Keywords: cognitive function, Comprehensive Geriatric Assessment (CGA), depression, hearing impairment, visual impairment.

Introduction

During the last 50 years, the survival rates and consequently the demographic profile of the Japanese population have dramatically changed. The average lifespan of Japanese men and women is 78.3 and 85.2 years, respectively, which is the longest in the world. The proportion of people aged over 65 years reached 18% of the total population in 2002, and is expected to reach 25% by 2020.

Because it is known that a number of undetected problems exist in elderly people, a systematic approach to detect geriatric problems, the Comprehensive Geriatric Assessment (CGA) emerged and started in the 1980s.[1-3] Today, evidence from randomized controlled trials or systematic reviews on the CGA is increasingly available, supporting the use of hospital-based programs with extended ambulatory follow up.[4,5] In primary care settings, however, time and staffs are limited, which makes it difficult to adopt the CGA. Therefore, the CGA for outpatients should be concise, meet the demand of the patients, and be a guide for the subsequent intervention according to the results of CGA.

The first aim of this study was to validate the usefulness of the CGA in primary clinical settings by examining functional and sociomedical problems in elderly patients. Through the analysis, we studied which factor can affect activities of daily living (ADL) and depressive moods in elderly patients. We also tried to find the incidence of patients with cognitive impairment or depressive moods in the patients who had visited our clinic for the first time.

Sensory impairment, cognitive impairment, functional disability and depression are common problems affecting aged people. However, few studies have directly compared their associations in outpatients. The second purpose of the study therefore was to examine associations among these factors and to determine whether sensory impairment is associated with cognitive function, functional disability or depression in elderly patients.

Methods

Subjects

All elderly (basically 65 years or older) patients who came to Kyoto University Hospital for the first time or had not been seen for the past 6 months in this hospital were asked to attend the health promotion clinic. This was a general clinic and screened many problems in elderly patients, not specialized to memory loss. We started an outpatient CGA in this clinic in May 2001. Three hundred and nine consecutive patients aged 65 and older (mean age ± SD: 75.5 ± 6.6) who visited the outpatient clinic from March 2002 through June 2004 were enrolled for this study after the written informed consent was taken. The study protocol was approved by the Ethical Committee of Kyoto University School of Medicine.

Measurements

The CGA was performed on the day of patient visit by trained speech therapists in the room next to the consultation room after history taking and physical examination were performed. Intensive training and close supervision were provided to these speech therapists to increase interviewer reliability. Blood pressure was measured twice in the sitting position and hypertension was defined based on the World Health Organization (WHO) criteria as the mean pressure level over 140 mmHg in systolic or 90 mmHg in diastolic or in those taking antihypertensive drugs. Demographic data including age, gender, marital status, living conditions, working status, past medical history including cerebrovascular diseases, heart diseases, fracture and arthropathy, were determined by interviewing the patients themselves or their family. Uncertain data was recorded blank. Hearing and vision were assessed by the question: "Do you have difficulty hearing or seeing (even while wearing aids)?' Answers were scored as: 3 (no trouble in hearing or seeing in daily living); 2 (need loud voices or large letters, cannot hear low voices or read newspaper); or 1 (hardly or unable to hear or see). The scores 1 and 2 were defined as hearing or visually impaired. Cognitive status was assessed using the Mini-Mental State Examination (MMSE). Patients with an MMSE score of 23 or less were defined as cognitively impaired. In five of the patients we gave up performing MMSE because of sensory impairment or other reasons. We screened depressive symptoms using the Japanese version of the 15-item Geriatric Depression Scale (GDS-15).[6] Higher scores of GDS-15 indicate a greater degree of depressive mood. In this study, we used a cut-off point of 5/6. Therefore, we defined depression as a GDS-15 score of 6 or more.

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We used the Barthel Index for assessment of basic activities of daily living (BADL) and used a cutoff point of 100/95 as most of patients were full score. For higher levels of functional capacity, each subject's independence was rated by the Tokyo Metropolitan Institute of Gerontology Index of Competence (TMIG-IC).[7] This assessment consists of a 13-item index including three sublevels of competence: (i) instrumental self-maintenance; (ii) intellectual activities; and (iii) social role. In this study, we defined decline of ADL as a TMIG-IC score of 9 or less, slightly lower score than the age-specific mean of TMIG-IC, 10.7.[7] Mobility was assessed using timed 'up and go'.

Timed 'up and go'

This test of balance is commonly used to examine functional mobility in elderly subjects.[8] The test requires the subject to stand up, walk 3 m (10 ft), turn, walk back and sit down. The time to complete the test is strongly correlated to functional mobility. Elderly people who can complete the test in less than 17 s are independent in transfer tasks, which are normal activities in daily living.[9] We then defined completion in more than 17 s as gait difficulty.

Statistical analysis

Commercially available statistical software, STAT View (SAS Institute, Cary, NC, USA) was used. Continuous data were analyzed by the Mann–Whitney's *U*-test. Dichotomous data were analyzed by analysis. Multiple logistic regression analysis was used to determine the relationships between the GDS-15 and TMIG-IC and screened items in the CGA including age and sex. Associations were considered statistically significant at a level of $P < 0.05$.

Results

Table 1 summarizes the patient characteristics in the study population. The mean age of the patients was 75.5 and the percentage of males was 36.6%. Memory loss was the most frequent chief complaint in our outpatient clinic. Among the 309 patients, 59 patients (19.0%) came to the hospital complaining of memory loss and three patients with hallucinations or delusions, which typically occurs later in the course of dementia.[10] Thirty-six of the 59 patients who complained of memory loss were given a diagnosis of probable Alzheimer's disease (AD) according to diagnostic standards developed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.[11] Five of the 59 patients with a chief complaint of memory loss were diagnosed with depression.

Table 1 Baseline characteristics of study patients

Parameter	Value
Total subjects (*n*)	309
Age, mean (SD)	75.5 (6.6)
Male subjects	113 (36.6%)
Cerebrovascular diseases ($n = 308$)	
Yes	21 (6.8%)
No	287 (93.2%)
Heart diseases ($n = 301$)	
Yes	46 (15.3%)
No	255 (84.7%)
Fracture or joint disease ($n = 304$)	
Yes	108 (35.5%)
No	196 (64.5%)
Anti-hypertensive drug ($n = 302$)	
Yes	93 (30.8%)
No	209 (69.2%)
Chief complaints ($n = 309$)	
Memory loss	59 (19.1%)
Psychiatric symptoms	3 (1.0%)
Others	247 (80.0%)

The numbers do not always add up to 309 because of unapplicable values on some variables.

Table 2 shows the diagnostic tests and cutoff points used in this assessment and the prevalence of each screened problem. The problem with highest prevalence was hypertension. Approximately 30% of the patients were taking antihypertensive drugs, while 63.8% of total patients were hypertensive at the physical examination at our clinic. Although it might be expected, patients taking antihypertensive drugs tended to be hypertensive. The proportion of depressive patients was 41.9% in this study when we used the cutoff point 5/6 on the GDS-15. The incidence of impaired ADL and gait disturbance was similar in the TMIG-IC using the cutoff point of 9/10 or in timed 'up and go' using the cutoff point of 17 s.

Patients with cognitive impairment were older, complaining of memory loss more frequently than those without cognitive impairment (Table 3). Among 76 patients who had scores of 23 or less in the MMSE, 38 patients had a chief complaint of memory loss, while 38 patients had chief complaints other than memory loss, such as headache, dizziness and so forth.

