The validity of two novel indices of fall tendency, the 22 items fall risk index[8] and the 13 points simple screening test,[3] which were used in our previous study, have been confirmed in community-dwelling elderly, but not in geriatric outpatients. Therefore, in the present investigation, the association of these two indices with falls was also evaluated to confirm their validity in geriatric outpatients in a longitudinal study.

Methods

Patients

From 2006 to 2007, a total of 190 consecutive patients aged 65 years or older who were receiving treatment for chronic diseases, such as hypertension, dyslipidemia, diabetes and osteoporosis, who were seen every 2–4 weeks at the outpatient clinic of the Research Institute of Aging Science, Tokyo, were enrolled. All the patients were able to walk independently and their condition was stable. Patients who had acute illness or overt dementia were excluded. Anthropometric and medical information including past history of stroke, myocardial infarction, malignancy and prescribed drugs was obtained from each patient at baseline from the medical chart recorded by the physician in charge. However, 18 patients were excluded, because they were lost to follow up soon after enrolment and the medical information was not fully obtained. All prescribed drugs had not been changed in the included patients for at least 2 months before enrolment. The patients were followed up for 2 years.

Occurrence of falls

During the follow-up period, the patients and their family members responded to the annual questionnaire asking about the occurrence of falls within the past year. The questionnaire was repeated for 2 years.

Indices of fall tendency

After enrolment, the patients were examined for two indices to investigate the fall tendency. These were (i) a questionnaire of the 22 items portable fall risk index;[8] and (ii) the 13 points simple screening test to assess the fall tendency.[3]

Ethical consideration

The present study was approved by the Institutional Review Board of the Research Institute of Aging Science. We obtained written consent from all participants and/or their guardians.

Data analysis and statistical methods

Values are expressed as mean ± standard deviation. In order to analyze the relationship between falls and comorbidity or drugs, variables were compared using Student's *t*-test or χ^2-test as appropriate. Significant factors found in univariate analysis were included in multivariate logistic regression analysis to determine the association of falls with other variables. Receiver–operating curve (ROC) analysis was carried out to identify the optimal cut-off value of the number of drugs for predicting falls within 2 years. The value with the highest sum of sensitivity and specificity was used as the optimal cut-off value. Logistic regression analysis was carried out to assess the validity of the two indices of fall tendency, adjusted by age and sex. *P*-values <0.05 were considered statistically significant. Data were analyzed using JMP version 8.0.1 (SAS Institute, Cary, North Carolina, USA).

Results

Baseline medical information and two indices of fall tendency were evaluated in 172 patients (Table 1). Drugs prescribed in less than 5% of the patients are not shown. Because only patients who were in a stable condition and were able to walk independently were included, patients with Parkinson's disease, severe paresis or painful arthralgia were not included. Calcium channel blockers prescribed in the present study were all long-acting agents, and the prescribed aspirin dosage was 100 mg in all cases. Only a few patients were receiving insulin therapy, sulfonylureas, angiotensin converting enzyme inhibitors, β-blockers, α-blockers, non-steroidal anti-inflammatory drugs or anticoagulants. No patients were taking neuroleptics or antiparkinsonian drugs.

After 1 year, all patients, except for one who died of congestive heart failure, were followed up ($n = 171$, follow-up rate 99.4%). Falls occurred in 22 patients. Only a higher age was associated with falls within 1 year on univariate analysis (non-fallers: 76.4 ± 6.8 years, fallers: 81.0 ± 6.9 years, $P = 0.004$).

After another year (2 years after enrolment), one patient had died of lung cancer, and five patients were lost to follow up. A total of 165 patients were evaluated (follow-up rate 95.9%), and 10 patients had fallen during the second year; thus a total of 32 patients had fallen within 2 years. As shown in Table 2, higher age, osteoporosis, number of comorbid conditions and number of drugs were significant factors associated with falls. To determine the association of falls with these significant factors, multivariate logistic regression analysis was carried out, and as shown in Table 2, the number of drugs was the only factor that was significantly associated with falls within 2 years.

As polypharmacy was assumed to be a risk for falls within 2 years, the cut-off of the number of the drugs was analyzed. Figure 1 shows the ROC curves to define the optimal cut-off point in relation to falls within

Table 1 Characteristics and univariate analysis of association with fallers and non-fallers within 2 years and risk factors

Total		Non-fallers ($n = 133$)	Fallers ($n = 32$)	P-value (Fallers vs. Non-fallers)
Age (years)	77.0 ± 7.0	76.3 ± 6.9	80.0 ± 6.9	0.007
Body mass index (kg/cm^2)	22.7 ± 3.2	22.7 ± 3.3	22.7 ± 3.1	0.98
No. comorbid conditions	1.9 ± 1.1	1.8 ± 1.1	2.3 ± 0.9	0.009
No. drugs	3.2 ± 2.8	2.8 ± 2.7	4.9 ± 2.5	<0.0001
Female ($n = 122$)	–	72.9%	78.1%	0.66
Hypertension ($n = 106$)	–	62.4%	71.8%	0.41
Dyslipidemia ($n = 76$)	–	47.3%	40.6%	0.56
Diabetes ($n = 23$)	–	12.8%	18.8%	0.40
Osteoporosis ($n = 59$)	–	30.8%	56.3%	0.01
History of stroke ($n = 6$)	–	2.3%	9.4%	0.09
History of myocardial infarction ($n = 3$)	–	0.8%	6.3%	0.10
History of cancer ($n = 8$)	–	5.3%	3.1%	0.99
Calcium channel blocker ($n = 59$)	–	33.3%	46.9%	0.16
Angiotensin II receptor blocker ($n = 56$)	–	33.3%	37.5%	0.68
Statin ($n = 40$)	–	23.5%	28.1%	0.65
Aspirin ($n = 31$)	–	19.0%	24.1%	0.61
Bisphosphonate ($n = 9$)	–	4.6%	9.4%	0.38
H2-blocker ($n = 9$)	–	3.8%	12.1%	0.80
Proton pump inhibitor ($n = 11$)	–	5.3%	12.1%	0.23
Hypnotic ($n = 31$)	–	16.7%	28.1%	0.14

Values are expressed as mean ± SD ($n = 165$).

Table 2 Logistic regression analysis of association of falls within 2 years with age, sex, other significant factors found in univariate analysis, and polypharmacy

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (/1 year)	1.08 (1.03–1.13)†	1.06 (0.99–1.13)	1.06 (0.99–1.13)
Sex (male = 0, female = 1)	1.39 (0.56–3.48)	0.98 (0.29–3.23)	0.75 (0.23–2.38)
Osteoporosis ($n = 0$, Y = 1)	3.12 (1.43–6.84)†	2.76 (0.92–7.38)	3.02 (0.96–6.15)
No. comorbid conditions (/disease)	1.63 (1.14–2.32)*	0.90 (0.55–1.47)	0.99 (0.62–1.56)
No. drugs (/drug)	1.29 (1.12–1.48)‡	1.30 (1.08–1.57)*	–
Five or more drugs ($n = 0$, Y = 1)	5.04 (2.25–11.3)‡	–	4.50 (1.66–12.2)†

*$P < 0.05$, †$P < 0.005$, ‡$P < 0.0005$. CI, confidence interval.

2 years: the area under the ROC was 0.731, and the optimal cut-off value of the number of drugs was five (sensitivity 0.576, specificity 0.788). Logistic regression analysis showed that taking five or more drugs was significantly associated with an increased risk of falls (odds ratio 4.5, 95% CI 1.7–12.2) after adjustment for age, sex, osteoporosis and number of comorbid conditions (Table 2).

Also, the association between falls and two indices of fall tendency was evaluated to confirm the validity of each index in geriatric outpatients. As both indices included the questionnaire asking whether patients were "taking five or more drugs," the number of drugs was excluded from this analysis because of duplication in the statistical model. As shown in Table 3, the 22 items fall risk index showed a tendency towards an association with falls within 2 years, odds ratio 1.12 (95% CI 1.00–1.26; $P = 0.05$), whereas the 13 points screening test was significantly associated with falls after adjustment for age, sex and other factors significantly associated in the univariate analysis. Therefore, these indices are considered to be good predictors of falls in geriatric outpatients, as has been shown in community-dwelling elderly subjects.

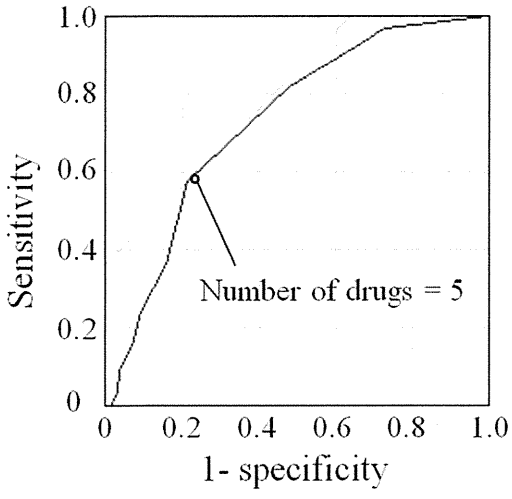

Figure 1 Receiver–operating curves to define optimal cut-off value of number of drugs at baseline in relation to falls within 2 years. Area under the curve was 0.731, optimal cut-off value of the number of drugs was five (sensitivity = 57.6%, specificity = 78.8%).

Discussion

The risk of falls has been assessed in community-dwelling elderly, and history of falls, physical ability and living environment were found to be predictors of falls. Also, in nursing home residents, cognitive function, gait disturbance and urinary incontinence are reported to be risk factors for falls,[9,10] and length of stay, disease condition, surgical procedures and some specific drugs are reported to be risk factors in hospital inpatients.[11,12]

Nevertheless, the risks in geriatric outpatients have not been sufficiently assessed, although assessment of fall risk in geriatric outpatients is important; their medical conditions or drugs might cause falls, and drugs, such as antiplatelet agents or anticoagulants, might cause critical bleeding after a fall. Also, physicians could prevent falls in their patients by giving advice during regular consultations, if risk factors are identified.

In our previous cross-sectional study assessing geriatric outpatients, polypharmacy was significantly correlated with indices of fall tendency, and the present follow-up study of geriatric outpatients showed the impact of polypharmacy on falls within 2 years. Statistical analyses showed that polypharmacy was a risk factor for falls, independent of age, sex and comorbidity.

