE. Third, our controls were not free from selection bias either because they were not randomly selected from the general population. In Kyushu, controls were recruited from nursing college students and care workers in nursing homes. Their lifestyles may be different from the general population. However, the risk of SLE from smoking may have been underestimated in Kyushu because the high prevalence of smoking among nursing students and nurses is a serious social problem.[24–26] On the other hand, in Hokkaido, controls were participants in a health checkup in a local town. They may well have had more healthy lifestyles than the general population. Fourth, we cannot clearly explain the reason why high frequency of alcohol consumption increased the risk of SLE in Kyushu but did not in Hokkaido. Last, although SLE is thought to be a multi-factorial disease in which complex environmental and genetic factors interact,[2,4] we did not evaluate genetic factors in this paper.

On the other hand, this study has its strengths as well. The present study showed that there was a common risk factor in the two different regions of Kyushu, southern Japan, and Hokkaido, northern Japan, even though controls were not matched. Although there are some studies on

the lifestyle related risk factors for SLE among the Japanese population,[6,11] they did not estimate the risk of SLE after controlling for other factors. As far as we know, this is the first report showing that smoking is a risk factor for SLE among Japanese females after controlling for age and other factors.

In conclusion, the present study may support the belief that smoking is a risk factor for SLE among Japanese females. In addition to smoking, walking, leisure-time physical exercise, and high frequency of drinking were proposed as the probable risk factors. On the other hand, sufficient sleep is suggested as a preventive factor. However, further studies are required to confirm the results of the present study.

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パーキンソン病関連疾患の性差

Sex Difference in Parkinson's Disease

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はじめに

　パーキンソン病（パーキンソン病と進行性核上性麻痺，大脳皮質基底核変性症）は，1978年に特定疾患治療研究事業の対象疾患として医療費公費負担制度が適用され，2003年10月にパーキンソン病関連疾患に名称が変更された。2003年度のパーキンソン病関連疾患の医療受給者数は，地域保健老人保健事業報告[1]によれば，7万532人と，潰瘍性大腸炎に次いで多い。パーキンソン病関連疾患は，パーキンソニズムなどの錐体外路徴候のほか，自律神経症状，小脳症状，抑うつ，失神，構音障害など多くの臨床症状を呈する疾患であり，これまでに患者の神経症状や自律神経症状，精神症状の頻度などが報告されている。また，パーキンソン病関連疾患患者の重症度の指標として，Hoen-Yahrの臨床重症度分類（以下Yahrの臨床重症度）がわが国で一般的に使用され報告されている。

　特定疾患治療研究事業対象疾患については，2003年度より，特定疾患の医療受給の申請時に提出される臨床調査個人票が電子入力されるようになったため，受給者の性，年齢，推定発病年齢，受療状況，ADL，要介護度，身体障害手帳交付の有無のほか，臨床症状，検査所見，治療方法，合併症などの情報を系統的に集計解析することが可能になった。2003年度に電子入力された臨床調査個人票は，受給者全体の50%弱であるが，性，年齢別入力状況に大きな差がないため，疾患ごとの臨床症状についての検討が可能である[2]。そこでこのデータを用いて，わが国のパーキンソン病関連疾患の受給者（男性1万2,395人，女性1万7,836人）の性別の臨床像の違いを明らかにする。解析した重症度や症状の区分は，**表1**に示すとおりである。

医療受給者の年齢と発病年齢と発病からの期間の性差

　年齢別医療受給者数は，男女とも60～80歳代が多く，70歳代が全体の約45%を占めて最も多い（**図1**）。医療受給者の平均年齢は男性が70.2歳で女性が72.4歳で女性が2.2歳高い。性別発病時年齢別医療受給者数は，男女

表1 解析項目

・Yahrの臨床重症度
　1度　一側性パーキンソニズム
　2度　両側性パーキンソニズム　姿勢反射障害なし
　3度　軽～中等度パーキンソニズム　姿勢反射障害あり　日常生活に介助不要
　4度　高度障害を示すが，歩行は介助なしにどうにか可能
　5度　介助なしにはベッド車椅子生活

・日常生活機能障害度（厚生労働省研究班）
　1度　日常生活，通院にほとんど介助を要しない
　2度　日常生活，通院に部分的介助を要する
　3度　日常生活に全面的介助を要し独力では歩行起立不能