We then performed multiple logistic regression analysis to determine which factor screened in the CGA can affect the GDS-15 (Table 4) or TMIG-IC (Table 5). Among the factors studied, hearing impairment was significantly associated with high GDS scores. Impaired ADL (lower TMIG index), female gender, and the presence of hypertension were also correlated with GDS scores. However, age, MMSE, Barthel Index, timed 'up

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Table 2 Prevalence of each screened problem

	Problem	Diagnostic test	Cut-off point	No of patients	Prevalence
Cognition	Cognitive impairment	MMSE ($n = 304$)	Score = 23	59	19.4%
Mood	Depression	GDS-15 ($n = 309$)	Score = 6	130	42.1%
Activity	Decline of BADL	Barthel Index ($n = 307$)	Score = 95	29	9.4%
	Decline of ADL	TMIG-IC ($n = 309$)	Score = 9	83	26.9%
	Gait disturbance	Timed 'up and go' ($n = 283$)	Score = 17	78	27.6%
Sensory	Visual impairment	'Do you have difficulty seeing?' ($n = 309$)	Yes	31	10.0%
	Hearing impairment	'Do you have difficulty hearing?' ($n = 309$)	Yes	37	12.0%
Physical	Hypertension	Blood pressure (mmHg) ($n = 301$)	SBP = 140 or DBP = 90	191	63.5%

ADL, activities of daily living; BADL, basic activities of daily living.

Table 3 Characteristics of patients with or without cognitive impairment

MMSE score	≤23 ($n = 76$)	≥24 ($n = 227$)	P
Mean age (SD), years	78.1 (6.4)	74.6 (6.5)	<0.001*
Chief complaints of memory loss			
Yes	38	21	
No	38	206	<0.001†
Regular medical treatment			
Yes	58	191	
No	18	36	0.1229†

*The Mann–Whitney's U-test was used. †The χ^2 test was used. MMSE, the Mini-Mental State Examination.

Table 4 Independent significant associations of each screened problem with depression: multiple logistic regression analysis

Variable	Adjusted Odds ratio	95%CI	P-value
Age	1	1.0–1.0	n.s.
Male gender	0.5	0.3–1.0	$P < 0.05$
MMSE	1	1.0–1.1	n.s.
Barthel Index	1	0.7–1.5	n.s.
Timed 'Up & Go'	1	0.9–1.1	n.s.
TMIG	1.3	1.1–1.5	$P < 0.01$
Hearing impairment	5	1.5–16.1	$P < 0.01$
Visual impairment	1.2	0.5–3.1	n.s.
Hypertension	2	2.1–3.6	$P < 0.05$

95%CI, 95% confidence interval; n.s., not significant.

Table 5 Independent significant associations of each screened problem with lower TMIG-IC score: multiple logistic regression analysis

Variable	Adjusted odds ratio	95%CI	P-value
Age	1	1.0–1.0	n.s.
Female gender	1.6	0.8–3.0	n.s.
MMSE	1.1	1.0–1.2	$P < 0.01$
GDS-15	0.9	0.8–1.0	$P < 0.05$
Barthel Index	1.4	0.9–2.4	n.s.
Timed 'up and go'	0.9	0.8–1.0	n.s.
Hearing impairment	3.2	1.2–8.8	$P < 0.05$
Visual impairment	3.2	1.0–10.0	$P < 0.05$
Hypertension	1.4	0.7–2.5	n.s.

GDS-15, 15-item Geriatric Depression Scale.

and go' or visual impairment were not associated with GDS scores. On the other hand, hearing and visual impairment was significantly associated with a lower TMIG index. MMSE and GDS scores were also significantly associated with a lower TMIG index, while age, gender, Barthel Index, timed 'up and go' or the presence of hypertension was not associated with a lower TMIG index.

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Discussion

In this study we have demonstrated that an outpatient CGA is very useful in detecting geriatric problems, such as cognitive impairment and depressive mood in elderly patients. We also showed that asking about visual and hearing impairment is helpful in detecting functional disabilities and depressive moods.

From the high prevalence of patients with cognitive impairment in our clinic, screening the elderly patients with the MMSE would be more important to detect the patients with cognitive impairment. However, the MMSE is not sensitive enough to detect patients with mild cognitive impairment (MCI). Recently, new methods to improve the detection of MCI have been developed,[12,13] and we should adopt them in outpatient clinical practice for those complaining of memory loss, but with normal MMSE scores.

An early diagnosis of AD is important because early treatment of AD with acetylcholine esterase inhibitors prolongs the period in which the patient's cognitive function is maintained at a relatively high level,[14] and may modify the rate of progression. Further, early diagnosis of AD provides some comfort to the patients and their family by explaining the changes in the patient's behavior and also allows the practitioner to counsel the patients and their family about prognosis. Nevertheless, two-thirds of patients are moderately demented at the time of first diagnosis.[15,16] This is partly due to the lack of recognition of dementia by their family members or primary care physicians.[17] Education should be extended to promote awareness of the early symptoms and signs of dementia among not only the general public but also the health-care professionals.

Among 130 patients (41.9% of total patients) with GDS scores of 6 or over, 40 patients (30.8%) received antidepressant drug therapy later in our clinic. The reported prevalence of depression in elderly people varies among different ethnic groups.[18] Compared to the prevalence of depression in Japanese community-dwelling elderly, in which 33.5% of participants had GDS scores suggestive of depression (GDS 6 or over),[19] it is quite reasonable to suggest that the prevalence of depression in geriatric outpatients was slightly higher than that in community-dwelling elderly. More attention should be paid to this highly prevalent and treatable condition in elderly patients in view of under treatment of depression in general practice.[20,21]

Despite the fact that visual impairment is common in elderly persons[22] and that visual disability has profound effects on functions and quality of life (QOL), the effect of routine screening for visual impairment has yet to be proven in clinical trials. The Cochrane Database of Systematic Reviews found no evidence for community-based screening of elderly people asking questions about subjective visual impairment. One of the factors contributing to the lack of effectiveness is that individuals who reported visual problems in a screening may not have asked for further care because of the lack of perception of a 'need' for intervention about their visual impairment.[23] Recently, the potential impact of visual impairment on functional status or depression is supported by a number of studies.[24–28] In our study, visual impairment was significantly correlated with functional impairment. Because at least 40% of visual impairment can be treatable or preventable,[22] geriatricians and primary care physicians should pay more attention to reduce visual disabilities for the improvement of functional status in elderly persons.

Hearing impairment is associated with mental health and a predictor of future decline of functional ability.[25,26,29] Our results indicate that a substantial number of elderly patients complaining of hearing loss or hearing impairment showed lower instrumental ADL; and more effects of hearing impairment were seen in mental health than visual impairment, possibly because hearing loss restricts interchange with others and contributes to isolation of elderly people. Moreover, Smeeth pointed out that not only ownership of hearing aids but also adequate and regular use of them were critical for people with hearing loss.[30] Clinicians could alleviate a major source of disability in elderly people by improvement in detection and management of hearing impairment.

Although the CGA was performed in a university hospital, where the percentage of referred patients was relatively high, the frequency of patients with past medical history of cerebrovascular disease, heart disease, fracture, and arthropathy or hypertensive patients was close to that in general hospitals.[15] Our health promotion clinic was not specifically for patients with cognitive impairment. Therefore, patients in this study were elderly patients with various medical problems.

Our study has several limitations. First, sensory impairment was based on self-reported items in multiple screening tests, and we did not conduct further examination including audiometry or visual acuity test. However, we need a simple test that could be administered in primary care settings for elderly patients. Moreover, self-reported sensory impairment has been validated in several studies.[31,32] Although further study in the relationship between clinical testing and self-reported items are needed, the prevalence of sensory impairment in our data was similar to those found in others.[31–33]

Second, these are cross-sectional data, and we performed neither follow-up assessment nor intervention. A comprehensive strategy of intervention and follow-up assessment would be needed to determine whether or not sensory impairments result in depression and functional impairment and whether or not screening elderly people for sensory impairment is effective.

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In summary, we have shown that outpatient CGA is useful to detect impaired ADL, cognitive impairment, or depressive moods of elderly patients, although it is time consuming. Asking about sensory impairment, such as visual and hearing impairment would also be important to assess the geriatric problems of elderly patients. Concise and practical assessment in the outpatient clinic would be necessary to improve the QOL of elderly people.