Besides polypharmacy, several medications and comorbid conditions have been reported as risks for falls.[13–22] Among these, diabetes,[5,6] insomnia,[13] hypnotics,[13–15] antiarrhythmics[22] and antihypertensive agents[14] were not significantly associated with fall risk in the present study. Just 11 patients (45.9% of diabetic patients) were prescribed hypoglycemic agents, such as a sulfonylurea ($n = 8$) or insulin ($n = 3$), and the relatively low rate of prescription of hypoglycemic agents might have affected our result. Neither hypnotics nor antihypertensives were associated with falls. This result might be a result of the small sample size. Anti-arrhythmics were taken by just three patients (digoxin: $n = 2$, class IA anti-arrhythmic drug: $n = 1$). Other drugs, such as major tranquillizers,[14] antidepressants[17,18] and antiparkinsonian agents,[19,22] might increase fall risk; however, no patient used these drugs in the present study. In the present study, most of the patients were in a stable condition throughout the 2 years, though their drugs were changed gradually according to their medical conditions during the observation period. We only used the number of drugs at baseline for statistical analysis; however, the number of drugs increased from 3.2 ± 2.8 to 3.9 ± 3.0 during the 2 years. There were 17 patients whose number of drugs had been decreased, 70 patients not changed and 78 patients increased. The number of drugs after 2 years was also associated with falls ($P < 0.0005$). The optimal cut-off point for the number of drugs was again five (area under ROC curve 0.780, sensitivity 0.576, specificity 0.788). Furthermore, the changes in number of drugs were also associated with falls ($P < 0.05$), and the optimal cut-off point for the change in number of drugs was +1 (area under ROC curve 0.649, sensitivity 0.727, specificity 0.409).

Table 3 Logistic regression analysis of association between 2-year fall occurrences with two indices of fall tendency; 22 items fall risk index and 13 points simple screening test

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (/year)	1.08 (1.03–1.15)**	1.06 (0.99–1.13)	1.06 (1.00–1.13)
Sex (male = 0, female = 1)	1.39 (0.56–3.48)	0.75 (0.23–2.43)	0.79 (0.24–2.56)
Osteoporosis ($n = 0$, Y = 1)	3.12 (1.43–6.84)**	2.56 (0.96–6.82)	2.61 (0.98–6.95)
No. comorbid conditions (/disease)	1.63 (1.14–2.32)*	1.24 (0.83–1.86)	1.32 (0.88–1.97)
Fall risk index (/item)	1.23 (1.11–1.37)***	1.12 (1.00–1.26)	–
Simple screening test (/point)	1.19 (1.06–1.33)**	–	1.14 (1.01–1.29)*

*$P < 0.05$, **$P < 0.005$, ***$P < 0.0005$. CI, confidence interval.

Consequently, polypharmacy, especially taking five or more drugs, should be considered a risk for falls.

There were several limitations of the present study. First, the falls were self-reported by the patients. Although all the patients had no overt dementia, they might have forgotten the incident of falling. We attempted to count the total fall occurrences in each patient; however, we could not differentiate the repeated falls in the second year from the fall occurrence in the first year. In fact, we asked 22 patients who reported falls in the first year about fall occurrence during the second year, but they did not accurately recall whether they experienced falls in the first or second year. Second, five patients were lost to follow up at 2 years for unknown reasons. The follow-up ratio was acceptable, although some of the patients might have fallen, have been no longer able to come to the clinic and moved to nursing homes. This might have slightly influenced the result. Also, the cause of falls in polypharmacy patients is not explained. Potentially inappropriate medications, which could cause adverse drug reactions, are usually seen in patients with polypharmacy, and falls might be the consequence of adverse drug reactions, such as dizziness, instability and light-headedness. Pathophysiological assessments and drug-reducing interventions are expected to elucidate the causal relationship.

Additionally, we showed that the 22-item fall risk index and its simple screening test were useful to predict falls in geriatric outpatients. Although both indices have been validated in community-dwelling elderly people, the present finding also showed their association with fall risk among geriatric outpatients. The difference of statistical significance between fall risk index and simple screening test might be a result of small sample size or the difference in the contribution of each item to total scores between the two indices. "Taking five or more drugs" accounts for only one item out of the 22-item fall risk index; in contrast, the same questionnaire accounts two points in the 13-point simple screening test. Because polypharmacy was a strong risk factor of falls in elderly outpatients in the present study, the proportion of polypharmacy in the scores might have caused the discrepancy. Taken together, it is likely that 13-point screening test was more suitable to our subjects who were taking several medicines.

In summary, the present study showed that geriatric outpatients with polypharmacy were at a high risk of falls, especially those receiving five or more drugs. Our finding might add new information for pharmacotherapy and geriatric research in elderly patients with chronic diseases. Intervention studies examining the effect of drug reduction for the prevention of falls are required in the future.

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Disclosure statement

The authors declare no conflict of interest.

References

1 Stel VS, Pluijm SM, Deeg DJ, Smit JH, Bouter LM, Lips P. A classification tree for predicting recurrent falling in community- dwelling older persons. *J Am Geriatr Soc* 2003; **51**: 1356–1364.
2 Kojima S, Furuna T, Ikeda N, Nakamura M, Sawada Y. Falls among community-dwelling elderly people of Hokkaido, Japan. *Geriatr Gerontol Int* 2008; **8**: 272–277.
3 Okochi J, Toba T, Takahashi T *et al.* Simple screening test for risk of falls in the elderly. *Geriatr Gerontol Int* 2006; **6**: 223–227.
4 Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc* 1999; **47**: 40–50.
5 Berlie HD, Garwood CL. Diabetes medications related to an increased risk of falls and fall-related morbidity in the elderly. *Ann Pharmacother* 2010; **44**: 712–717.
6 Araki A, Ito H. Diabetes mellitus and geriatric syndromes. *Geriatr Gerontol Int* 2009; **9**: 105–114.
7 Kojima T, Akishita M, Nakamura T *et al.* Association of polypharmacy with fall risk among geriatric outpatients. *Geriatr Gerontol Int* 2011; **11**: 438–444.
8 Toba K, Okochi J, Takahashi T *et al.* Development of a portable fall risk index for elderly people living in the community. *Nippon Ronen Igakkai Zasshi* 2005; **42**: 346–352. (In Japanese.)
9 Kron M, Loy S, Sturm E *et al.* Risk indicators for falls in institutionalized frail elderly. *Am J Epidemiol* 2003; **158**: 645–653.
10 van Doorn C, Gruber-Baldini AL, Zimmerman S *et al.* Dementia as a risk factor for falls and fall injuries among nursing home residents. *J Am Geriatr Soc* 2003; **51**: 1213–1218.
11 Halfon P, Eggli Y, Van Melle G, Vagnair A. Risk of falls for hospitalized patients: a predictive model based on routinely available data. *J Clin Epidemiol* 2001; **54**: 1258–1266.
12 Tanaka M, Suemaru K, Ikegawa Y *et al.* Relationship between the risk of falling and drugs in an academic hospital. *Yakugaku Zasshi* 2008; **128**: 1355–1361.
13 Ensrud KE, Blackwell TL, Redline S *et al.* Sleep disturbances and frailty status in older community-dwelling men. *J Am Geriatr Soc* 2009; **57**: 2085–2093.
14 Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc* 1999; **47**: 30–39.
15 Woolcott JC, Richardson KJ, Wiens MO *et al.* Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med* 2009; **169**: 1952–1960.

16 Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med* 1988; **319**: 1701–1707.
17 Kelly KD, Pickett W, Yiannakoulias N *et al.* Medication use and falls in community-dwelling older persons. *Age Ageing* 2003; **32**: 503–509.
18 Thapa PB, Gideon P, Cost TW, Milam AB, Ray WA. Antidepressants and the risk of falls among nursing home residents. *N Engl J Med* 1998; **339**: 875–882.
19 Bloem BR, Steijns JA, Smits-Engelsman BC. An update on falls. *Curr Opin Neurol* 2003; **16**: 15–26.
20 Arai H, Akishita M, Teramoto S *et al.* Incidence of adverse drug reactions in geriatric units of university hospitals. *Geriatr Gerontol Int* 2005; **5**: 293–297.
21 Iwata M, Kuzuya M, Kitagawa Y, Suzuki Y, Iguchi A. Underappreciated predictors for postdischarge mortality in acute hospitalized oldest-old patients. *Gerontology* 2006; **52**: 92–98.
22 Baranzini F, Diurni M, Ceccon F *et al.* Fall-related injuries in a nursing home setting: is polypharmacy a risk factor? *BMC Health Serv Res* 2009; **9**: 228.

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REFERENCES

1. Sikkes SAM, Visser PJ, Knol DL et al. Do instrumental activities of daily living predict dementia at 1- and 2-year follow-up? Findings from the Development of Screening guidelines and diagnostic Criteria for Predementia Alzheimer's disease study J Am Geriatr Soc 2011;59:2273–2278.
2. Folstein MF, Folstein SE, McHugh PE. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–189.
3. Nasreddine ZS, Phillips NA, Bédirian V et al. The Montreal Cognitive Assessment (MoCA): A brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695–699.
4. Nouri FM, Lincoln NB. An extended activities of daily living scale for stroke patients. Clin Rehabil 1987;1:301–305.
5. Regal P. Antithyroid antibodies, cognition and IADL in the elderly. Int J Geriatr Psychiatry 2012;27, in press.

FACTORS ASSOCIATED WITH PROLONGED HOSPITAL STAY IN A GERIATRIC WARD OF A UNIVERSITY HOSPITAL IN JAPAN

To the Editor: We read with interest the article by Lakhan and colleagues,[1] which showed the high prevalence and worsening of geriatric syndrome during acute care hospitalization. Because falls, incontinence, impairment in activities of daily living (ADLs), and other geriatric syndrome components increase the care burden and limit discharge planning in acute care hospitals, geriatric syndrome might cause prolonged hospital stays. A prolonged hospital stay is one of the major determinants of medical cost and is thus a serious problem in geriatric medicine. Previous studies have shown that clinical events during hospitalization,[2,3] basic ADLs,[4] and nonmedical factors such as delayed transfer to a nursing facility or disagreement on the discharge plan among family members[5] are risk factors for prolonged hospital stay. Furthermore, because older adults have multiple comorbid conditions and are susceptible to adverse drug reactions (ADRs), these factors might be related to length of hospital stay. To test this hypothesis, the association between geriatric conditions such as geriatric syndrome, ADLs, and ADRs and prolonged hospital stay were comprehensively investigated using the database of the geriatric ward of the University of Tokyo Hospital from 1995 to 2010. The ethics committee of the Graduate School of Medicine, University of Tokyo approved this study.