・神経症状の重症度（7項目）

（1）静止時振戦
　0．なし
　1．ごくわずかでたまに出現
　2．軽度の振幅で持続的に出現か，中等度の振幅で間歇的に出現
　3．中等度の振幅で大部分の時間出現
　4．大きな振幅の振戦が，大部分の時間出現

（2）指タップ（母指と示指をできるだけ大きな振幅でタッピング）
　0．正常
　1．やや遅いか，振幅がやや小さい
　2．中等度の障害　早期に疲労を示す。動きが止まることもある
　3．高度の障害　運動開始時からリズムが乱れ，時に動きが止まる
　4．ほとんどタッピングの動作にならない

（3）筋強剛
　0．なし
　1．軽微な固縮，または他の部位の随意運動で誘発される固縮
　2．軽度～中等度の固縮
　3．高度の固縮，しかし関節可動域は正常
　4．著明な固縮。正常可動域を動かすには，困難を伴う

（4）椅子からの立ち上がり
　0．正常
　1．可能だが遅い。一度でうまくいかないこともある
　2．肘掛けに腕をついて立ち上がる必要がある
　3．立ち上がろうとすると倒れこむことあり。しかし最後には
　　独力で立ち上がれる
　4．立ち上がるには介助が必要

（5）歩行
　0．正常
　1．緩慢，小刻み・引きずりも出現。加速歩行や
　　突進はない
　2．困難だが独歩可能。加速歩行，小刻み歩行，
　　前方突進，すくみが出現することあり
　3．すくみや高度の歩行障害があり，歩行に介助
　　を要する
　4．介助があっても歩けない

（6）姿勢
　0．正常
　1．軽度の前屈姿勢（高齢者では正常の範囲内）
　2．中等度の前屈姿勢，一側にやや傾くこともある
　3．高度の前屈姿勢，脊椎後彎を伴う。一側へ中
　　等度に傾くことあり
　4．高度の前屈，究極の異常前屈姿勢

（7）姿勢の安定性（立ち直り反射障害と後方突進現象）
　0．なし
　1．後方突進現象があるが，自分で立ち直れる
　2．後方突進現象があり，支えないと倒れる
　3．極めて不安定で，何もしなくても倒れそうに
　　なる
　4．介助なしには起立が困難

・その他の臨床症状（21項目）

排尿困難	幻覚	垂直性核上性眼球運動障害
失禁	失語	持続性注視方向性眼振
陰萎	失認	進行性の構音障害
頑固な便秘	失行	体幹部や頚部に強い筋強剛
失神	肢節運動失行	小脳症状
痴呆	他人の手兆候	四肢の腱反射
抑うつ	四肢症状の非対称性	バビンスキー兆候

とも50〜70歳代が多く，60歳代が約35%を占めて最も多い（図2）。発病時年齢の平均は男性が61.5歳で女性が63.1歳で女性が1.6歳高い。性別発病後期間別医療受給者数は，男女とも5年以上10年未満が約35%で最も多い。発病後期間の平均は男性が8.6年で女性が9.2年である。

医療受給者の臨床像の性差

Yahrの臨床重症度は，3度以上の者は男女とも約95%で，4度以上の者は男性は45.9%，女性は54.0%で女性のほうが重症度が高い。これを年齢別に見ると，男女とも年齢が高くなるにつれて重症度が高い者の割合が増えるが，どの年齢もおおむね女性の重症度が高い（図3）。

日常生活機能障害度は，2度以上の者は男女とも約95%で，3度以上の者は男性は25.8%，女性は33.8%で女性のほうが重症度が高い。年齢別にみると，男女とも年齢が高くなるにつれて障害度が高い者の割合が増えるが，どの年齢もおおむね女性の重症度が高い（図4）。