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Cognitive impairment and frontal-subcortical geriatric syndrome are associated with metabolic syndrome in a stroke-free population

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Abstract

Background: Metabolic syndrome (Met.S) consists of a conglomeration of obesity, hypertension, glucose intolerance, and dislipidemia. Frontal-subcortical geriatric syndrome (FSCS) is caused by ischemic disruption of the frontal-subcortical network. It is unknown if Met.S is associated with FSCS.

Methods: We evaluated 422 community-dwelling elderly (≥60) in Brazil. FSCS was defined as the presence of at least one frontal release sign (grasping, palmomental, snout, or glabellar) plus coexistence of ≥3 the following criteria: (1) cognitive impairment, (2) late-onset depression, (3) neuromotor dysfunction, and (4) urgency incontinence. All values were adjusted to age and gender.

Results: Met.S was present in 39.3% of all subjects. Cases without any of the FSCS components represented 37.2% ('successful neuroaging' group). People with 1–3 of the FSCS components ('borderline pathological neuroaging' group) were majority (52.6%), whereas those with 4–5 of these components (FSCS group) were minority (10.2%). Met.S was significantly associated with FSCS (OR = 5.9; CI: 1.5–23.4) and cognitive impairment (OR = 2.2; CI: 1.1–4.6) among stroke-free subjects. Number of Met.S components explained 30.7% of the variance on the number of FSCS criteria ($P < 0.001$). If Met.S were theoretically removed from this population, prevalence of FSCS would decline by 31.6% and that of cognitive impairment by 21.4%.

Conclusions: Met.S was significantly associated with a 5.9 and 2.2 times higher chance of FSCS and cognitive impairment, respectively. Met.S might be a major determinant of 'successful' or 'pathological' neuroaging in western societies.
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Keywords: Frontal-subcortical; Metabolic syndrome; Successful aging; Cognitive impairment; Vascular depression; Executive dysfunction; Neuromotor dysfunction; Urgency-type incontinence; Elderly; Brazil

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Keywords: Frontal-subcortical; Metabolic syndrome; Successful aging; Cognitive impairment; Vascular depression; Executive dysfunction; Neuromotor dysfunction; Urgency-type incontinence; Elderly; Brazil

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Table 1
Baseline characteristics between Met.S and control groups

	Metabolic syndrome		
	No	Yes	*P*-value[a]
N (%)	256 (60.7)	166 (39.3)	–
Age	68.3	67.9	0.455
Gender (%)	166 (64.8)	97 (58.4)	0.186
White/Mestizo	1.21:1.0	1.23:1.0	0.592
Income (US$)	712	662	0.342
Education (years)	3.11	2.88	0.199
Live alone (%)	39 (15.2)	23 (13.9)	0.677
Anemia (%)	66 (25.8)	35 (21.1)	0.307
Albumin	4.23	4.28	0.372
Systolic BP (mmHg)	152.3	159.4	0.003
Diastolic BP (mmHg)	88	91	0.004
Mean arterial BP (mmHg)	106.5	112.0	0.001
Hypertension (%)	207 (80.9)	157 (94.6)	<0.001
Pulse pressure (mmHg)	65.5	69.4	0.085
Pulse rate (min)	73.3	74.8	0.036
BMI (kg/m^2)	26.4	30.4	<0.001
Obesity (BMI > 30 kg/m^2)	33 (12.9)	143 (86.2)	<0.001
Total cholesterol (mg/dl)	188.1	189.8	0.627
HDL-C (mg/dl)	48.9	34.8	<0.001
HDL-C < 40 (M) < 45 (F) mg/dl (%)	69 (27.0)	153 (92.2)	<0.001
T-Cho/HDL ratio	3.9	5.6	<0.001
LDL-c (mg/dl)	115.2	121.4	0.04
Triglycerides (mg/dl)	119.6	168.2	<0.001
Triglycerides < 150 mg/dl (%)	22 (8.6)	115 (69.3)	<0.001
Glucose (mg/dl)	110.7	144.1	<0.001
Glucose intolerance (%)	19 (7.4)	59 (35.6)	<0.001
Diabetes mellitus 2 (%)	30 11.7	73 (44.0)	<0.001
Number of metabolic syndrome components	0.93	2.9	<0.001
Sleep (hours)	7.28	7.32	0.874
Taking drugs (%)	230 (89.8)	148 (89.2)	0.786
Alcohol (>once a week)	63 (24.6)	31 (18.7)	0.293
Smoking past (%)	61 (23.8)	43 (25.9)	0.364
Smoking present (%)	32 (12.5)	20 (12.0)	0.851
Bone fracture (%)	78 (30.5)	46 (27.7)	0.574
Osteoarthrosis (%)	119 (46.5)	82 (49.4)	0.552
Heart diseases (%)	73 (28.5)	52 (31.3)	0.602
Ischemic heart disease (%)	23 (9.0)	17 (10.2)	0.656
Stroke (%)	21 (8.2)	27 (13.6)	0.109
Actively working (%)	171 (66.8)	91 (54.8)	0.008
Regular exercise[b] (%)	106 (41.4)	32 (19.3)	0.003

BP, blood pressure; BMI, body mass index; HDL-c, HDL-cholesterol; T-Cho, total cholesterol; LDL-c, LDL-cholesterol.
[a] *t*-Test for numeric and Chi-square for categorical variables.
[b] Greater than or equal to three times a week.

individual features presented a consistent association with the other components of the syndrome, except for the association between cognitive impairment and the Functional Reach test, which was of borderline significance.

Age alone explained 47% of all MMSE variance in the Met.S group, but just 12.8% in the control group (difference = 34.2%; $P < 0.001$). Analogously, the difference on the GDS variation according to age was 18.7% between the Met.S and the control groups. For all evaluated neurofunctional variables there was a significant trend for the control group to keep a more homogeneous score through the different ages when compared with the Met.S group, suggesting a faster (pathological) neuroaging process in this last group ($P < 0.001$ for all differences).

There was a significant association between Met.S and incontinence (OR = 4.8; CI: 1.0–21.1), but not between stroke and incontinence (CI: 0.5–11.9).

Fig. 1A depicts the cognitive (MMSE), affective (GDS), neuromotor (Up&Go and Functional Reach), executive (ECF-WM and ECF-ADL), and physical function (ADL) scores according to the number of Met.S risk factors. There was a consistent and significant worsening on these respective scores with increasing number of Met.S components. There were no significant differences on average age or gender distribution in these different groups.

Fig. 1B shows the respective OR for the investigated neurofunctional variables. All variables were associated with a significant higher risk for lower performance when the num-

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Table 2
Metabolic syndrome (Met.S) as an associated factor for dysfunction in several neurofunctional variables and consistency of associations among the diverse variables utilized to assess the FSCS

	Met.S	Met.S PAR (%)	Frontal-subcortical geriatric syndrome components (consistency of their associations)						
			Cognitive impairment	Depression	Up&Go test	Functional Reach	Fear of falling	Falls	Urgency incontinence	ECF-WM
Met.S	–	–								
Cognitive impairment	2.23 1.1–4.6	22.5	–							
Depression	2.93 1.8–4.9	20.6	2.9 1.8–4.9	–						
Up&Go test	3.8 1.6–9.0	28.4	2.3 1.5–3.5	1.83 1.1–3.1	–					
Functional Reach	NS	NS	1.44 0.95–2.2	1.77 1.0–3.4	1.6 1.0–2.6	–				
Fear of falling	2.0 1.1–3.7	19.7	3.1 1.9–4.9	4.1 2.4–7.0	2.1 1.3–3.4	2.1 1.3–3.4	–			
Falls	2.2 1.1–4.4	21.4	2.9 1.9–4.4	2.54 1.5–4.3	2.3 1.5–3.6	1.6 1.0–2.4	3.71 2.3–3.0	–		
Urgency incontinence	4.6 1.0–21.1	30.8	3.1 2.7–3.5	5.2 1.5–18.3	2.0 1.8–2.3	4.2 1.0–17.6	5.3 1.5–19.2	3.9 1.1–14.1	–	
ECF-WM	2.2 1.1–4.5	27.1	NA	2.2 1.3–3.9	4.0 2.3–6.9	1.7 1.1–2.5	3.1 1.9–5.0	2.4 1.5–3.7	4.04 1.0–16.3	–
ECF-ADL	2.4 1.1–5.2	22.9	6.1 3.8–9.7	7.0 3.6–13.7	3.4 2.0–5.8	1.8 1.2–2.7	4.3 2.5–7.1	1.8 1.2–2.8	11.0 4.1–29.5	4.3 2.8–6.5

PAR, population attributable risk (see Section 2); ECF-WK, executive control function-working memory; ECF-ADL, executive control function-related activities of daily living; NS, not significant (if $P > 0.05$); NA, not applicable. See Section 2 for cut points of continuous variables.

ber of Met.S components was equal or higher than three ($P < 0.05$ for all).