All records of patients aged 65 and older from 1995 to 2010 were reviewed. Data on length of stay, acute hospitalization, ADRs, body mass index (BMI), number of diseases and drugs, geriatric syndrome, and Barthel Index were collected. Twenty-three components of geriatric syndrome such as falls, cognitive impairment, urinary incontinence, constipation, and insomnia were included in the analysis. Records lacking information on any of the variables were excluded. Cases of scheduled short-term hospitalization were excluded. Finally, the records of 1,616

Table 1. Characteristics of Study Patients and Analyses for Length of Hospital Stay (N = 1,616)

Characteristic	Value	Univariate Analysis (R or Hospital Stay, Days, Mean ± SD)	Standardized Regression Coefficient
Age, mean ± SD	78.3 ± 7.0	0.001	−0.099[d]
Sex, *n* (%)			
Female	778 (48.1)	26.8 ± 20.2	
Male	838 (51.9)	27.6 ± 24.6[a]	
Acute hospitalization, *n* (%)			
Yes	300 (18.5)	26.2 ± 21.0	
No	1,316 (81.5)	31.8 ± 28.2[a,d]	
Adverse drug reaction, *n* (%)			
Yes	190 (11.8)	26.4 ± 19.5	0.078[c]
No	1,426 (88.2)	33.3 ± 38.1[a,d]	
Body mass index, kg/m^2, mean ± SD	22.0 ± 4.1	−0.59[d]	−0.062[b]
Barthel Index (points out of 100), mean ± SD	83.1 ± 26.1	−0.178[d]	−0.13[d]
Number of diseases, mean ± SD	5.3 ± 2.3	1.43[c]	0.082[c]
Number of drugs, mean ± SD	6.8 ± 3.6	0.411[b]	–
Number of geriatric syndrome components, mean ± SD	4.6 ± 3.6	1.66[d]	0.19[d]

All data were collected soon after admission. For sex, acute hospitalization, and adverse drug reactions, a simple *t*-test was performed for univariate analysis, and values are expressed as mean ± standard deviation (SD).

[a]*P*-values are for comparison to female or no. Pearson correlation coefficients (R) are shown for the remaining factors in univariate analysis. All variables shown were included in stepwise regression analysis, and factors significantly associated were analyzed in multiple regression analysis (coefficient of determination = 0.32).

[b]$P < .05$.

[c]$P < .005$.

[d]$P < .001$.

patients were analyzed (mean age 78.3 ± 7.0, 52% male). All data were obtained soon after admission. Values are expressed as means ± standard deviations and were analyzed using JMP version 9.0.2 (SAS Institute, Inc., Cary, NC). $P < .05$ was considered statistically significant.

Mean length of stay was 27.3 ± 22.6 days (range 1–322 days). The results of univariate and multivariate analyses for length of stay are shown in Table 1. Multiple stepwise regression analysis showed that ADRs, number of diseases, and number of geriatric syndrome components were positively associated with longer hospital stay, whereas age, BMI, and Barthel Index were negatively associated. The number of geriatric syndrome components was significantly associated with hospital stay independent of number of diseases.

The present analysis demonstrated that geriatric factors such as ADRs, multiple diseases, low BMI, ADL dependence, and number of geriatric syndrome components were associated with longer hospital stay in a large group. The finding that ADRs are a risk for prolonged hospital stay is consistent with a previous report,[6] and ADL dependence has been reported as a risk in a smaller group.[4] Furthermore, the number of geriatric syndrome components and undernutrition were risk factors for prolonged hospital stay in a large-scale study. Frailty, which is also known to be a risk factor,[7] was not examined independently in the present study, but ADL dependence and undernutrition, both of which are major components of frailty, were found to be risk factors, so it is reasonable to assume that frailty was associated with length of hospital stay in the current cohort as well. The present study revealed that the accumulation of geriatric syndrome components was a risk factor for prolonged hospital stay independent of multiple diseases and, presumably, frailty. Thus, geriatric syndrome should be comprehensively managed during hospitalization. The reason for the negative association between age and length of stay is unclear, but the presence of young-old patients with disability or complicated conditions on the geriatric ward might have influenced the results.

In summary, the present study provides new insight into the significance of geriatric conditions in relation to prolonged hospital stay in older adults. ADL dependence, undernutrition, ADRs, and geriatric syndrome should be carefully assessed and interventions provided when caring for older inpatients.

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REFERENCES

1. Lakhan P, Jones M, Wilson A et al. A prospective cohort study of geriatric syndromes among older medical patients admitted to acute care hospitals. J Am Geriatr Soc 2011;59:2001–2008.
2. Nobili A, Licata G, Salerno F et al. Polypharmacy, length of hospital stay, and in-hospital mortality among elderly patients in internal medicine wards. The REPOSI Study. Eur J Clin Pharmacol 2011;67:507–519.
3. Hauck K, Zhao X. How dangerous is a day in hospital? A model of adverse events and length of stay for medical inpatients. Med Care 2011;49:1068–1075.
4. Umegaki H, Ando F, Shimokata H et al. Factors associated with long hospital stay in geriatric wards in Japan. Geriatr Gerontol Int 2003;3:120–127.
5. Foer D, Ornstein K, Soriano TA et al. Nonmedical factors associated with prolonged hospital length of stay in an urban homebound population. J Hosp Med 2012;7:73–78.
6. Hoonhout LH, de Bruijne MC, Wagner C et al. Nature, occurrence and consequences of medication-related adverse events during hospitalization: A retrospective chart review in the Netherlands. Drug Saf 2010;33:853–864.
7. Satish S, Winograd CH, Chavez C et al. Geriatric targeting criteria as predictors of survival and health care utilization. J Am Geriatr Soc 1996; 44:914–921.

ACTIVITIES OF DAILY LIVING RATHER THAN DEPRESSIVE SYMPTOMS INCREASE THE RISK OF MORTALITY IN JAPANESE COMMUNITY-DWELLING ELDERLY PEOPLE: A 4-YEAR LONGITUDINAL SURVEY

To the Editor: The article entitled "Depressive Symptoms Increase the Risk of Mortality in Older Mexican Community-Dwelling Adults" by Piña-Escudero et al.[1] deeply impressed us. Although it has been shown that older adults with depressive symptoms (DSs) have fewer quality-adjusted life years than those with chronic medical conditions,[2] Piña-Escudero et al. in their 2-year longitudinal study, showed that DSs increase mortality risk regardless of multiple covariates such as medical conditions and disability in activities of daily living (ADL). Similarly, results of a meta-analysis of 25 studies suggest that depression increases the risk of mortality,[3] although those studies did not assess ADL in detail. The risk of mortality in Japanese community-dwelling elderly people is reported herein, focusing on DSs and ADLs in a 4-year longitudinal survey.

The study population included 1,818 community-dwelling individuals aged 65 and older in Tosa Town, Japan; 1,600 (88.0%) participants who completed self-reported geriatric questionnaires in 2006 were included in the study. The questionnaires consisted of questions on ADLs and the 15-item Geriatric Depression Scale (GDS-15).[4] For ADL assessment, participants rated their

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Short communication

3,4-Diaminopyridine improves neuromuscular transmission in a MuSK antibody-induced mouse model of myasthenia gravis

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ABSTRACT

This study investigated the effect of 3,4-diaminopyridine (3,4-DAP), a potent potentiator of transmitter release, on neuromuscular transmission *in vivo* in a mouse model of myasthenia gravis (MG) caused by antibodies against muscle-specific kinase (MuSK; MuSK-MG) and *ex vivo* in diaphragm muscle from these mice. 3,4-DAP significantly improved neuromuscular transmission, predominantly by increasing acetylcholine (ACh) release, supporting presynaptic potentiation as an effective treatment strategy for MuSK-MG patients who have defective transmitter release. In MuSK-MG, we suggest that only low-dose acetylcholinesterase (AChE) inhibitors be used to avoid side effects, and we propose that 3,4-DAP may be effective as a symptomatic therapy.

1. Introduction

Myasthenia gravis (MG) is caused by autoantibodies against postsynaptic membranes at neuromuscular junctions (NMJs), leading to failure of neuromuscular transmission mediated by acetylcholine (ACh) and clinical symptoms of ptosis, fatigue and muscle weakness. While the majority of MG cases (~90%) have antibodies against ACh receptors (AChRs; AChR-MG), MG caused by antibodies against muscle-specific kinase (MuSK; MuSK-MG) is frequently severe and requires emergent and aggressive therapy to manage respiratory distress (Vincent et al., 2008).

The therapeutic protocol for MG includes symptomatic and immunosuppressive treatments. In general, first-line symptomatic treatment is required in most patients until immunosuppressive treatment is effective. The strategy of symptomatic drugs is to improve neuromuscular transmission by increasing presynaptic transmitter release and potentiating postsynaptic effects. Acetylcholinesterase (AChE) inhibitors, which could potentiate postsynaptic effects, are generally effective for most AChR-MG patients. However, MuSK-MG patients are frequently unresponsive to these drugs or develop cholinergic crisis, characterized by increasing muscle weakness that causes dysphagia and respiratory insufficiency (Evoli et al., 2003; Sanders et al., 2003; Hatanaka et al., 2005; Evoli et al., 2008). In addition, MuSK-MG patients receiving AChE inhibitors may show abnormal patterns of repetitive firing to low-frequency motor nerve stimulation via electromyography (EMG). The emergence of repetitive firing indicates an increased sensitivity to ACh (Punga et al., 2006), which may result from the interference of MuSK with accumulation of AChE in synaptic basal lamina of NMJs (Cartaud et al., 2004). Recently, our animal model in which 100% of mice develop experimental autoimmune MG (EAMG) after immunization with MuSK protein reproduced the same EMG patterns showing hypersensitivity to ACh as MG patients. These mice also exhibited decreased levels of AChE and AChE-anchoring protein collagen Q at postsynaptic membranes, revealing the mechanism by which AChE inhibitor treatment exacerbates MuSK-MG symptoms *in vivo* (Mori et al., 2012).

Animal models of EAMG are integral for developing and assessing appropriate medications for patients afflicted with MuSK-MG. The current study focused on improving neuromuscular transmission in MG by increasing transmitter release. Specifically, we determined whether 3,4-diaminopyridine (3,4-DAP), a potent potentiator of transmitter release, could improve neuromuscular transmission *in vivo* in mice with MuSK-EAMG and *ex vivo* in diaphragm muscle from these mice.

2. Materials and methods

2.1. Immunization of mice

All procedures were approved by the Animal Care and Use Committee of Tokyo Metropolitan Geriatric Hospital and Institute of

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Gerontology. Female A/WySnJ mice aged 8 weeks or older (The Jackson Laboratory) were anesthetized and injected with 20 μg MuSK emulsified with complete Freund's adjuvant (CFA) on day 0, then boosted with 20 μg MuSK emulsified with incomplete Freund's adjuvant (IFA) on day 14. Recombinant MuSK protein was prepared as described previously (Mori et al., 2012). Control mice were injected with PBS and CFA on day 0, then boosted with PBS and IFA on day 14.