神経症状の重症度は，1度以上のものは，指タップ，筋強剛，立ち上がり，歩行，姿勢，姿勢安定性が男女とも90%以上で，静止時振戦が男女とも約80%である。3度以上の者は立ち上がり，歩行，姿勢，姿勢安定性で女性のほうが多く，静止時振戦，指タップ，筋強剛では3度以上の者は男女とも同程度である（図5）。年齢別に
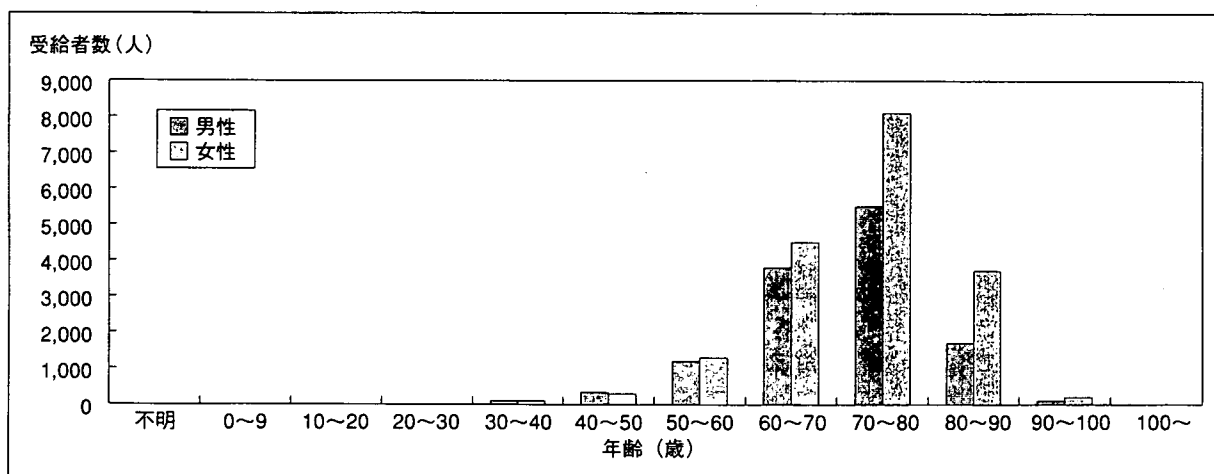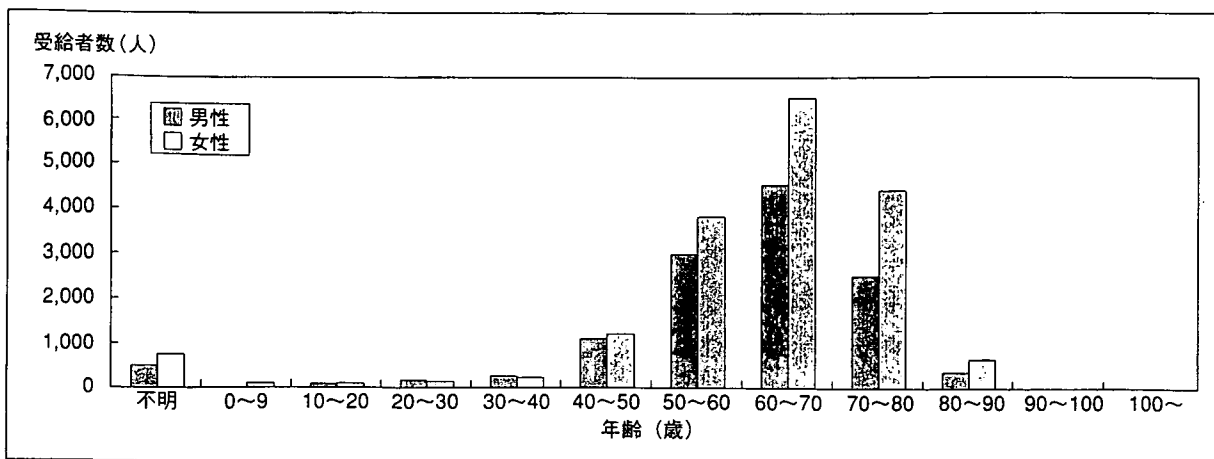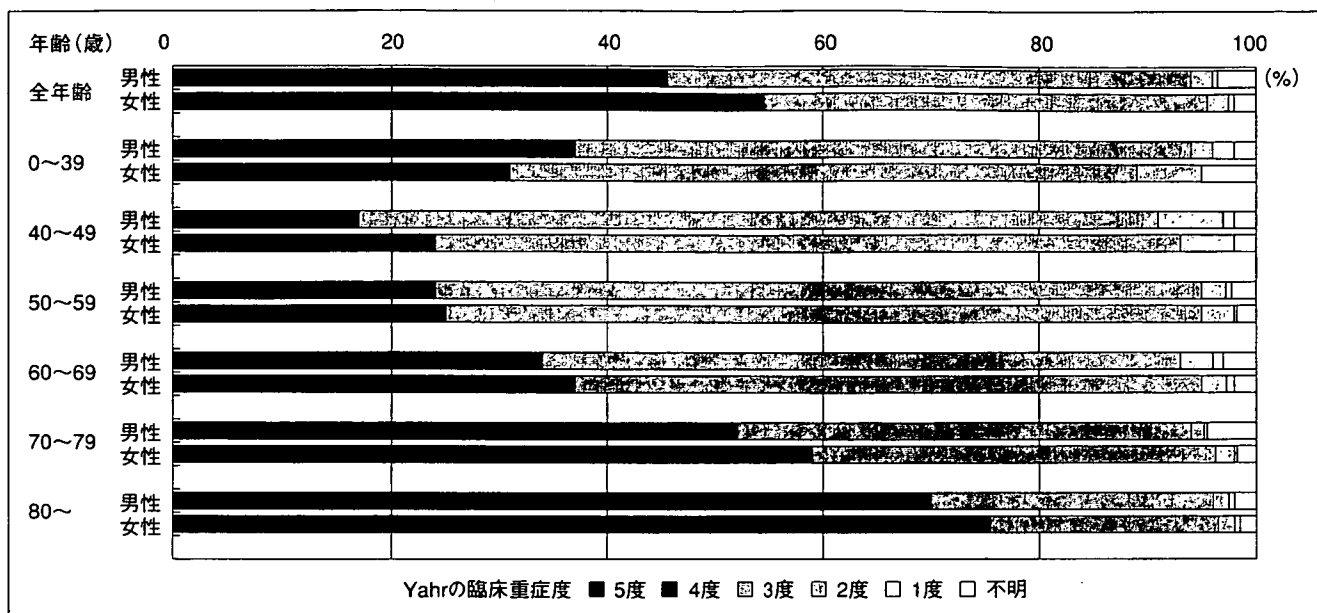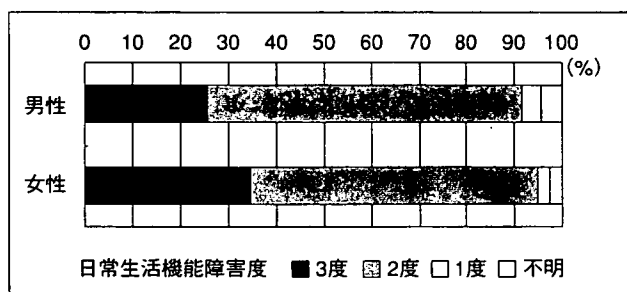