Fig. 1C illustrates the proportion of cases considered to present "successful neuroaging", 'borderline pathological neuroaging', and FSCS. From zero to three or more Met.S components, there was a significant decrease in the percentage of 'successful neuroaging' cases, along with increasing prevalence of FSCS ($P < 0.001$, adjusted to age and gender), whereas cases with 'borderline pathological neuroaging' did not present significant differences in its distribution. The additional risk of 1 Met.S component for coexisting FSCS was 1.59 ($P = 0.017$, adjusted for age and gender).

Met.S was associated with a 2.2 (CI: 1.0–4.6; $P = 0.035$) higher likelihood of having a low ECL-WM and a 2.4 (CI: 1.1–5.2; $P = 0.021$) higher chance of impairment in the ECF-ADL (adjusted for non-ECF-ADL, IADL, age and gender). Correlation between ECF-WM and ECF-ADL scores ($R = 0.419$; $P < 0.001$) was much stronger than that between ECF-WM and the non-ECF-ADL scores ($R = 0.177$).

Obesity was associated only with falls (OR = 1.67; CI: 1.0–2.6) but this association disappeared once the Met.S cases were removed (CI: 0.44–2.5). Neither the other variables related to neuromotor function, nor those reflecting cognitive, affective, executive or urinary function were associated with obesity. Obesity was also not associated with FSCS itself (CI: 0.71–3.1). Moreover, adjustment for BMI did not significantly alter the associations between FSCS features and Met.S shown above.

4. Discussion

Both Met.S [30] and FSCS [82] are relatively newly 'reborn' nosological concepts. Insulin resistance increases with age in most subjects [17,18]. The relationship between insulin resistance, cerebrovascular disease and neurodegenerative diseases is tantalizing in its potential to offer an integrated model for aging of the body and of the brain [18].

In the present study, 37.2% of all elderly presented no component of the FSCS and were considered as making the 'successful' neuroaging group specifically for this regard. Interestingly, a very recent metanalysis on successful aging included 29 studies and has shown that, in average, 35.8% of the investigated elderly were considered as presenting 'successful' aging [22].

In contrast, 8.6% of all clinical stroke-free elderly had a diagnosis compatible with FSCS. The Rotterdam Study has found that among community-dwelling elderly, taking 70 years as mean age (similar to our population), prevalence of silent brain infarct was nearly 17% [93]. The same study has also reported that silent brain infarcts were five times as prevalent as symptomatic ones in the general elderly popu-

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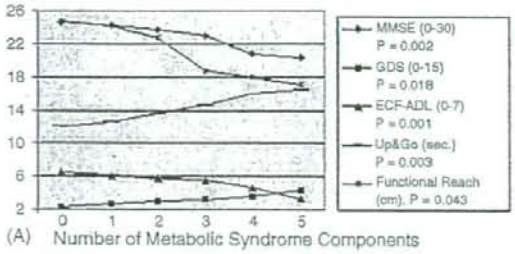

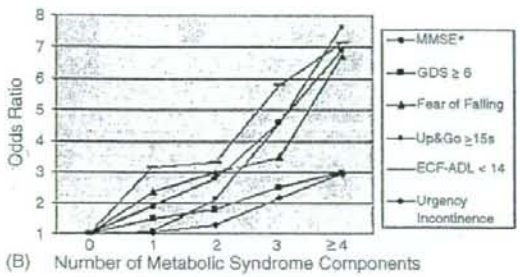

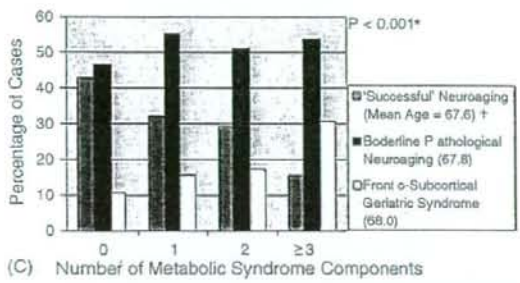

Fig. 1. (A) Cognitive, neuromotor, affective, executive, and functional variables scores according to the number of metabolic syndrome components. (B) Odds ratio for lower performance in the different neurofunctional tests according to the number of metabolic syndrome components. (C) Groups by degree of 'neuroaging' vs. number of metabolic syndrome components. MMSE, mini-mental state examination; GDS, geriatric depression scale; ECF-WK, executive control function-working memory. ECF-ADL, executive control function-related activities of daily living.

lation [93]. If this is true also for our population we would expected a prevalence of silent brain infarctions of roughly 47% (9.5% × 5), which is well above the 10.2% prevalence of FSCS here found. Therefore, among those 51.1% who had 1–3 features of the FSCS and were classified as belonging to the borderline 'pathological' neuroaging group, many subjects might still have silent strokes. This implies that our definition of FSCS had possibly a high specificity but might have excluded many milder cases in the spectrum from normality (successful neuroaging) to the FSCS. Indeed, because just 10 (2.4%) cases in our population had urgency incontinence, FCSC diagnosis was highly dependent upon the concomitant presence of cognitive impairment, depression and gait disorder. In fact, just 3 (7%) cases out of 43 depended on urgency incontinence for a diagnosis of FSCS.

As we have excluded cases with stroke episodes, and WML/lacunar strokes were already shown to be associated with FSCS and its individual compounds [53,82], we believe that frontal-subcortical small-vessel disease may be the one important mediating factor for the association between Met.S and FSCS found in this study.

The present study included just people aged 60 years and over. This moment coincides with a sharper acceleration of the decline in the cognitive function and functional status for a large proportion of individuals [75]. Rates of polio- and leuko-araiosis also accelerate geometrically after age 60, correlating with cortical and subcortical atrophy, ventricular enlargement and decreased synaptic density during aging [75,82]. However, even tough leukoaraiosis is age-related, it is accelerated by hypertension, DM and oligaemia [82]. Indeed, there are evidences that Met.S and hyperinsulinemia: (1) accelerate the aging process [33], (2) are strongly associated with lacunar strokes and WML [6,50,63,71], and (3) are a risk factor for dementia [49].

FSCS was strongly associated with Met.S (OR = 6.9). Removing stroke cases decreased the power of the association by 14.5% (OR = 5.9), without changing the significance of the association. Moreover, stroke presented just a weak trend towards an association with Met.S (CI: 0.88–3.3; $P = 0.109$). Taken together these results suggest that asymptomatic lacunar strokes and WML might be responsible for an appreciable part of this association. These results may also imply that Met.S might be more closely related to microvascular cerebrovasculopathy (FSCS etiology) than to major stroke episodes.

Among the stroke-free population, prevalence of FSCS would be reduced by 32.6% if Met.S were theoretically eliminated.