2.2. EMG

Changes in compound muscle action potential (CMAP) were determined as described previously (Mori et al., 2012). Decrement was calculated as the percent amplitude change between the first CMAP and the smallest CMAP that were evoked by a train of 10 impulses. If the amplitude of the first CMAP was also the smallest, the decrement was designated as 0%. 3,4-DAP (Tokyo Kasei) was freshly prepared in PBS and administered at 8 mg/kg, i.p. A typical mouse weighing 20 g received 100 μl of 1.6 mg/ml 3,4-DAP. EMG was performed 20 min later.

2.3. Ex vivo electrophysiology

Membrane potentials and miniature endplate potentials (MEPPs) were recorded using a specimen composed of left phrenic nerve and hemi-diaphragm muscle as described previously (Mori et al., 2012). To measure evoked endplate potentials (EPPs), μ-conotoxin GIIIB (1 μM final concentration, Peptide Institute) was applied to suppress muscle contraction, and the phrenic nerve was stimulated with supramaximal voltage at 0.7 Hz. 3,4-DAP was applied to the specimen-immersed chamber (100 μM final concentration), and synaptic events were recorded 20 min later. Amplitudes of EPPs and MEPPs were standardized to a membrane potential of −75 mV. Quantal content was calculated by using the values of mean MEPP amplitude, mean EPP amplitude and membrane potential in the same muscle fiber in the formula described previously (McLachlan and Martin, 1981). A total of 8–15 NMJs were assessed from each mouse.

2.4. Statistics

Group differences between control and MuSK-injected mice were analyzed by either unpaired *t*-tests or Mann–Whitney *U*-tests. Paired *t*-tests were used to analyze the effects of 3,4-DAP treatment in EMG experiments. One-way ANOVAs were used to assess parameters of synaptic events from *ex vivo* electrophysiology experiments. Statistical significance was set at $P<0.05$.

3. Results

3.1. 3,4-DAP improves neuromuscular transmission

About two weeks after treatment with recombinant MuSK protein (see Materials and methods), all five A/WySnJ mice exhibited MG-like phenotypes, including weight loss and muscle weakness. In addition, while EMG recordings from control gastrocnemius muscle in response to 3-Hz repetitive nerve stimulation showed no abnormal CMAP decrements (defined as >10%) (0.26 ± 0.14%; range 0–0.76%) (Fig. 1A and D), MuSK-injected gastrocnemius muscle showed significant decrements (24.0 ± 2.62%; range 16.6–32.4%) (Fig. 1B and D), indicating neuromuscular transmission failure. Again, the amplitude of the first CMAP in MuSK-injected mice (69.8 ± 7.24 mV) was significantly decreased relative to controls (102.6 ± 3.75 mV) (Fig. 1E). A single injection of 3,4-DAP (8 mg/kg) to MuSK-injected mice reversed the CMAP decrease (3.45 ± 1.51%; range 0.6–8.9%; Fig. 1C and F) and significantly increased the amplitude of the first CMAP from 12.0 mV to a maximum of 34.7 mV (25.4 ± 3.93 mV; Fig. 1G). Similarly, 3,4-DAP also significantly increased the first CMAP amplitude in control mice (15.3 ± 3.45 mV) (data not shown). These results demonstrate that 3,4-DAP improved neuromuscular transmission in MuSK-injected

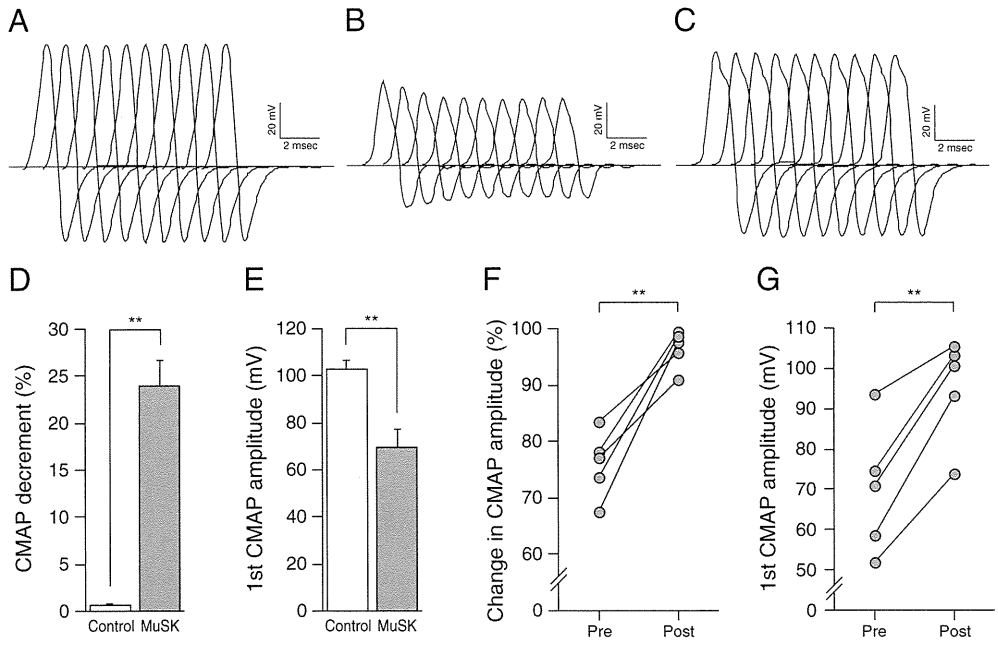

Fig. 1. Effect of 3,4-DAP on CMAP decrement.Representative EMG traces from gastrocnemius muscles of control mice (A) and MuSK-injected mice before (B) and after (C) treatment with 3,4-DAP. MuSK-injected mice exhibited significant CMAP decrement (D) and reduction in the amplitude of the first CMAP (E) (n = 5 mice/group). $^{**}P<0.01$ by Mann–Whitney *U*-test (D) or unpaired *t*-test (E). (F) Changes in CMAP decrement before and after 3,4-DAP administration in MuSK-treated mice. 3,4-DAP significantly improved CMAP decrement (84.1 ± 7.2%; range, 60.7 to 95.4%). (G) Changes in the first CMAP amplitude before and after 3,4-DAP administration in MuSK-treated mice. 3,4-DAP significantly increased CMAP amplitude (39.1 ± 7.5%, range, 12.8 to 59.3%). $^{**}P<0.01$ (paired *t*-test).

Table 1
Effect of 3,4-DAP on synaptic event parameters in control and MuSK-injected diaphragms.

		No. of NMJs (no. of mice)	MEPP amplitude (mV)	EPP amplitude (mV)	EPP area (mV × ms)	Quantal content
Control	Before 3,4-DAP	52 (5)	0.91 ± 0.05	25.5 ± 1.22	139.5 ± 7.72	41.5 ± 1.85
	After 3,4-DAP	69 (5)	1.08 ± 0.04	38.9 ± 1.23	436.7 ± 17.7	70.5 ± 3.03
MuSK-MG	Before 3,4-DAP	35 (4)	0.47 ± 0.03	11.4 ± 1.47	49.7 ± 5.73	30.1 ± 2.83
	After 3,4-DAP	54 (4)	0.64 ± 0.04	26.9 ± 1.73	178.7 ± 0.16	72.4 ± 4.30
*P, Control before 3,4-DAP *vs.* MuSK-MG before 3,4-DAP			<0.0001	<0.0001	<0.0001	<0.001
**P, Control before 3,4-DAP *vs.* Control after 3,4-DAP			<0.01	<0.0001	<0.0001	<0.0001
**P, MuSK-MG before 3,4-DAP *vs.* MuSK-MG after 3,4-DAP			<0.01	<0.0001	<0.0001	<0.0001

Data are means ± SEM. *P determined in Mann–Whitney *U*-test, and **P determined in one-way ANOVA.

mice, supporting its potential to relieve muscle fatigability and increase muscle strength, as previously described (Wirtz et al., 2009).

3.2. 3,4-DAP induces presynaptic potentiation

To examine the mechanisms underlying 3,4-DAP-induced improvement of neuromuscular transmission, we used intracellular recording of muscle fibers from excised hemi-diaphragms. As described previously (Mori et al., 2012), MEPP amplitude, EPP amplitude and mean quantal content (steady state number of quanta released by a single nerve impulse at 0.7 Hz) were significantly decreased in MuSK-injected mice compared to controls (Table 1). These results suggest that both defective transmitter release and attenuated postsynaptic sensitivity contribute to decreased EPP amplitude and CMAP decrement. Application of 3,4-DAP (100 μM) increased EPP amplitude and area by 136% and 259%, respectively (Fig. 2A, B and Table 1) and increased mean quantal content by 141% compared to pre-treatment (Table 1). No significant effect of 3,4-DAP on resting membrane potential was observed (baseline, 64.8 ± 1.78 mV; 3,4-DAP, 61.2 ± 1.61 mV). Similar effects were observed in control diaphragms (Table 1). These results indicate that 3,4-DAP potentiated ACh release from presynaptic membranes of NMJs and increased both the amplitude and duration of EPPs, resulting in reversal of CMAP decrement and increase in CMAP amplitude, as observed in EMG *in vivo*. Unexpectedly, MEPP amplitude, which is not affected by aminopyridines (Thomsen and Wilson, 1983; Giovannini et al., 2002), was increased by 36% by 3,4-DAP. Moderate, but significant, increases in MEPP amplitude were also observed in controls. Thus, increased postsynaptic membrane sensitivity may also contribute to 3,4-DAP-induced improvement in neuromuscular transmission (Table 1).

4. Discussion

Aminopyridines such as 4-AP and 3,4-DAP have been proposed to be potassium channel blockers, but a recent study demonstrated that these compounds stimulate voltage-gated calcium channels (VGCCs) (Wu et al., 2009), prolong the duration of nerve action potentials and increase ACh release from nerve terminals of NMJs (Thomsen and Wilson, 1983). In particular, 3,4-DAP has the advantage of lower brain penetration than 4-AP (Lemeignan et al., 1984) and thus is the drug of choice for neuromuscular disorders such as Lambert–Eaton myasthenic syndrome (LEMS) (Sanders, 2003).