図1　性別・年齢別受給者数

図2　性別・発病時年齢別受給者数

図3　性別年齢階級別Yahrの臨床重症度

図4　性別日常生活機能障害度

みると，7項目とも年齢が高くなるにつれて男女とも重症度3以上の者の割合がおおむね高くなる。また，立ち上がり，歩行，姿勢，姿勢安定性の重症度3以上の者の割合は，どの年齢においてもおおむね女性のほうが男性よりも高い。

性別その他の臨床症状ありの者の割合は，頑固な便秘が男性で58.9％，女性で56.6％と最も高く，以下男性では，排尿困難，失禁，陰萎の順に高く，女性では抑うつ，失禁，痴呆の順で高い。排尿困難，失神，進行性の構音障害，垂直性核上性眼球運動障害は男性が女性より高く，抑うつは女性が男性より高い（図6）。年齢別にみると，排尿困難は50歳以上で男性が高く，失神と垂直性核上性眼球運動障害は60歳以上で男性が高く，抑うつ

症状は50歳以上で男性が高い（図7）。

まとめ

わが国のパーキンソン病患者の平均年齢は過去の調査では，男性61.4歳，女性61.9歳[3]，と報告され，性差はみられていない。今回は男女とも過去に比べ平均年齢が10歳近く高く，女性のほうが男性に比べて高かった。ただし，特定疾患治療研究事業におけるパーキンソン病の対象範囲は，Yahrの臨床重症度が3度以上かつ日常生活機能障害度が2度以上の者と定めているため，より軽度の患者を含めた平均年齢は今回の結果より低くなると考えられる。