Met.S was also individually associated with lower cognitive and neuromotor functions, depressive symptoms, fear of falling, falls, functional dependence and urgency incontinence. Because Met.S was associated with FSCS, hyperinsulinism and the other four major components of Met.S (obesity, HT, glucose intolerance, and dislipidemia) are probably still actuating to promote vascular disease at older age. Indeed, the number of Met.S components explained 30.7% of the variance on the number of FSCS criteria. When both variables are considered as dichotomies, i.e. having or not Met.S and FSCS, this value is significantly reduced (14.6%), suggesting the effect to be incremental. However, due to the crossectional nature of this research, these values might account for just a fraction of all the cumulative variance on FSCS attributable to Met.S. In fact, for a given cerebrovas-

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cular risk factor the maximum explanatory variance upon outcomes might be found some 10–20 years, or even more, before this outcome [14].

Diagnosis of previous stroke was strongly associated with FSCS (OR = 4.2). Unfortunately, diagnose of ischemic stroke subtype was not available in this sample. However, considering that: (1) in LA lacunar strokes are often more common than atherothrombotic ones [87]; (2) silent lacunar strokes often precede clinical stroke and increase its risk by 4–10 times [51]; (3) subjects with clinical stroke have a three-fold higher chance for coexisting subcortical silent lacunar strokes [93], the association between clinical stroke and FSCS was not surprising.

Interestingly, FSCS was even more strongly associated with Met.S (OR = 5.9) than with stroke (OR = 4.2), suggesting that Met.S might have a preference for small-vessel disease, lacunar infarction and WML, all neuropathological characteristics of FSCS. Indeed, there is evidence that Met.S is less associated with large atherothrombotic stroke than with small, lacunar strokes and WML [6].

Met.S was responsible for nearly 20% of cases with 'fear of falling'. This is not surprising since gait disorders are common in cerebrovascular diseases and vascular dementia, and even predicts the development of the later [94]. Walking is generally viewed as an automated, over-learned, rhythmic motor task. New evidences suggest, however, that walking is a complex motor task. Walking was shown to be associated with higher-level cognitive resources, specifically executive function, which is dependent upon the frontal lobes [40]. Frontal gait is common in the elderly, increases the number of necessary steps, and requires longer walking an ascertained distance [40]. Frontal gait in the elderly is most often the result of cerebrovascular disease [40].

There was a significant association between Met.S and incontinence (OR = 4.8), but absence of association between stroke and incontinence (CI: 0.5–11.9). This phenomenon suggests that Met.S may impair urinary continence not through major strokes but mainly due to small-vessel disease and WML in the frontal-subcortical network. Indeed, there is evidence that, both urinary inhibition and lower motor function depend on neural fibers that pass through periventricular white matter [92], which are generally compromised by multiple WML and lacunes in the FSCS. Upper motor function is usually spared because fibers descending to the upper limbs are located further to the ventricle, being better irrigated and, hence, disturbed less frequently [44].

All individual criteria for FSCS presented a consistent association with the other features of the syndrome. This finding provides further evidence that the concept of FSCS, besides having a common etiology [54,82], is 'statistically consistent'.

Age alone explained as much as 47% of all MMSE variance in the Met.S group, but just 12.8% in the control group (difference = 34.2%). Analogously, the difference on the GDS variation according to age was 18.7% between the Met.S and the control groups. For all neurofunctional variables evaluated there was a significant trend for the control group to keep a more homogeneous score through the different ages as compared with the Met.S group, suggesting a faster (pathological) neuroaging process in this last group.

There was a consistent and significant worsening in the neurofunctional scores with the increase in the number of individual Met.S components. Moreover, with the increasing number of Met.S components there was a significant decrease in the percentage of 'successful neuroaging' cases, along with an increase in the prevalence of FSCS cases. Mean additional risk of 1 Met.S component for coexisting FSCS was 1.59.

The decrease in performance with age for each neurofunctional variable was significantly lower in the non-Met.S group than in the Met.S group ($P < 0.001$ for all). In the case of GDS there was no change at all in its mean across ages among those without Met.S. The strength of the inverse relationship between the MMSE and GDS scores was much stronger in the Met.S group ($R = -0.38$; $P < 0.001$) than in the non-Met.S group ($R = -0.11$; $P = 0.064$; $P < 0.05$ for difference), where it did not reach significance, suggesting a less important vascular relationship between MMSE and GDS in the non-Met.S group than in the Met.S group. Moreover, there were no cases of GDS ≥ 12 in the non-Met.S group, whereas the Met.S group presented three cases where GDS ≥ 12 (5.6%), in despite of the higher number of subjects in the former group (60.7%). This suggests that not just risk of depression is higher among the Met.S group, but also that depressive cases tended to be more severe in this group. Indeed, mean GDS was higher among Met.S depressed subjects (10.1) than among non-Met.S ones (8.0; $P = 0.047$).

The strong inverse relationship between MMSE and GDS scores found in this population ($R = -0.353$; $P < 0.001$) completely disappeared after adjusting for the presence of FSCS ($R = 0.206$). We believe this is not merely an effect of grouping both cognitive impairment and depression cases together when using these variables as criteria for FSCS. Indeed, among those with 'successful neuroaging' alone there was no significant correlation between MMSE and GDS ($P = 0.22$). Taken together, these results suggest that the usual association between cognitive impairment and depression in the general elderly population seems to be mainly due to a common vascular cause among those experiencing 'pathological' aging.

Elderly with Met.S were 2.2 and 2.4 times more likely to present lower ECL-WM and ECF-ADL scores, respectively, than controls. Furthermore, correlation between ECF-WM and ECF-ADL scales ($R = 0.419$; $P < 0.001$) was much stronger than that between ECF-WM and the non-ECF-ADL scale ($R = 0.177$), possibly indicating the expected shared ECF measurement between both. This is in accord with the finding that, among older people, insulin resistance is independently associated with poor performance in frontal cortex neuropsychological tests related to ECF [34].

Lack of regular exercise was significantly more common in the Met.S group. Physical activity has been shown to reduce both the risk of Met.S and stroke [78]. Reaven himself

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acknowledged that the obvious treatment for what he termed "Syndrome X" (Met.S) is weight maintenance and physical activity [47].

4.1. Frontal-subcortical syndrome, neurodegeneration, and the cerebrovascular hypothesis

A large body of evidence has been suggesting that AD [20,48,55,60,70,88], Parkinson disease (PD) [9,12,26,57] and late-onset depression [2,5,13,28,58,70] are strongly associated with vascular (pathological) aging as well as among themselves more than what it would simply be expected by probability. At instance, 70% of patients with PD develop dementia [9]. Moreover, often the presence of frontal-subcortical atrophy seems to be partially related to the coexistence of cognitive impairment, PD and late-onset depression [9,12,57,58,70]. These disorders, though clinically and neuropathologically distinct, seem to share a common risk profile [26]. Patients with AD, PD and hypertension exhibit similar ultrastructural breakdown of cerebral capillaries [26]. There is increasing evidence that this shared risk is accelerated vascular aging, which, in turn, is promoted by cardiovascular risk factors [26]. Cerebrovascular disease disproportionably affects frontal systems [44] and frontal system atrophy is also common to AD, vascular dementia (VaD), and late-onset depression [9].