In MuSK-MG, *in vitro* electrophysiology has shown decreased ACh release in NMJs (Burges et al., 1994; Niks et al., 2010). Consistent with these studies, the current study showed decreased ACh release in NMJs of MuSK-MG mice, demonstrating that the presynaptic defect, in addition to the smaller postsynaptic effect (Mori et al., 2012), could contribute to failure of neuromuscular transmission. In AChR-MG, which is caused exclusively by postsynaptic defects, enhanced ACh release has been attributed to compensatory increases in transmitter release due to retrograde signaling from the postsynaptic area to presynaptic terminals (Cull-Candy et al., 1980; Plomp et al., 1995). However, it seems that dysfunction of MuSK is unable to trigger such a mechanism. In this study, 3,4-DAP significantly improved both CMAP decrement and amplitude, mainly via increased ACh release from nerve terminals. Thus, these results suggest that presynaptic potentiation could be an effective strategy to treat MuSK-MG patients who have defective transmitter release. Interestingly, our results also showed that 3,4-DAP increased MEPP amplitude in both control (19%) and MuSK-MG (36%) mice. It has been demonstrated that aminopyridines have no effect on postsynaptic function in normal or LEMS IgG-treated NMJs (Thomsen and Wilson, 1983; Giovannini et al., 2002), whereas other study demonstrated that 4-AP produced a slight, non-significant increase in MEPP amplitude (7–11%) in normal NMJs (Kim et al., 1980). Detailed analysis will be needed to elucidate the effect of 3,4-DAP on the increased sensitivity of postsynaptic membranes in the NMJs of normal and MuSK-MG mice.

Symptomatic treatment for MG includes increasing presynaptic transmitter release and potentiating postsynaptic effects. In fact, administration of aminopyridines such as 3,4-DAP and 4-AP has been shown to improve muscle strength and neuromuscular transmission in AChR-MG patients and might therefore be valuable adjunctive treatments to AChE inhibitors (Lundh et al., 1979, 1985). However, in MuSK-MG, AChE inhibitors cause hypersensitivity of postsynaptic membranes to ACh, increasing the risk for cholinergic crisis and leading to muscle cramps and fasciculations (Punga et al., 2006; Mori et al., 2012). Therefore, in MuSK-MG, we suggest that only low-dose AChE inhibitors should be used to avoid side effects, and we propose that 3,4-DAP may be useful as a symptomatic therapy.

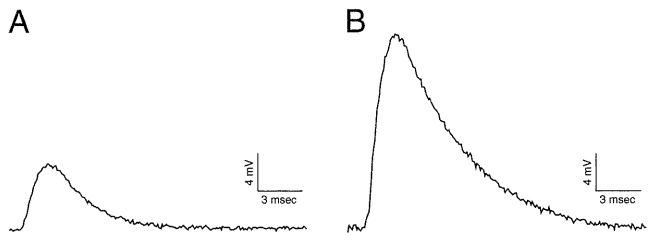

Fig. 2. Effect of 3,4-DAP on EPP.Representative EPP traces at NMJs before (A) and after (B) application of 3,4-DAP to diaphragm from MuSK-treated mice. 3,4-DAP increased both the amplitude and duration of EPPs.

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References

Burges, J., Vincent, A., Molenaar, P.C., Newsom-Davis, J., Peers, C., Wray, D., 1994. Passive transfer of seronegative myasthenia gravis to mice. Muscle Nerve 17, 1393–1400.

Cartaud, A., Strochlic, L., Guerra, M., Blanchard, B., Lambergeon, M., Krejci, E., Cartaud, J., Legay, C., 2004. MuSK is required for anchoring acetylcholinesterase at the neuromuscular junction. J. Cell Biol. 165, 505–515.

Cull-Candy, S.G., Miledi, R., Trautmann, A., Uchitel, O.D., 1980. On the release of transmitter at normal, myasthenia gravis and myasthenic syndrome affected human end-plates. J. Physiol. 299, 621–638.

Evoli, A., Tonali, P.A., Padua, L., Monaco, M.L., Scuderi, F., Batocchi, A.P., Marino, M., Bartoccioni, E., 2003. Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. Brain 126, 2304–2311.

Evoli, A., Bianchi, M.R., Riso, R., Minicuci, G.M., Batocchi, A.P., Servidei, S., Scuderi, F., Bartoccioni, E., 2008. Response to therapy in myasthenia gravis with anti-MuSK antibodies. Ann. N. Y. Acad. Sci. 1132, 76–83.

Giovannini, F., Sher, E., Webster, R., Boot, J., Lang, B., 2002. Calcium channel subtypes contributing to acetylcholine release from normal, 4-aminopyridine-treated and myasthenic syndrome auto-antibodies-affected neuromuscular junctions. Br. J. Pharmacol. 136, 1135–1145.

Hatanaka, Y., Hemmi, S., Morgan, M.B., Scheufele, M.L., Claussen, G.C., Wolfe, G.I., Oh, S.J., 2005. Nonresponsiveness to anticholinesterase agents in patients with MuSK-antibody-positive MG. Neurology 65, 1508–1509.

Kim, Y.I., Goldner, M.M., Sanders, D.B., 1980. Facilitatory effects of 4-aminopyridine on normal neuromuscular transmission. Muscle Nerve 3, 105–111.

Lemeignan, M., Millart, H., Lamiable, D., Molgo, J., Lechat, P., 1984. Evaluation of 4-aminopyridine and 3,4-diaminopyridine penetrability into cerebrospinal fluid in anesthetized rats. Brain Res. 304, 166–169.

Lundh, H., Nilsson, O., Rosen, I., 1979. Effects of 4-aminopyridine in myasthenia gravis. J. Neurol. Neurosurg. Psychiatry 42, 171–175.

Lundh, H., Nilsson, O., Rosen, I., 1985. Improvement in neuromuscular transmission in myasthenia gravis by 3,4-diaminopyridine. Eur. Arch. Psychiatry Neurol. Sci. 234, 374–377.

McLachlan, E.M., Martin, A.R., 1981. Non-linear summation of end-plate potentials in the frog and mouse. J. Physiol. 311, 307–324.

Mori, S., Kubo, S., Akiyoshi, T., Yamada, S., Miyazaki, T., Hotta, H., Dezaki, J., Kishi, M., Konishi, T., Nishino, Y., Miyazawa, A., Maruyama, N., Shigemoto, K., 2012. Antibodies against muscle-specific kinase impair both presynaptic and postsynaptic functions in a murine model of myasthenia gravis. Am. J. Pathol. 180, 798–810.

Niks, E.H., Kuks, J.B., Wokke, J.H., Veldman, H., Bakker, E., Verschuuren, J.J., Plomp, J.J., 2010. Pre- and postsynaptic neuromuscular junction abnormalities in musk myasthenia. Muscle Nerve 42, 283–288.

Plomp, J.J., Van Kempen, G.T., De Baets, M.B., Graus, Y.M., Kuks, J.B., Molenaar, P.C., 1995. Acetylcholine release in myasthenia gravis: regulation at single end-plate level. Ann. Neurol. 37, 627–636.

Punga, A.R., Flink, R., Askmark, H., Stalberg, E.V., 2006. Cholinergic neuromuscular hyperactivity in patients with myasthenia gravis seropositive for MuSK antibody. Muscle Nerve 34, 111–115.

Sanders, D.B., 2003. Lambert–Eaton myasthenic syndrome: diagnosis and treatment. Ann. N. Y. Acad. Sci. 998, 500–508.

Sanders, D.B., El-Salem, K., Massey, J.M., McConville, J., Vincent, A., 2003. Clinical aspects of MuSK antibody positive seronegative MG. Neurology 60, 1978–1980.

Thomsen, R.H., Wilson, D.F., 1983. Effects of 4-aminopyridine and 3,4-diaminopyridine on transmitter release at the neuromuscular junction. J. Pharmacol. Exp. Ther. 227, 260–265.

Vincent, A., Leite, M.I., Farrugia, M.E., Jacob, S., Viegas, S., Shiraishi, H., Benveniste, O., Morgan, B.P., Hilton-Jones, D., Newsom-Davis, J., Beeson, D., Willcox, N., 2008. Myasthenia gravis seronegative for acetylcholine receptor antibodies. Ann. N. Y. Acad. Sci. 1132, 84–92.

Wirtz, P.W., Verschuuren, J.J., van Dijk, J.G., de Kam, M.L., Schoemaker, R.C., van Hasselt, J.G., Titulaer, M.J., Tjaden, U.R., den Hartigh, J., van Gerven, J.M., 2009. Efficacy of 3,4-diaminopyridine and pyridostigmine in the treatment of Lambert–Eaton myasthenic syndrome: a randomized, double-blind, placebo-controlled, crossover study. Clin. Pharmacol. Ther. 86, 44–48.

Wu, Z.Z., Li, D.P., Chen, S.R., Pan, H.L., 2009. Aminopyridines potentiate synaptic and neuromuscular transmission by targeting the voltage-activated calcium channel beta subunit. J. Biol. Chem. 284, 36453–36461.

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【トピックス】<第35回日本基礎老化学会大会奨励賞受賞>

老齢マウスの筋線維タイプ特異的な筋萎縮の病態解明

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1. はじめに

加齢に伴い骨格筋量は減少する。一般的に、骨格筋量は40歳から徐々に減少し始め、80歳までには30-40%の筋量が失われることが知られている[1]。筋肉量減少に伴う筋萎縮は転倒等によるケガの危険性を増加させ[2]、場合によっては寝たきり状態となり要介護問題へと発展し得るため非常に重要な研究課題である。基礎疾患を伴わない加齢性の筋萎縮（加齢性筋肉減少症：サルコペニア）の原因としては酸化ストレスの増加をはじめ、ミトコンドリア機能の低下など様々な要因が提唱されているが詳細な発症メカニズムは未解明である[3]。

筋は多様な細胞から構成される複雑な組織である。筋を構成する筋線維は、収縮特性・代謝特性・疲労耐性等の違いから遅筋線維と速筋線維に大別することができ、酸化的な代謝特性を持ち持久力を発揮するTypeⅠ筋線維や嫌気的な代謝特性を持ち瞬発力を発揮するTypeⅡb筋線維、そして両方の性質を持つTypeⅡaやⅡx筋線維といった、それぞれ性質が全く異なる筋線維タイプに分類されている(表1)[4]。従って、筋は解剖学的及び機能的にも異なる細胞から構成される集団として捉える必要がある。そして、加齢性の筋萎縮に伴い筋線維タイプが変化することはこれまで多く報告されている[5-7]。

筋線維タイプ	遅筋線維	速筋線維		
	Ⅰ	Ⅱa	Ⅱx	Ⅱb
収縮スピード	遅い	速い（Ⅱb＞Ⅱx＞Ⅱa）		
疲労耐性	高い	高い	やや高い	低い
代謝	酸化系	酸化系/解糖系	解糖系	解糖系
エネルギー効率	優	やや優	劣	劣
解剖学的（色）	赤	赤	白	白
筋線維の大きさ	やや大きい	小さい	中間	大きい