パーキンソン病の平均発病年齢は過去の調査では男性55.8歳，女性56.8歳と報告され，性差はみられていない[3]。今回は過去の報告と比べて男女とも平均発病時年齢は5歳近くとやや高く，女性のほうが男性に比べて高かった。

Yahrの臨床重症度の性差について報告はこれまでなかった。しかし今回の結果では，Yahrの臨床重症度と日常生活機能障害度が高いものの割合が女性で男性よりやや多いという結果が得られ，Yahrの臨床重症度の性
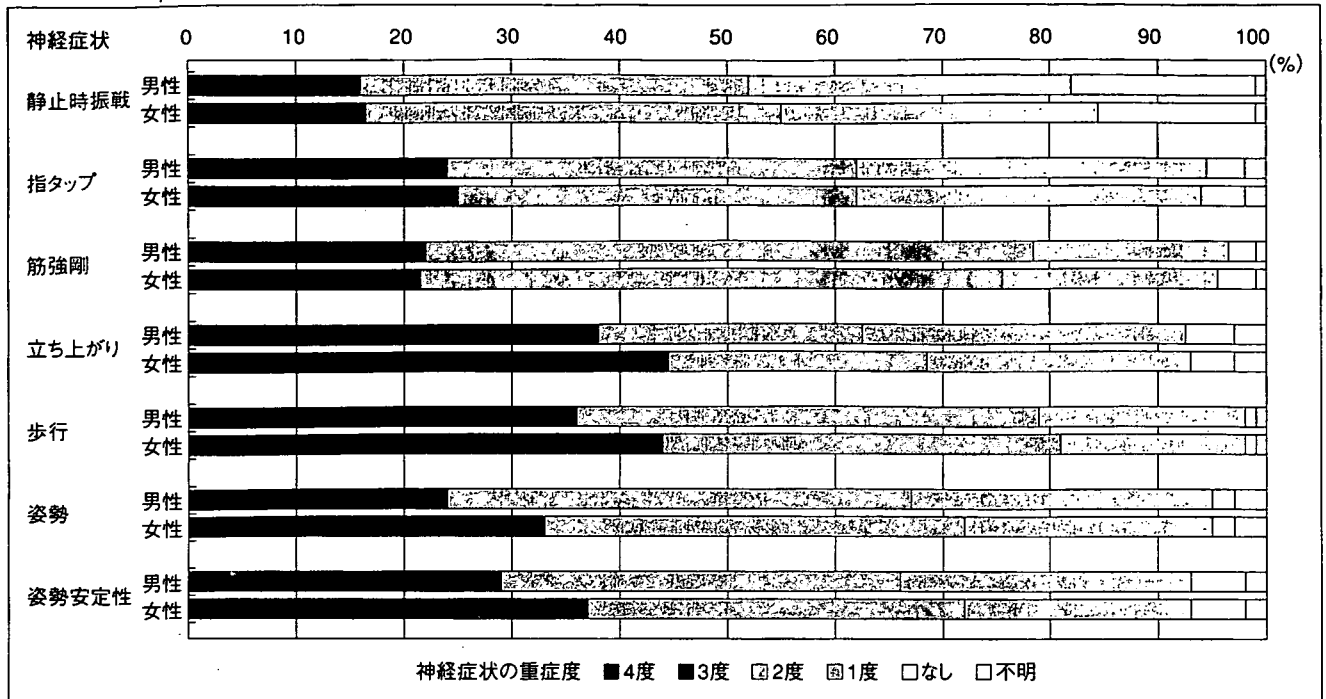
図5　性別神経症状の重症度

凡例: 神経症状の重症度　■4度　■3度　☑2度　▨1度　□なし　□不明

縦軸項目（上から）: 神経症状（0〜100%）、静止時振戦（男性・女性）、指タップ（男性・女性）、筋強剛（男性・女性）、立ち上がり（男性・女性）、歩行（男性・女性）、姿勢（男性・女性）、姿勢安定性（男性・女性）