While stroke reflects a dramatic disturbance of the cerebrovasculature, FSCS may be the consequence of insidious chronic changes in the microcirculation [82]. The frontal-subcortical network is particularly susceptible to suboptimal oxygen and glucose offer [44]. While atherosclerosis of these thin arterioles may cause lacunes, WML would be caused by chronic partial ischemia to the terminal, watershed zones [44]. These zones are located mainly in the frontal-subcortical region, are irrigated by long penetrating branches of the anterior and middle cerebral arteries, and are more susceptible to disturbances of generalized poor perfusion [44]. Additionally, there is a higher susceptibility of the cerebral microvascular endothelium to the mitogenic and metabolic effects of insulin compared with endothelium from other vessel territories [99]. Indeed, cerebrovascular endothelial cell proliferation, swelling and luminal narrowing are a feature of hyperinsulogenic states such as diabetes and Met.S, and also a common consequence of the oligoischemic brain [17,99]. Age-related alterations in energy metabolism contribute to an increased vulnerability of the aging brain to anoxic damage [79]. Besides neurodegeneration, mild chronic hypoperfusion (−30%) may lead also to a non-infarctional state with impaired neuronal function [79], in resemblance to what happens with the 'hibernating' myocardium. Atleast a part of the neurofunctional deficit in cerebral ischemic states may be related to the consequent 'transmission failure' (neurotransmitter deficits) [85].

It has been shown that the degree of WML and lacunar infarcts found in the MRI strongly correlates and predicts aspects of the FSCS [50,82]. In a very recent study, Met.S, but not conventional risk factors, was independently associated with intracranial atherosclerosis and lacunar stroke, both neuropathological correlates of FSCS [82]. Moreover, a study of identical elderly male twins showed that the most significant determinant of late life WML were glucose levels, HDL-c, and systolic blood pressure, all which are components of the Met.S [14].

Risk of AD was found to double among hyperinsulinemic elderly [60], and this effect seems to be independent of the apolipoprotein E4 phenotype [55]. Cognitive impairment with but not without subcortical features is also associated with features of insulin resistance syndrome [18]. Hyperinsulinemia was shown to independently increase the risk of WML [99]. A study evidenced that insulin levels are significantly higher in patients with lacunar stroke or subcortical atherosclerotic encephalopathy than in normal control subjects [99]. In older asymptomatic hypertensive subjects, hyperinsulinemia is associated with lacunar-type silent cerebral infarcts, particularly those located in the subcortical white matter [50]. It has been also shown that reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy even among the non-diabetic elderly [16].

4.2. Metabolic syndrome and cerebral small-vessel disease in Latin America

Met.S is a virtually inexistent clinical entity in primitive societies and reflects well the overfeeding and sedentary environment to which modern societies are influenced. Because it agglutinates the major risk factors for atherosclerosis and cardiovascular diseases, it might appropriately be considered the most common chronic epidemic syndrome in modern western societies [62].

High BMI values explain the variance of roughly 37% of all strokes in both North and Latin America (highest PAR in the world) [45]. Latin American elderly have already one of the highest BMI among all the world regions [45]. At any given BMI point Hispanic older people seem to be at a higher risk for DM and Met.S than Blacks and non-Hispanic Whites [7]. Moreover, Hispanics have the highest rates of Met.S in the USA [30].

Besides Met.S impairment in cognition, a study has shown Met.S to be a risk factor for the development of functional disability among Mexican-American older people [73]. The SABE Study has found that in many Latin American countries functional dependence among the elderly is high, and that, among all surveyed countries, Brazil has one of the highest prevalences of functional disability [74].

There is a higher influence of DM in predicting both cognitive and functional decline among Hispanic-Americans than among both Blacks and Whites [7], and cerebral small-vessel disease/microangiopathy may be the immediate cause. Older Hispanic Americans are at almost three-fold higher risk for concomitant cognitive and functional decline than the other two ethnic groups. Besides, asymptomatic small-vessel (lacu-

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nar) strokes seem to be more common among Hispanics living both in the USA and Latin America [87] than in non-Hispanic Whites.

In the NHANES III [69] Study, Met.S was associated with a two times higher chance of having stroke. Average age and Met.S criteria being similar to the one in the present study, a lower prevalence of Met.S (24%) was found as compared with the present study prevalence (36.3%). Moreover, in that study the prevalence of stroke was 2.9%, therefore substantially lower than the prevalence found (9.5%) among our Brazilian elderly. Because, in a give elderly population, prevalence of asymptomatic stroke is usually five-times higher than that of symptomatic ones [93], the above comparison points to a larger (in populational terms) association between Met.S and stroke, and possibly FSCS, in Brazil.

4.3. Frontal-subcortical syndrome: a conceptual framework for neuropathological aging

As a group, humans show a steeper decline in both cognitive and functional performances from the seventh decade on [75]. Leukoaraiosis and lacunes might be one of the pathological hallmarkers of this transition [75]. However, rates of cerebral degenerative and cognitive/functional changes differ widely from one person to another [82]. This difference has been shown to be related to cerebral small-vessel disease [70]. Indeed, age-related leukoaraiosis has been reported to be associated with lacunar strokes and selective cognitive, affective, executive, neuromotor, and sphincteric dysfunction, all known for having a role in the loss of independence at older ages [75]. The extreme manifestation of this process would lead to FSCS, but the elderly who experiences 'successfully' aging would decline much slower. Risk factors for cerebrovascular disease, including Met.S, may be the main modifiable determinants of pathological neuroaging.

FSCS may be a key element in explaining the concomitant and interrelated decline in cognitive, affective, executive and neuromotor functions among the elderly.

Our proposed criteria for FSCS can easily be accessed in a neurogeriatric consultation by FRR elicitation, by performing a simple MMSE test, diagnosing late-onset depression, evaluating the presence of 'fear of falling' or falls, and diagnosing urgency incontinence; excluded dementia and bedridden cases.

Features of the FSCS are often inadvertently attributed to normal aging and, therefore, considered to be not amenable to intervention. Moreover, because FSCS entails also a dysexecutive feature, these patients are often labeled as non-compliant, stubborn, or unmotivated [82]. Recognizing this syndrome as an age-associated disease that, like Alzheimer's disease, does dramatically increase in prevalence with age but does not necessarily affect all elderly (and therefore is not 'normal') is, hence, the first step in improving medical care for this large group of elderly people. A second step would involve a better control of cerebrovascular risk factors from early adulthood to late life, and preventing/managing Met.S may be a central goal. Besides, drugs which increase insulin sensitivity are a promise. There is already some evidence that some of these drugs may positively affect cognitive function in humans [95].

The vascular hypothesis for the FSCS is supported by: (1) the high rate of occurrence of FSCS and its individual components in patients with hypertension, diabetes, coronary disease, and now possibly also Met.S; (2) the high rate of the syndrome in patients with cerebral small-vessel disease; (3) the high prevalence of an advanced degree of WML and lacunes in patients with FSCS.

Clinically manifested stroke is the most common condition responsible for functional decline among older people in both western and eastern societies [15,35]. An equivalent but more insidious (and less perceptible) process is possibly happening with asymptomatic lacunar strokes, ischemic WML, and FSCS. In fact, according to recent projections, worldwide stroke-related disability is projected to increase during the following 15 years and this disability will grow even more among developing countries [66,67]. As FSCS is a cerebrovascular disease which is extremely prevalent among the oldest-old, its burden certainly should keep increasing with the worldwide populational aging. This would account for a large amount of not readily predictable burden due to cerebrovascular disease [66,67].

4.4. Limitations

This study has several limitations. Even tough it is well known that frontal-subcortical structures are highly vulnerable to the aging process, firm separation between what is 'normal' aging and what represents 'disease' remains difficult [82]. For this reason we made an intermediary third group to account for the 'borderline pathological' cases, what might have minimized the (binomial) categorization problem. Since epidemiological studies cannot prove cause-and-effect when the end-point is an outcome of a chronic non-communicable condition, this epidemiological evidence can be cited only as being consistent with the hypothesis in question.

It is possible that more people have deceased precociously from cardiovascular causes in the Met.S group than in the control group. This would make the Met.S group appear to be healthier due to a survival effect. However, the consideration of such possible survival effect would tend to magnify, rather than decrease, the differences found between these two groups in this study.