表1 筋線維タイプの特性
骨格筋を構成する筋線維は表に示した性質の違いから、遅筋線維と速筋線維に大別される。
酸化的な代謝特性を持ち、持久力に優れるTypeⅠ,Ⅱa,Ⅱx筋線維や嫌気的な代謝特性を持ち、瞬発力に優れるTypeⅡb,(Ⅱx)筋線維に分類することができ、各筋線維タイプは全く異なる性質を持つ。 このように筋は、多様な細胞から構成される非常に複雑な組織である。

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しかしながら、筋萎縮の機構と筋線維タイプの変化との因果関係については未解明である。そこで我々は、若齢(8ヶ月齢)及び老齢(32ヶ月齢)のC57BL/6NCrマウス(♀)における下肢筋の凍結筋横断切片を作製し、筋萎縮に伴う筋線維タイプレベルの筋機能の変化を、組織化学的・病理学的方法で体系的に解析を行った。本稿では、速筋の長指伸筋（TypeⅡa,x,b 筋線維で構成される)と遅筋のひらめ筋（TypeⅠ,Ⅱa筋線維から構成される)を対象にして、筋線維タイプ単位の筋萎縮とミトコンドリア機能の変化に着目した研究成果について紹介する。

2. 老齢マウスは筋線維タイプ特異的に筋萎縮の様式が異なる

老齢マウスのひらめ筋及び長指伸筋は共に筋重量の減少と、顕著な萎縮を示した。次に、各筋線維タイプ別の筋萎縮を解析するためにATPase(pH4.7)染色と各筋線維タイプに対する免疫染色を行った。その結果、老齢マウスのひらめ筋(TypeⅠ,Ⅱa筋線維から構成される)はTypeⅡa筋線維特異的な筋線維数の減少を示したが、筋線維の面積はTypeⅠ,Ⅱa筋線維共に維持された。一方、老齢マウスの長指伸筋(TypeⅡa,x,b筋線維で構成される)ではTypeⅡb筋線維特異的な筋線維数の減少と筋線維面積の低下を示した。このように、老齢マウスのひらめ筋と長指伸筋は筋線維タイプ特異的に異なる筋萎縮の様式を示すことが明らかとなった(表2)。

	ひらめ筋		長指伸筋		
	TypeⅠ	TypeⅡa	TypeⅡa	TypeⅡx	TypeⅡb
筋線維数	変化なし	減少	変化なし	変化なし	減少
筋線維面積	変化なし	変化なし	変化なし	変化なし	減少
筋線維タイプ群化	群化	変化なし	群化	群化	脱群化
ミトコンドリア活性	低下	変化なし	変化なし	変化なし	変化なし

表2
下肢骨格筋の加齢変化
表に示したように、老齢マウスのひらめ筋と長指伸筋は筋線維タイプ特異的に筋萎縮の様式やミトコンドリア活性の変化が異なることが明らかとなった。

3. 老齢マウス骨格筋における筋線維タイプ群化

これまで、加齢に伴い神経筋接合部の機能・形態が変化し筋線維の脱神経支配が生じて筋の萎縮が進行することが示唆されている[8-10]。そして、老齢マウスや高齢者の萎縮した筋の断面を解析すると随伴して同じ筋線維タイプの群化が報告されている[5,6]。筋線維タイプの

群化とは同じ筋線維タイプが群を形成して存在する状態であり、筋線維タイプの分布異常である。これは筋線維の脱神経支配に伴い、代償性に近隣の筋線維の神経筋接合部からの神経終末の分枝が伸張して再神経支配されることで起きると考えられている[11]が、その機構はよく分かっていない。

そこで、老齢マウスの除神経・再神経支配が筋線維タイプに及ぼす影響を調べるために、独自の評価方法によって筋線維タイプの群化を定量的に解析した。興味深いことに老齢マウスの長指伸筋において、顕著な萎縮を示したTypeⅡb筋線維の脱群化や、それに伴うTypeⅡa及びⅡxの群化が確認された(表2)。老齢マウスのひらめ筋においてもTypeⅠ筋線維の群化が確認された(表2)。今後は、脱神経支配と筋萎縮との関連性も含めて筋線維特異的な群化のメカニズムについて解析を行う。

4. Type1 筋線維 特異的なミトコンドリア呼吸酵素活性の低下

エネルギー代謝が盛んに行われている骨格筋において、ミトコンドリア機能の低下は筋機能の低下や筋萎縮を引き起こすと考えられている[12]。実際に高齢者や老齢動物の骨格筋において、ミトコンドリアの活性が低下することは既に知られている[12,13]。しかし、これまでの研究は筋全体についての生化学的な手法によるミトコンドリア機能解析であり、筋線維タイプ単位でミトコンドリア活性に着目した報告は非常に少ない。そこで、まずは速筋と遅筋におけるミトコンドリア機能の加齢変化を調べるために、nicotinamide adenine dinucleotide dehydrogenase (NADH; 呼吸鎖複合体Ⅰ), succinate dehydrogenase (SDH; 呼吸鎖複合体Ⅱ), cytochrome c oxidase (COX; 呼吸鎖複合体Ⅳ)染色によるミトコンドリア呼吸酵素活性の解析を行った。その結果、老齢マウスのひらめ筋におけるSDH活性は維持されたが、NADH及びCOX活性は顕著に低下しておりミトコンドリアの機能が低下していることが確認された(表2)。一方、老齢マウスの長指伸筋におけるミトコンドリア活性は維持された(表2)。

次に、ひらめ筋の連続切片を作製した。そして、TypeⅠとTypeⅡ(a)の筋線維タイプを区別するためにATPase(pH4.7)染色を行い、COX染色及びNADH染色によって筋線維単位でのミトコンドリア呼吸酵素活性を解析した。その結果、老齢マウスのひらめ筋はType1筋線維特異的にCOX活性及びNADH活性の低下を示すことが明らかとなった(表2)。

これまで老化によりひらめ筋全体のミトコンドリア機能が低下すると考えられていたが、我々の結果はTypeⅠ筋線維特異的にミトコンドリア呼吸酵素活性の低下が起きていることを示している。それでは、なぜTypeⅠ筋線維特異的にミトコンドリア活性が低下するのであろうか？ 近年、ミトコンドリアの融合と分裂といった形態変化がミトコンドリアの機能維持に必要であるとの報告がなされているが[14,15]、骨格筋におけるミトコンドリア形態の加齢変化を解析した研究は極めて少ない。興味深いことに、ミトコンドリアの形態は遅筋線維と速筋線維で異なることが示唆されていることから[16]、加齢に伴い筋線維タイプ特異的にミトコンドリアの形態が変化することが予想される。今後は、筋線維タイプ単位のミトコンドリア形態変化と機能変化に着目して、老化による筋萎縮と筋機能低下の因果関係について研究を行いたいと考えている。

5. おわりに

今回の我々の結果は、ミトコンドリア活性の低下と筋萎縮の因果関係について再考を要することを示している(図)。顕著なミトコンドリア活性の低下を示したTypeⅠ筋線維は筋持久力の低下に関連していると考えられるが、筋線維数と筋線維面積は減少していなかった。一方で、ひらめ筋のTypeⅡa筋線維や長指伸筋のTypeⅡb筋線維はミトコンドリア活性が維持されたが、筋線維数の減少や筋線維面積の低下が見られた。これらの結果は筋機能の低下と筋萎縮のメカニズムが複数存在することを示している。今後は、前述した筋線維タイプレベルでのミトコンドリア形態変化に着目した解析に加えて神経筋接合部の加齢変化ついても合わせて詳細に解析したい。

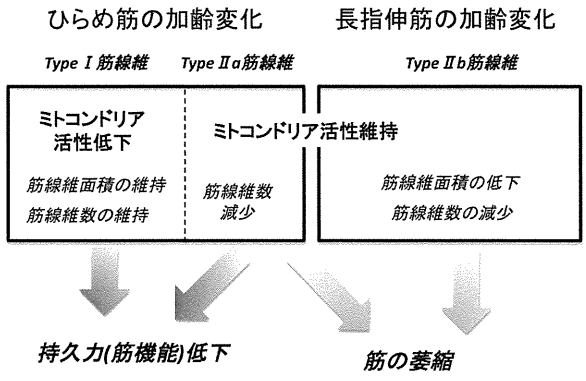

図 加齢性筋萎縮の多様なメカニズム

引用文献

[1] Lexell, J., C.C. Taylor, and M. Sjostrom. What is the cause of the aging atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. J Neurol Sci 84:275-294, 1988.

[2] Wolfson L, Judge J, Whipple R et al. Strength is a major factor in balance, gait, and the occurrence of falls. J Gerontol A Biol Sci Med Sci 50: 64-67, 1995.

[3] Hall DT, Ma JF, Marco SD et al. Inducible nitric oxide synthase (iNOS) in muscle wasting syndrome, sarcopenia, and cacthexia. Aging 3:702-715, 2011.

[4] Bloemberg D and Quadrilatero J. Rapid determination of myosin heavy chain expression in rat, mouse, and human skeletal muscle using

multicolor immunofluorescence analysis. PLoS ONE 7:e35273, 2012.
[5] Chai RJ, Vukovic J, Dunlop S et al. Striking denervation of neuromuscular junctions without lumbar motoneuron loss in geriatric mouse muscle. PLoS ONE 6:e28090, 2011.
[6] Short KR, Vittone JL, Bigelow ML et al. Changes in myosin heavy chain mRNA and protein expression in human skeletal muscle with age and endurance exercise training. J Apple Physiol 99:95-102, 2005.
[7] Rowan SL, Rygiel K, Purves-Smith FM et al. Denervation causes fiber atrophy and myosin heavy chain co-expression in senescent skeletal muscle. PLoS ONE 7:e29082, 2012.
[8] Jang YC and Van Remmen H. Age-assosiated alterations of the neuromuscular junction. Exp Gerontol 46:193-198, 2011.
[9] Lexell J. Human aging, muscle mass, and fiber type composition. J Gerontol A Biol Sci Med Sci 50:11-16, 1995.
[10] 埜中征哉. 臨床のための筋病理. 4:218-221, 2012.
[11] Doherty TJ. Invited review: Aging and sarcopenia. J Appl Physiol 95:1717-1727, 2003.
[12] Bua EA, Mckiernan SH, Wanagat J et al. Mitochondrial abnormalities are more frequent in muscles undergoing sarcopenia. J Appl Physiol 92:2617-2624, 2002.
[13] Short KR, Bigelow ML, Kahl J et al. Decline in skeletal muscle mitochondrial function with aging in humans. Proc Natl Acad Sci U S A 102:5618-5623, 2005.
[14] Picard M, Ritchie D, Thomas MM et al. Alterations in intrinsic mitochondrial function with aging are fiber type-specific and do not explain differential atrophy between muscles. Aging Cell 10:1047-1055, 2011.
[15] Seo AY, Joseph AM, Dutta D et al. New insights into the role of mitochondria in aging: mitochondrial dynamics and more. J Cell Sci 123:2533-2542, 2010.
[16] Huei F.J, Pei J.T, Syue M et al. Mitochondrial fission contributes to mitochondrial dysfunction and insulin resistance in skeletal muscle. Mol Cell Biol 32:309-319, 2012
[17] Shaw CS, Jones DA and Wagenmakers AJ. Network distribution of mitochondria and lipid droplets in human muscle fibers. Histochem Cell Bio 129:65-72, 2008.