図6　性別その他の臨床症状ありの者の割合

凡例: 男性、女性

横軸項目: 排尿困難、失禁、陰萎、頑固な便秘、失神、痴呆、抑うつ、幻覚、失語、失認、失行、肢節運動失行、他人の手兆候、四肢症状の非対称性、垂直性核上性眼球運動障害、持続性注視方向性眼振、進行性の構音障害、体幹部や頚部に強い筋強剛、小脳症状、四肢の腱反射低下、四肢の腱反射亢進、バビンスキー兆候陽性
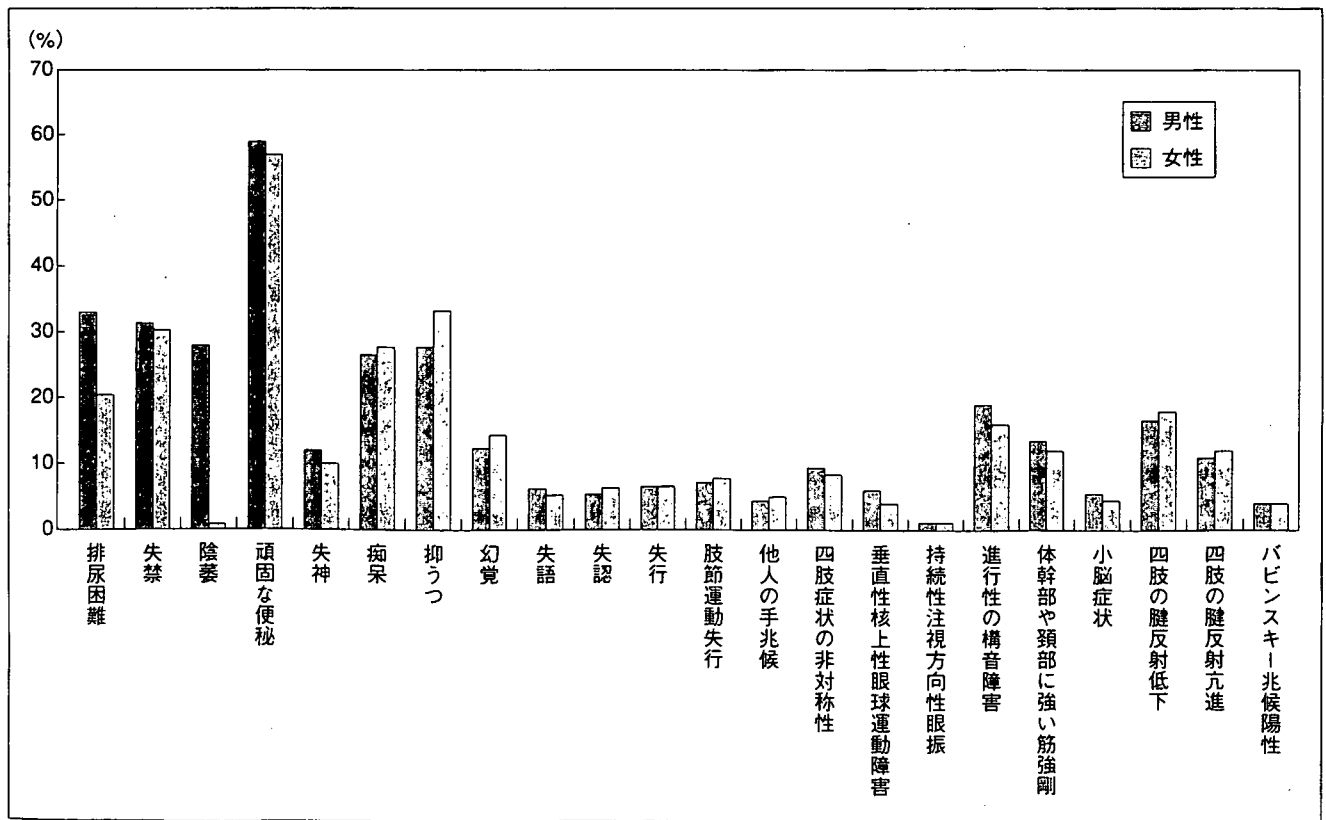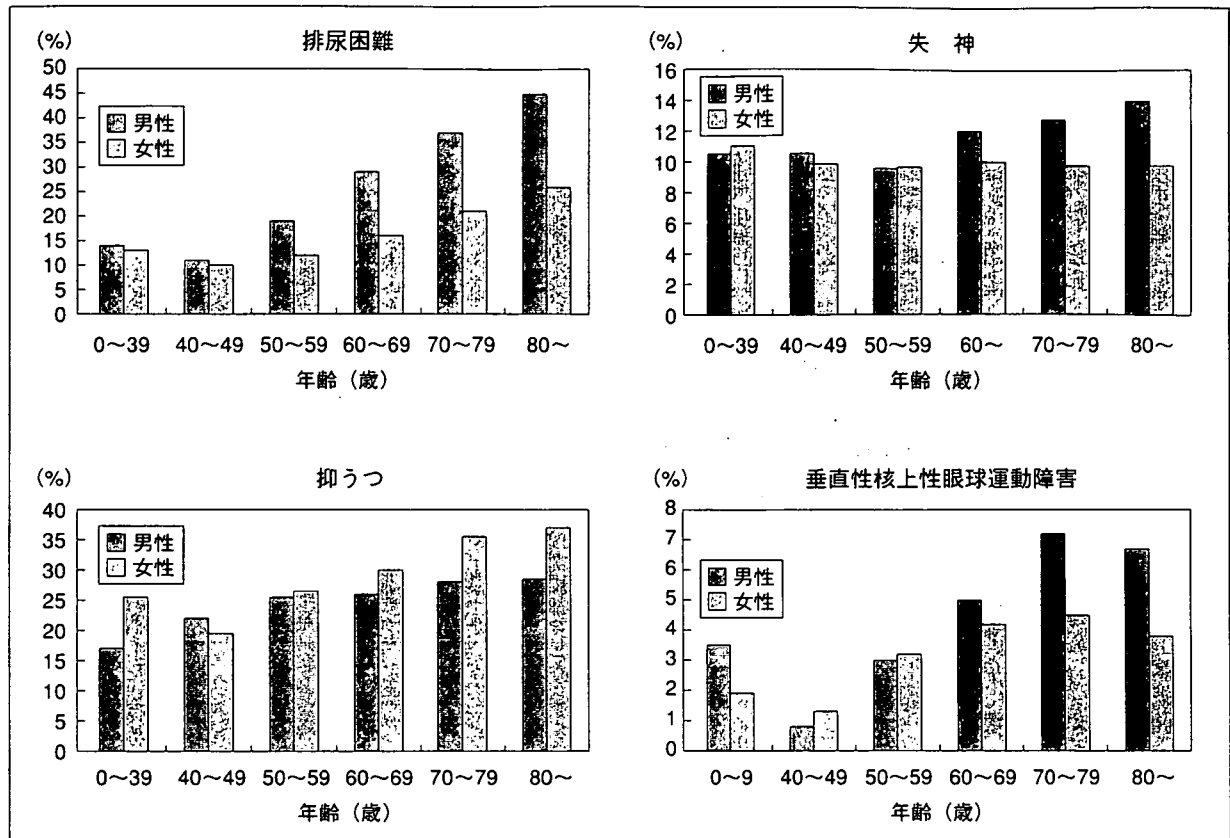
図7　性別年齢階級別その他の臨床症状ありの者の割合

差が明らかにできた。発病後期間は女性が男性よりやや長いが，発病後期間の違いがYahrの臨床重症度との性差に関係していた可能性が考えられる。

神経症状の頻度の性差については固縮，振戦，寡動について重症度の性差はなかったと報告されている[4]。今回の結果では立ち上がり，歩行，姿勢，姿勢安定性などで重症度が高いものが女性に多かった。

その他の自律神経症状や精神症状などの性差の報告は少ないが，嚥下障害や言語障害，膀胱障害では男性が高いという報告があった[3]。今回は，排尿困難，失神，進行性の構音障害，垂直性核上性眼球運動障害で男性が高く，抑うつで女性が高いという結果であった。性別年齢階級別にみると排尿困難は高齢の男性で高く，抑うつは高齢の女性で高くなっている。この結果は高年齢の患者において，男性で前立腺疾患による排尿困難や，女性で

のうつ病による抑うつなど他の疾患によるものが含まれている可能性が考えられる。

パーキンソン病関連疾患の臨床像の性差について概説した。Yahrの臨床重症度や日常生活機能障害度で，神経症状の重症度，排尿困難，失神，抑うつなどのある者の割合で，性別に違いが見られた。

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