For diagnose of FSCS we relied solely on the medical history, neurologic examination, and battery of neurofunctional tests. However, FSCS is not an image diagnosis but rather a clinical one [82], for frontal-subcortical lacunes and WML are of high sensibility but low specificity for FSCS [21,92,93]. Even so, further studies incorporating brain images are required for grading the extension of leukoaraiosis, measuring the degree of frontal lobe (and hippocampal) atrophy, as well as to look for the possible associations between the pro-

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gression of these variables and baseline Met.S. The inclusion of brain image techniques would also provide a 'golden standard' method with which several clinical criteria for FSCS could be confronted to.

We relied also on FRR as a criterion for FSCS. In the elderly FRR are neither very sensitive nor specific [23]. Nonetheless, in the absence of dementia, coexistence of cognitive impairment, late-onset depression, and gait disturbance are considered to be highly specific of frontal-subcortical small-vessel disease and atrophy; indeed these characteristics are considered to be 'phenotypic' of FSCS [82]. Presence of the above three disorders coexisted in 88.1% of the cases classified as FSCS in this sample.

Some of our subjects might have normal-pressure hydrocephalus (NPH), which is also characterized by gait disturbance, cognitive impairment and urine incontinence [92]. However this 'classical' triad of Hakim and Adams is rarely found in patients with NPH, the most common presentation being gait disorder alone [92], idiopathic NPH is also often associated with leukoaraiosis [92]. In this case the differential diagnosis between NPH and FSCS becomes difficult and, even more often, blurred. Some studies have suggested that idiopathic NPH is of cerebrovascular cause [92]. However, NPH is a rare cause of dementia (1–5%), whereas FSCS is a very common pathology in the elderly [92]. In this study the 12 cases of dementia were excluded. Besides, 74% of our individuals with FSCS presented evidence of depression, a feature not typical in 'pure' NPH. Because the vast majority of patients presenting mental deterioration, gait disorder and bladder dysfunction has FSCS [92], we cogitate that if some 'pure' NPH case was still present in our sample, it did not interfered significantly with our results.

4.5. Final remarks

The results hereby presented are consistent with the above evidences that link metabolic syndrome, vascular disease, and subclinical inflammation to cognitive, affective, executive, neuromotor and functional decline. To our knowledge, this is the first study to comprehensively evaluate the association between Met.S and FSCS.

Both AD and PD may occur before one reaches old age. Though rarely, even VaD itself can also occur before old age in the case of multiple large strokes. FSCS, however, is a geriatric disease par excellence for it does not seem to occur before the seventh or eighth decade of life, being therefore of possible lesser genetic determinism. This suggests a high potential for prevention. More than 10 years ago, Hachinsk has alluded to the vascular dementias as "preventable senility" [37]. Now it is time to consider that FSCS itself may be the 'preventable senility' par excellence.

Vascular disease, especially small-vessel disease and microangiopathy, may be the most common pathway to FSCS dysfunction with aging. William Osler has once mentioned that "longevity is a vascular question; a man is as old as his arteries" [72]. In the case of the brain, however, it might be more appropriate to restate that as "a person's brain is as old as his/her arterioles and capillaries".

5. Conclusions

FSCS was strongly associated with Met.S (OR = 5.8; CI: 1.7–20.3; $P = 0.006$), independently of age, gender or presence of stroke. Features of the Met.S explained 30.7% of the variance in the number of FSCS components. Met.S was also significantly associated with lower cognitive, executive, and neuromotor functions, depressive symptoms, fear of falling, falls and urgency incontinence ($P < 0.05$ for all). Met.S' PAR for FSCS was 31.6%.

Since Hispanics are at high risk for Met.S and silent strokes, these associations should be replicate in other, non-Hispanic populations to be proved universal. Future researches should also confirm Met.S to be longitudinally related to the development of FSCS, if possible including also brain image techniques. Additionally, randomized trails on non-pharmacological (exercise, diet and weight loss) or pharmacological (enhancers of insulin sensitivity) management of Met.S, and their capacity to prevent the development of FSCS, would be welcomed.

Preventing and treating Met.S may be an important step in 'preventing senility' and promoting 'successful' (neuro)aging.

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HIGH PREVALENCE OF DIABETES MELLITUS IN OLDER PEOPLE IN A RURAL AREA IN LAOS

To the Editor: The global prevalence of diabetes mellitus (DM) has been estimated as 2.8% in 2000 and to become 4.4% in 2030, and the number of people with DM is expected to approximately double between 2000 and 2030.[1] However, the most striking demographic change in global terms will be the increase in the proportion of people aged 65 and older.[1] There is little population-based epidemiological data on DM in southeast Asia, and the prevalence of DM in Laos remains unknown.[1–5] In Laos, a developing Asian country, a previous study found a high prevalence of random blood glucose (RBG) higher than 140 mg/dL (28.3%) and higher than 200 mg/dL (11.6%) in community-dwelling older people.[6] The prevalence of DM according to RBG (subjects with RBG ≥ 200 mg/dL or those taking blood glucose–lowering medicine) in community-dwelling older people was much higher in Laos (11.6%) than in other nearby southeast Asian countries in the survey (1.6% in Vietnam, 1.7% in Indonesia, and 5.7% in Myanmar).[6–9] In this study, to clarify the exact prevalence of DM and impaired glucose tolerance (IGT), 75-g oral glucose tolerance tests (OGTTs) were conducted in Laos.

In the previous study, examination of RBG, medical history interviews, and physical examinations had been conducted on 504 Laotians aged 60 and older (male: female = 207:297, mean age 70.2) living in rural villages in the Lahanam and Paxon zones in Songkhon District in Savannakhet Province in Laos. The villages had a total population of 12,009 people, with 744 people aged 60 and older; and 504 older people were examined (67.7% of all eligible subjects). Of those tested, 72 had DM (RBG ≥ 200 mg/dL), 180 had high RBG (110–199 mg/dL), and 252 had normal RBG (< 110 mg/dL) (Figure 1).

In 2005, 252 people with high RBG (≥ 110 mg/dL) were recommended for OGTT; of these, 209 (82.9%) agreed to participate. According to the criteria of the World Health Organization, DM (fasting blood sugar (FBS) ≥ 126 mg/dL or 2-hour plasma glucose (PG) ≥ 200 mg/dL), IGT (FBS 110–125 mg/dL or 2-hour PG 140–199 mg/dL), and normal glucose tolerance (NGT) (FBS < 110 mg/dL and 2-hour PG < 140 mg/dL) were defined using OGTT, which indicated that there were 28 subjects (18.3%) with DM and 39 (25.5%) with IGT among the 153 subjects with RBG between 110 and 199 mg/dL and 44 subjects (78.6%) with DM and six (10.7%) with IGT among the 56 subjects with RBG of 200 mg/dL or higher (Figure 1).

From the results of OGTT, the estimated prevalence of DM or IGT was calculated for all 504 subjects (Figure 1). For this estimate, it was hypothesized that nonresponders in each of the two groups (RBG 110–199 mg/dL or RBG ≥ 200 mg/dL) would have the same prevalence of DM or IGT according to OGTT as the responders. The estimated prevalence of DM and IGT according to OGTT were as much as 17.7% and 10.7%, respectively. Because OGTT was not given to people with normal RBG (< 110 mg/dL), some people with IGT or DM who might have had high blood glucose levels only after glucose intake may have been overlooked.

A high prevalence of DM and IGT was shown in community-dwelling older people in a rural area of Laos, a developing southeast Asian country. This might reflect that the rate of increase of DM is much faster in developing countries than in developed ones.[1,2] By 2030, it is estimated that the number of people aged 65 and older with DM will be 82 million in developing countries and more than 48 million in

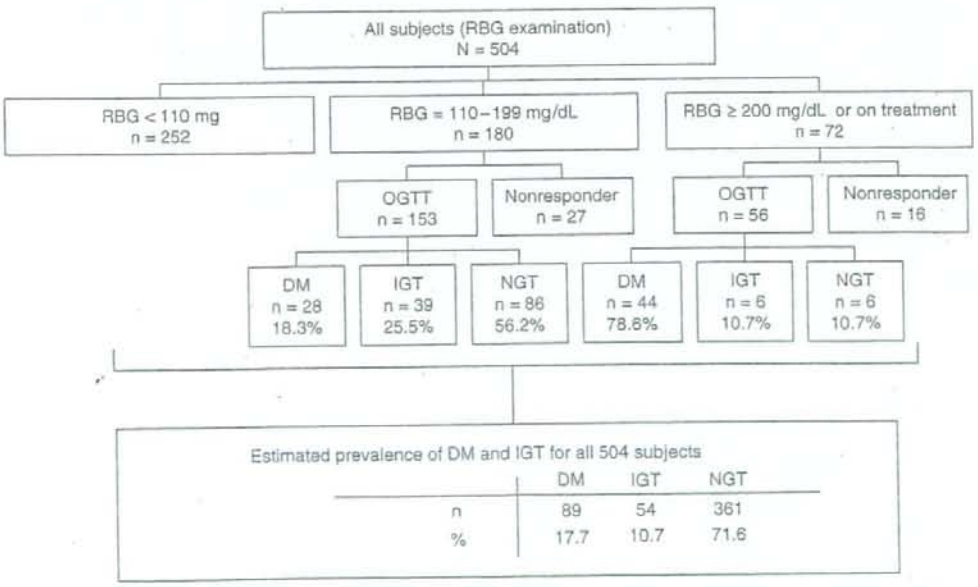

Figure 1. Estimated prevalence of diabetes mellitus (DM) and impaired glucose tolerance (IGT) in community-dwelling older people in Laos using 75-g oral glucose tolerance test (OGTT). OGTT was performed on 209 subjects, 82.9% of all people in the district noted with high random blood glucose (RBG) (≥ 110 mg/dL). NGT = normal glucose tolerance.

developed ones.[1] Even considering such study limitations as the small data sampling, the high prevalence of DM and IGT in community-dwelling older people in a developing country, Laos, is of particular note.

The high prevalence of DM in older people in a rural area in Laos could be associated with factors such as ethnic and genetic vulnerable factors, rapid economic development followed by nutritional transition, and other factors, such as the "fetal origins of disease" hypothesis, which postulates that early undernutrition increases the risk of certain chronic diseases in adulthood.[10] It will be necessary to investigate the causes behind the high prevalence of DM and IGT and their risk factors in Laos to prevent not only DM, but also related cardiovascular diseases, which are increasing in Asian countries.

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CARBOCYSTEINE THERAPY IN OLDER PEOPLE WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

To the Editor: As revealed by Yasuda et al. in their paper recently published in the *Journal of the American Geriatrics Society*,[1] the administration of the mucoactive agent, carbocysteine (S-carboxymethyl-L-cysteine), to patients with chronic obstructive pulmonary disease (COPD) may have additional beneficial effects on the reduction of common colds and episodes of exacerbation. Although, a statistically significant improvement was observed, there was, nevertheless, a range of interindividual variation apparent within their treated patient group.

Metabolism is usually a major factor influencing the efficacy of a therapeutic agent, and that of carbocysteine is known to be especially complex, with the pathways of decarboxylation, N-acetylation, sulfoxidation, and ester glucoronidation all being involved to differing degrees.[2–5] It is this consequent spectrum of metabolites to which an individual is exposed and not simply the administered parent compound. Several studies have indicated that the metabolism of carbocysteine varies widely within the same individual, with few sulfoxide (sulfur oxygenated) metabolites being produced after nighttime administration.[4,5] Such diurnal variation in metabolism, presumably under hormonal control, is overlaid on an underlying and apparently genetically determined ability to produce sulfur-oxygenated metabolites. This later spread of "sulfoxidation capacities" separates individuals with respect to their metabolic handling of the drug.[4,6,7] Clearly, the effects of this later inherent variation are phenotypically more pronounced after morn-

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A CLOSE ASSOCIATION BETWEEN HEARING IMPAIRMENT AND ACTIVITIES OF DAILY LIVING, DEPRESSION, AND QUALITY OF LIFE IN COMMUNITY-DWELLING OLDER PEOPLE IN JAPAN

To the Editor: The prevalence of impaired hearing increases greatly with age.[1] In the article entitled, "The relationship between hearing impairment and depression in older veterans,"[2] the authors showed that hearing impairment (HI) is strongly correlated with depression in older people. To confirm these findings, we compared quantitative scores in activities of daily living (ADLs), subjective quality of life (QOL), and depression of elderly subjects with HI and those without in community-dwelling older people living in three towns in Japan.

The study population consisted of 434 community-dwelling older people with HI aged 65 and older (210 men, 224 women; mean age 76.9 ± 6.9) and 2,170 age- and sex-matched older people without HI (adjusted ratio = 1:5, male:female = 1,050:1,120, mean age 76.9 ± 6.7) living in three towns: Tosa, Kahoku, and Urausu, in Kochi and Hokkaido Prefectures, Japan. Hearing function was assessed using a self-reported questionnaire, and the subjects were classified into four classes using a hearing function scale: those able to hear well (include those requiring a hearing aid) = 3, those able to hear loud voices only = 2, those able to hear only when the speaker shouts into his/her ear = 1, and those who can scarcely hear = 0. Subjects with HI were defined as those with a score of 0 to 2 and subjects without HI as those with a score of 3. Seven basic ADL items (walking, ascending and descending stairs, feeding, dressing, using the toilet, bathing, grooming) were assessed, each on a 4-level scale, whereby 3 = completely independent, 2 = needs some help, 1 = needs much help, and 0 = completely dependent. Scores for each item were summed to generate a total basic ADL score ranging from 0 to 21.[3] For higher-level daily activities, assessed using the Tokyo Metropolitan Institute of Gerontology (TMIG) Index of Competence, a 13-item index was used that included three sublevels of competence, each rated on a yes/no basis: (1) instrumental ADL: instrumental self-maintenance (5 items: the ability to use public transport, buy daily

Table 1. Comparison of Activity of Daily Living (ADL), Depression, and Quality-of-Life (QOL) Scores Between Community-Dwelling Elderly Subjects in Japan with and without Hearing Impairment (HI)

Variable	With HI (n = 434)	Without HI (n = 2,170)	*P*-value*
Age, mean ± SD	76.9 ± 6.9	76.9 ± 6.7	NS
Male, n (%)	210 (48.3)	1,050 (48.3)	NS
ADL scores, mean ± SD			
Basic ADLs (range 0–21)	18.1 ± 5.2	19.9 ± 3.0	<.01
Instrumental ADLs (range 0–5)	3.5 ± 1.9	4.3 ± 1.5	<.01
Intellectual ADLs (range 0–4)	2.3 ± 1.4	3.1 ± 1.2	<.01
Social Role (range 0–4)	2.4 ± 1.5	3.1 ± 1.2	<.01
Tokyo Metropolitan Institute of Gerontology - Index (range 0–13)	8.3 ± 4.1	10.6 ± 3.3	<.01
Depression			
Taking antidepressive drugs, n (%)	14 (6.7)	40 (3.7)	.045
GDS score (range 0–15), mean ± SD	7.3 ± 4.0	5.4 ± 3.9	<.01
With depression (GDS score ≥ 10), n (%)	122 (31.8)	351 (17.8)	<.01
QOL score (range 0–100), mean ± SD			
Subjective health	46.0 ± 22.5	59.7 ± 21.8	<.01
Family relationship	67.9 ± 25.3	77.4 ± 21.0	<.01
Friend relationship	65.2 ± 24.1	75.9 ± 20.5	<.01
Financial satisfaction	47.3 ± 24.6	56.9 ± 24.4	<.01
Subjective life satisfaction	52.5 ± 25.3	62.9 ± 24.4	<.01

*Based on Student *t* test for continuous variables and chi-square test for categorical variables.
SD = standard deviation; NS = not significant; GDS = Geriatric Depression Scale.