筋肉と神経―最新基礎知見を踏まえて

Skeletal muscle and motor neuron: underlying mechanisms in sarcopenia

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Shigemoto Kazuhiro Fukunaga Daichi Mori Syuichi

抄録▶サルコペニアの病因解明には，筋だけでなく運動神経細胞と神経筋シナプス，血管，自律神経を対象として体系的に研究する必要がある．加齢により運動神経細胞数の減少，筋線維の量的・質的変化，神経筋シナプスの形態変化が起きる．また，筋幹細胞の再生能や修復効率も低下する．これらの病理学的変化のメカニズムやサルコペニアの病態との因果関係については，今後の課題として残されている．

Key Words サルコペニア，運動神経細胞，神経筋シナプス，筋線維，サテライト細胞

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はじめに

サルコペニア（加齢性筋肉減少症）は認知症と並んで高齢者のactivity of daily living（ADL）とquality of life（QOL）を損なう主要な原因となることから，その早期診断や予防法などの対策は急務の課題である．サルコペニアの臨床診断は，筋力，筋量と身体能力の3つの因子を測定して評価される[1]．サルコペニアと診断されたケースでは，すでに病態が進んでおり改善させることは困難である．認知症と同様，サルコペニアにおいても早期診断に基づく有効な予防・治療法が必要であるがいまだ確立されておらず，またその原因についてもほとんど解明されていない．サルコペニアは筋力，筋量と身体能力で臨床上評価されるが，それらの指標を対象としたサルコペニアの基礎研究により原因を解明することは困難である．

サルコペニアの基礎研究

筋の機能を維持するためには，運動神経細胞と両者のつなぎ目である神経筋シナプスが重要な役割を果たしている（図1）．サルコペニアの病因を解明するためには，筋だけでなくそれらすべてを対象に体系的に解析しなくてはならない．そのためには，まずサルコペニアの病理学的特徴を明らかにする必要がある．サルコペニアの原因は，さまざまな要因による長時間の相互作用の結果によるものであり，またヒトを対象とした実験は不可能であることから，老化モデル動物はサルコペニア研究の重要なツールとなっている．

加齢による運動神経細胞数の減少

運動神経細胞は老化に伴いどのような変化を示すのであろうか？ この観点の研究報告は極めて少ないが，1977年にイギリスから発表されたデータがある[2]．死亡時に運動機能が正常に

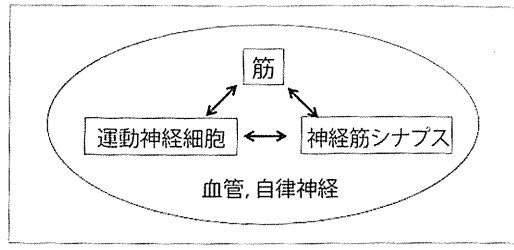

図1　サルコペニアの原因は筋以外にも存在する

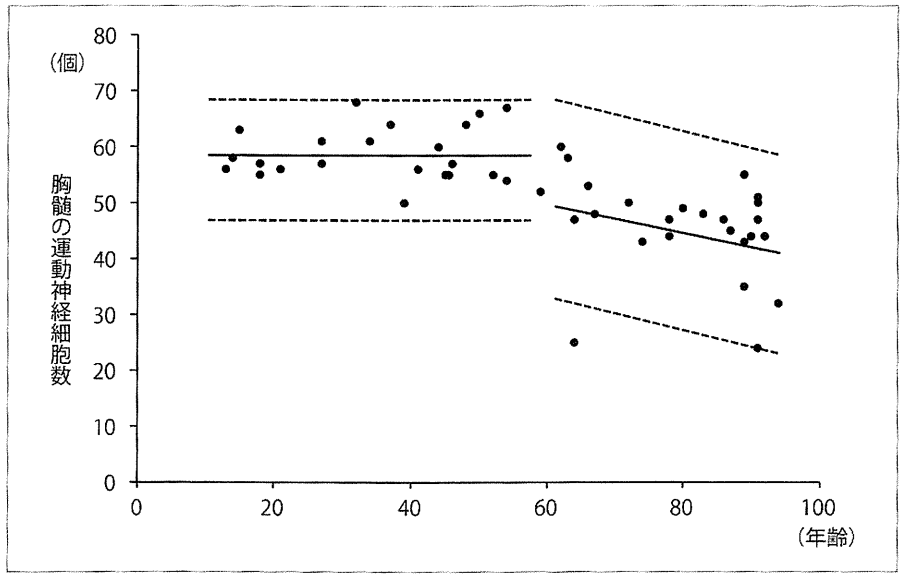

図2　加齢によるヒト脊髄の運動神経細胞数の減少
(J Neuro Sci 1977, Tomlinson et al. の図を改変)

保たれていた13～95歳までの47人の腰仙髄の一定区領域内の運動神経細胞を数えた結果を図2に示す．60歳を境にして急速に運動神経細胞数が減少していることがわかる．老化動物モデルでは，交系ラットの生後20カ月から腓腹筋を支配する運動神経細胞数が減少することが報告されている[3]．ラットの生後20カ月は，死亡率から換算するとヒトの60歳に相当する．加齢による脊髄の運動神経細胞の脱落は，臨床的なサルコペニアの病態と因果関係があると予想される．しかし，筋力低下や筋萎縮など臨床症状の出現と運動神経細胞数との関係(閾値)についてはよくわかっていない．老化モデル動物は，運動神経細胞の減少の原因解明とその病態研究に有用である．

サルコペニアと診断されたヒトの脊髄の病理組織像についての報告は少なく，認知症のように特徴的な組織像を示すかどうかも不明である．興味深いことに，超高齢社会を迎えて運動神経細胞の脱落が主原因とされているALS（筋萎縮性側索硬化症)の患者が増加しているが，一部の非定型のALSはもともと診断が難しく，サルコペニアとの鑑別が問題となりそうである．また，サルコペニアと認知症とは密接な因果関係があることから高齢者の脊髄の病理学的解析が必要である．

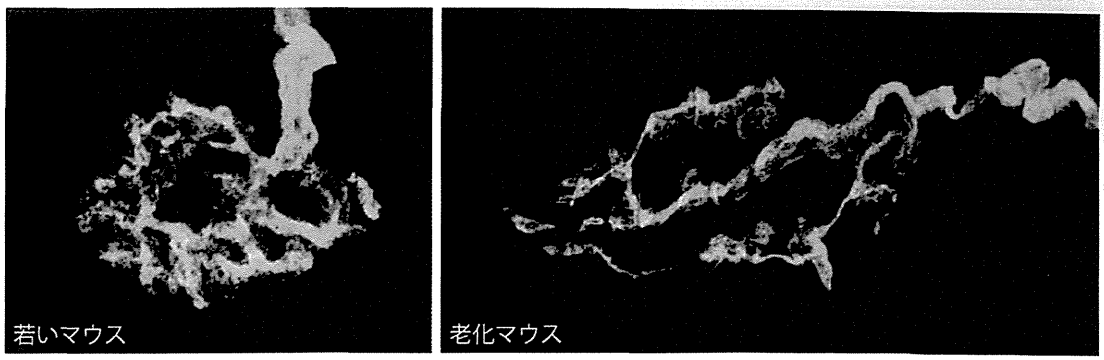

図3　老化による神経筋シナプスの形態変化
緑：運動神経終末，赤：アセチルコリン受容体

加齢による神経筋シナプスの変化

神経筋シナプスは筋と運動神経細胞のつなぎ目として神経伝達の機能を担うだけでなく，筋や運動神経自体の機能を維持するために重要な役割を果たす．加齢によりヒトや老化モデル動物(ラット，マウス)の神経筋シナプスの形態変化が顕著となる[4]．シナプスの形態が断片化，シナプス襞の減少，神経終末の分枝化，部分的あるいは完全な脱神経支配が観察される(図3)．高齢者の神経筋シナプスに関する研究は極めて少ないが，同様に形態が変化するという報告がある[5]．老化マウスの体幹，後肢や頚部の神経筋シナプスは，加齢による形態変化が顕著に観察され，一方，外眼筋や外肛門括約筋では形態が保たれている[6]．興味深いことにALSの進行に伴い患者の運動神経細胞が脱落する一方で，外眼筋を支配する脳幹の動眼神経や外転神経の神経細胞，また外肛門括約筋を支配する仙髄の神経細胞はALSの末期まで保たれることが多いとされる[7]．シナプスの機能・形態の異常は神経伝達の効率を下げて筋力低下や筋萎縮の原因になる．例えば，重症筋無力症では，自己抗体がシナプス形態および機能の維持機構を著しく障害して筋萎縮を誘導する[8~9]．シナプスの機能と形態は，運動神経終末と筋の双方からのシグナルにより保たれており，特に筋で発現するMuSK（muscle-specific kinase）蛋白が，このシナプスの相互維持に重要な役割を果たしていることがわかっている[9]．MuSKの上流および下流の分子機構が加齢により変化することが予想される．

ところで，神経筋シナプスは可塑性があり再生能を有している．そして，シナプス形態の加齢変化をカロリー制限や運動により予防できることが，マウスを使った実験で示された[4]．カロリー制限をすると全身のシナプス形態が若返るのに対して，運動の場合は負荷を受けた筋のシナプスだけが改善した．また，カロリー制限の方が運動負荷よりもシナプス形態の改善度がよかった．マウスのカロリー制限は，生後4カ月から始めて24カ月齢まで連続して行ったが，老年期に開始しても有効かどうかは不明である．運動負荷の場合は，22カ月齢のマウスに対して1カ月間だけでも有効性が確認された．ヒトも同様にシナプス形態が若返るかどうか興味が持たれる．

加齢による筋の質的変化

加齢による筋萎縮に伴う病理学的変化として，筋線維数や面積の減少だけでなく筋線維の質的な変化が起きる．筋収縮を担う筋線維は，収縮特性・代謝特性・疲労耐性などの違いから遅筋線維と速筋線維とそれぞれ性質が全く異な

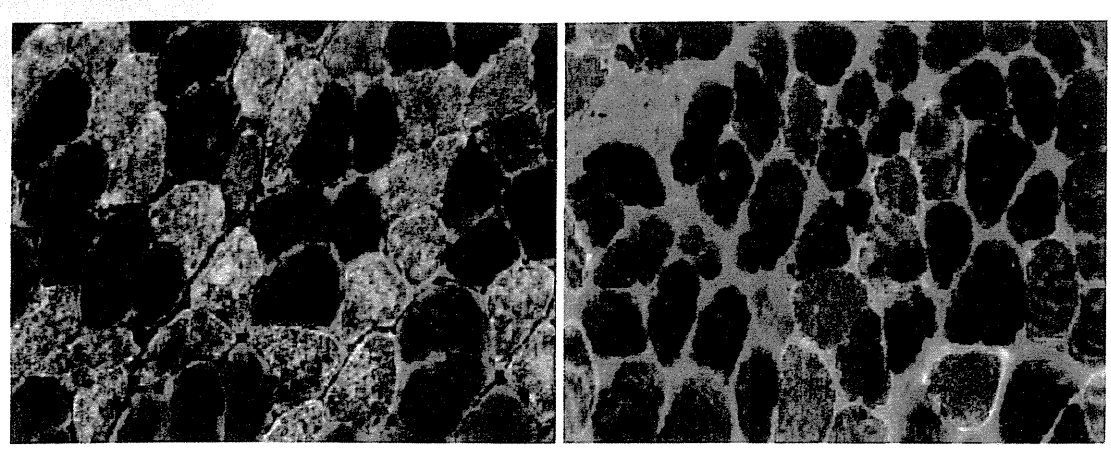

図4　老化により遅筋線維(赤) /速筋線維(緑)の比率が大きくなる(マウスのひらめ筋)

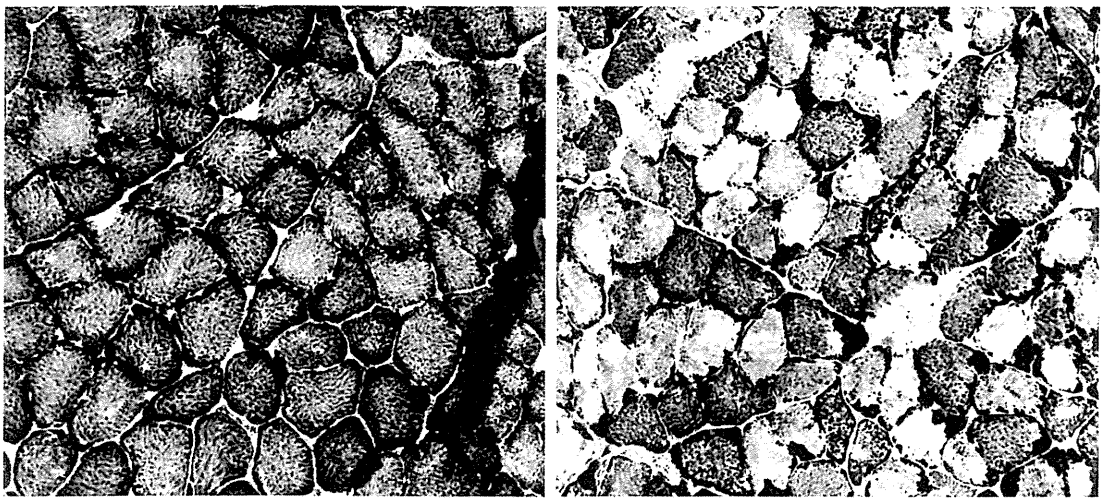

図5　老化による筋線維のミトコンドリア機能低下
シトクロームC酸化酵素活性が低下，筋線維が白く抜けて見える．

る筋線維タイプに分類される．そして，加齢により筋を構成する速筋に比べ遅筋線維の割合が増えることが知られている(図4)[10]．このような，加齢に伴う筋線維タイプの変化は，筋の代謝特性も変化していると予想されるが，実際はよくわかっていない．筋線維タイプ変化は老化動物だけでなくヒトの筋でも起きることが報告されている．

老化マウスでは，筋線維のミトコンドリア呼吸酵素活性が顕著に減少するが，筋全体に均一に起きるのではなく筋の部位そして筋線維ごとに程度が異なる(図5)[10]．ミトコンドリア機能の低下はサルコペニアの原因となると考えられるが，筋線維数と面積の減少とミトコンドリア呼吸酵素活性減少は必ずしも一致しておらず，筋力低下と筋萎縮との因果関係について検討が必要である．サルコペニア患者の筋でも，老化動物と同じ様式でミトコンドリア酵素活性が低下していると予想されるが，詳細な検討が必要である．ミトコンドリア酵素活性が保たれている筋を高齢者から採取することは非常に難しく，老化モデル動物の研究はサルコペニアの原

因を知るうえで今後も重要な手がかりとなるであろう．

筋の再生能

筋組織にはサテライト細胞という幹細胞が筋線維の表面に存在している．サテライト細胞は筋損傷を修復する必要に応じて筋細胞へ分化する．また，サテライト細胞は自己増殖して，筋線維あたり一定数になるよう維持されている．サテライト細胞による筋の修復は，筋組織が破壊されるような筋疾患では顕著に起きているが，健康な筋ではほとんど観察することができない．正常の筋では，サテライト細胞の増殖を伴う再生と修復の頻度は少ないと考えられる．

一方，老化動物では，サテライト細胞の再生能や修復効率が低下することが報告されている．また，サテライト細胞の維持に必要な周辺組織の環境(ニッチ)の老化がサテライト細胞の再生能を低下させるとしている[11]．さらに，老化とともにサテライト細胞の再生能を低下させる血中因子(Wnt蛋白，補体成分のC1qなど)が増加することが報告されている[12,13]．

おわりに

骨格筋は筋線維だけでなく多様な細胞から構成される複雑な組織である．血管や自律神経も，骨格筋の機能と構造維持に重要な役割を果たしている．これらの加齢変化が運動器システム全体の体内環境にどのような病理学的変化と機能的変化をもたらすのか今後の課題として残されている．

文　献

1) Cruz-Jentoft AJ, Baeyens JP, Bauer JM et al : Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 39 : 412–423, 2010
2) Tomlinson BE, Irving D : The numbers of limb motor neurons in the human lumbosacral cord throughout life. J Neurol Sci 34 : 213–219, 1977
3) Kanda K, Hashizume K, Miwa T et al : Overloading a muscle does not alter the rate of motoneuronal loss in aged rats. Neurobiol Aging 17 : 613–617, 1996
4) Valdez G, Tapia JC, Kang H et al : Attenuation of age-related changes in mouse neuromuscular synapses by caloric restriction and exercise. Proc Natl Acad Sci USA 107 : 14863–14868, 2010
5) Oda K : Age changes of motor innervation and acetylcholine receptor distribution on human skeletal muscle fibres. J Neurol Sci 66 : 327–338, 1984
6) Valdez G, Tapia JC, Lichtman JW et al : Shared resistance to aging and ALS in neuromuscular junctions of specific muscles. PLoS One 7 : e34640, 2012
7) Mosier DR, Siklos L, Appel SH : Resistance of extraocular motoneuron terminals to effects of amyotrophic lateral sclerosis sera. Neurology 54 : 252–255, 2000
8) Shigemoto K, Kubo S, Maruyama N et al : Induction of myasthenia by immunization against muscle-specific kinase. J Clin Invest 116 : 1016–1024, 2006
9) Mori S, Kubo S, Akiyoshi T et al : Antibodies against muscle-specific kinase impair both presynaptic and postsynaptic functions in a murine model of myasthenia gravis. Am J Pathol 180 : 798–810, 2012
10) 福永大地，久保幸穂，森　秀一，他：老齢マウスの筋線維タイプ特異的な筋萎縮の病態解明．基礎老化研究 36：47–49, 2012
11) Conboy IM, Conboy MJ, Wagers AJ et al : Rejuvenation of aged progenitor cells by exposure to a young systemic environment. Nature 433 : 760–764, 2005
12) Brack AS, Conboy MJ, Roy S et al : Increased Wnt signaling during aging alters muscle stem cell fate and increases fibrosis. Science 317 : 807–810, 2007
13) Naito AT, Sumida T, Nomura S et al : Complement C1q activates canonical Wnt signaling and promotes aging-related phenotypes. Cell 149 : 1298–1313, 2012

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6

Behavioral Treatment for Geriatric Syndrome

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1. Introduction

Geriatric syndrome is a term used to capture complex clinical conditions such as frailty, falls and fractures, urinary incontinence, malnutrition, and declining mental health, which do not fit into discrete disease categories but are serious problems among the elderly population. They are highly prevalent in the elderly, especially in frail adults with low levels of functional capacity. These geriatric syndromes have a large effect on the development of disability, dependence, decrease in quality of life, morbidity, and mortality. Having multiple underlying factors involving impairments in multiple organ systems contribute to the occurrence of geriatric syndromes (Tinetti et al., 1995). Thus, prevention and treatment of geriatric syndromes such as frailty, falls, and urinary incontinence in its early stages are important strategies in maintaining health and independence among the elderly.

This chapter will focus on frailty, falls, and urinary incontinence, as they are the most common geriatric syndromes among community-dwelling elderly people.

1.1 Shared risk factors for distinct geriatric syndrome

A main feature of geriatric syndrome is that multiple risk factors contribute to their etiology. Research has suggested that vision and hearing impairment, anxiety, as well as upper and lower extremity impairments are associated with incontinence, falling, and occurrence of functional dependence.

The risk of each geriatric syndrome is greater with increasing number of predisposing factors possessed. Furthermore, incontinence and falling are associated with the occurrence of functional dependence. Geriatric syndromes; therefore, may contribute both indirectly, through shared risk factors, and directly to functional dependence in the elderly. One model unifying the concepts of geriatric syndromes has been proposed by Inouye et al., (2007) demonstrating that shared risk factors may lead to one or more geriatric syndromes, and eventually to frailty. Once frail, this may feedback to the development of more risk factors, which in turn may lead to other geriatric syndromes, further frailness, and ultimately disability, dependence, and even death.

Frailty can be defined as a condition in which three or more of the following criteria are present: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed,