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.

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.

Acknowledgments

We thank Akiko Masaki, Atsuko Kokuryu, Marie Kinjo, and Emiko Matsuyama for assessment of the patients. This study was supported by research grants from Osakagasgroup Welfare Foundation and Foundation for Total Health Promotion.

References

1 Epstein AM, Hall JA, Besdine R *et al.* The emergence of geriatric assessment units. The 'new technology of geriatrics'. *Ann Intern Med* 1987; **106**: 299–303.
2 Applegate WB, Miller ST, Graney MJ, Elam JT, Burns R, Akins DE. A randomized, controlled trial of a geriatric assessment unit in a community rehabilitation hospital. *N Engl J Med* 1990; **322**: 1572–1578.
3 Rubenstein LZ, Josephson KR, Wieland GD, English PA, Sayre JA, Kane RL. Effectiveness of a geriatric evaluation unit. A randomized clinical trial. *N Engl J Med* 1984; **311**: 1664–1670.
4 Stuck AE, Siu AL, Wieland GD, Adams J, Rubenstein LZ. Comprehensive geriatric assessment: a meta-analysis of controlled trials. *Lancet* 1993; **342**: 1032–1036.
5 Boult C, Boult LB, Morishita L, Dowd B, Kane RL, Urdangarin CF. A randomized clinical trial of outpatient geriatric evaluation and management. *J Am Geriatr Soc* 2001; **49**: 351–359.
6 Yesavage JA. Geriatric Depression Scale. *Psychopharmacol Bull* 1988; **24**: 709–711.
7 Koyano W, Shibata H, Nakazato K, Haga H, Suyama Y. Measurement of competence: reliability and validity of the TMIG Index of Competence. *Arch Gerontol Geriatr* 1991; **13**: 103–116.
8 Podsiadlo D, Richardson S. The timed 'Up & Go': a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991; **39**: 142–148.
9 Okumiya K, Matsubayashi K. The timed 'Up & Go' test and manual button score are useful predictors of functional decline in basic and instrumental ADL in community-dwelling older people. *J Am Geriatr Soc* 1995; **47**: 497–498.
10 Mega MS, Cummings JL, Fiorello T, Gornbein J. The spectrum of behavioral changes in Alzheimer's disease. *Neurology* 1996; **46**: 130–135.
11 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984; **34**: 939–944.
12 Shankle WR, Romney AK, Hara J *et al.* Methods to improve the detection of mild cognitive impairment. *Proc Natl Acad Sci USA* 2005; **102**: 4919–4924.
13 Nasreddine ZS, Phillips NA, Bedirian V *et al.* The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005; **53**: 695–699.
14 Doody RS, Geldmacher DS, Gordon B, Perdomo CA, Pratt RD. Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. *Arch Neurol* 2001; **58**: 427–433.
15 Callahan CM, Hendrie HC, Tierney WM. Documentation and evaluation of cognitive impairment in elderly primary care patients. *Ann Intern Med* 1995; **122**: 422–429.
16 Gifford DR, Cummings JL. Evaluating dementia screening tests: methodologic standards to rate their performance. *Neurology* 1999; **52**: 224–227.
17 Valcour VG, Masaki KH, Curb JD, Blanchette PL. The detection of dementia in the primary care setting. *Arch Intern Med* 2000; **160**: 2964–2968.
18 Burchard EG, Ziv E, Coyle N *et al.* The importance of race and ethnic background in biomedical research and clinical practice. *N Engl J Med* 2003; **348**: 1170–1175.
19 Wada T, Ishine M, Sakagami T *et al.* Depression in Japanese community-dwelling elderly – prevalence and association with ADL and QOL. *Arch Gerontol Geriatr* 2004; **39**: 15–23.
20 Hirschfeld RM, Keller MB, Panico S *et al.* The National Depressive and Manic–Depressive Association consensus statement on the undertreatment of depression. *JAMA* 1997; **277**: 333–340.
21 Charney DS, Reynolds CF III, Lewis L *et al.* Depression and Bipolar Support Alliance consensus statement on the unmet needs in diagnosis and treatment of mood disorders in late life. *Arch Gen Psychiatry* 2003; **60**: 664–672.
22 Tielsch JM, Javitt JC, Coleman A, Katz J, Sommer A. The prevalence of blindness and visual impairment among nursing home residents in Baltimore. *N Engl J Med* 1995; **332**: 1205–1209.
23 Smeeth L, Fletcher AE, Hanciles S, Evans J, Wormald R. Screening older people for impaired vision in primary care: cluster randomised trial. *BMJ* 2003; **327**: 1027.
24 West SK, Munoz B, Rubin GS *et al.* Function and visual impairment in a population-based study of older adults. The SEE project. Salisbury Eye Evaluation. *Invest Ophthalmol Vis Sci* 1997; **38**: 72–82.
25 Wallhagen MI, Strawbridge WJ, Shema SJ, Kurata J, Kaplan GA. Comparative impact of hearing and vision impairment on subsequent functioning. *J Am Geriatr Soc* 2001; **49**: 1086–1092.
26 Reuben DB, Mui S, Damesyn M, Moore AA, Greendale GA. The prognostic value of sensory impairment in older persons. *J Am Geriatr Soc* 1999; **47**: 930–935.
27 Rudberg MA, Furner SE, Dunn JE, Cassel CK. The relationship of visual and hearing impairments to disability: an analysis using the longitudinal study of aging. *J Gerontol* 1993; **48**: M261–M265.
28 Chou KL, Chi I. Combined effect of vision and hearing impairment on depression in elderly Chinese. *Int J Geriatr Psychiatry* 2004; **19**: 825–832.
29 Strawbridge WJ, Cohen RD, Shema SJ, Kaplan GA. Successful aging: predictors and associated activities. *Am J Epidemiol* 1996; **144**: 135–141.
30 Smeeth L, Fletcher AE, Ng ES *et al.* Reduced hearing, ownership, and use of hearing aids in elderly people in the UK – the MRC Trial of the Assessment and Management

of Older People in the Community: a cross-sectional survey. *Lancet* 2002; **359**: 1466–1470.
31 Reuben DB, Walsh K, Moore AA, Damesyn M, Greendale GA. Hearing loss in community-dwelling older persons: national prevalence data and identification using simple questions. *J Am Geriatr Soc* 1998; **46**: 1008–1011.
32 Sindhusake D, Mitchell P, Smith W *et al.* Validation of self-reported hearing loss. The Blue Mountains Hearing Study. *Int J Epidemiol* 2001; **30**: 1371–1378.
33 Iwano M, Nomura H, Ando F, Niino N, Miyake Y, Shimokata H. Visual acuity in a community-dwelling Japanese population and factors associated with visual impairment. *Jpn J Ophthalmol* 2004; **48**: 37–43.

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Neurobiology of Aging xxx (2006) xxx–xxx

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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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Received 23 March 2006; received in revised form 7 July 2006; accepted 17 July 2006

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.

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

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doi:10.1016/j.neurobiolaging.2006.07.013

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Neurobiology of Aging xxx (2006) xxx–xxx

NEUROBIOLOGY OF AGING

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doi:10.1016/j.neurobiolaging.2006.07.013

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-

Please cite this article as: Matheus Roriz-Cruz et al., Cognitive impairment and frontal-subcortical geriatric syndrome are associated with metabolic syndrome in a stroke-free population, Neurobiology of Aging (2006), doi:10.1016/j.neurobiolaging.2006.07.013

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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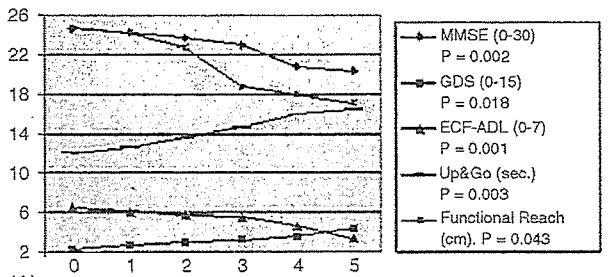
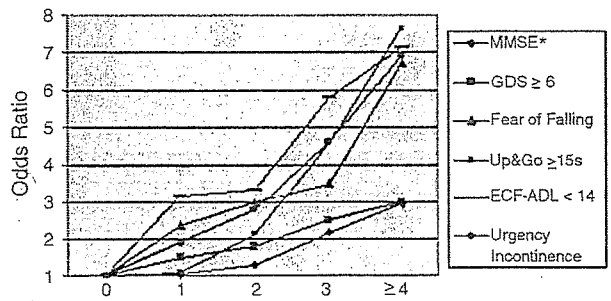


(A) Number of Metabolic Syndrome Components

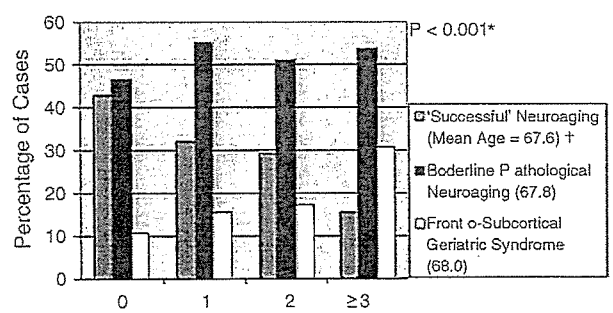
67.7	68.4	68.2	66.9	67.9	68.9	Mean Age.P = 0.313
60.3%	63.3%	62.1%	61.8%	61.9%	63.2%	Female.P = 0.834*

*Chi-square. ANOVA for all other P-values.



(B) Number of Metabolic Syndrome Components

*MMSE ≤ 3 points the predicted score for age and years of schooling.
P < 0.05 for all variables when number of metabolic syndrome components ≥ 3.
Multinominal logistic regression. Adjusted for age and gender.



(C) Number of Metabolic Syndrome Components

*Multinominal logistic regression. Adjusted for age and gender. Mean risk of 1 Met.S component for coexisting Fronto-Subcortical syndrome: OR = 1.59; P = 0.017.
†P = 0.23 for mean age difference (ANOVA).

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.

References

[1] Abbatecola AM, Paolisso G, Lamponi M, et al. Insulin resistance and executive control dysfunction in older persons. J Am Geriatr Soc 2004;52:1713–8.
[2] Alexopoulos GS, Meyers BS, Young RC, et al. Vascular depression' hypothesis. Arch Gen Psychiatry 1997;54:915–22.
[3] Almeida OP, Almeida SA. Short versions of the geriatric depression scale: a study of their validity for the diagnosis of a major depressive episode according to the ICD-10 and DSM-IV. Int J Geriatr Psychiatry 1999;14:858–65.
[4] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: APA; 2002. p. 356–419, [text revised].
[5] Baldwin R, O'Brien J, et al. Vascular basis of late-onset depressive disorder. Br J Psychiatry 2002;180:150–60.
[6] Bang OY, Kim JW, Lee MA, et al. Association of the metabolic syndrome with intracranial atherosclerotic stroke. Neurology 2005;26:296–8.
[7] Black S, Rush RD. Cognitive and functional decline in adults aged 75 and older. J Am Geriatr Soc 2002;50:1978–86.
[8] Brown JS, McGhan WF, Chokroverty S. Comorbidities associated with overactive bladder. Am J Manage Care 2000;6:S574–9.
[9] Bruck A, Kurki T, Kaasinen V, et al. Hippocampal and prefrontal atrophy in patients with early non-demented Parkinson's disease is related to cognitive impairment. J Neurol Neurosurg Psychiatry 2004;75:1467–9.
[10] Bruzzi P, Green SB, Byar DP, et al. Estimating the population attributable risk for multiple risk factors using case-control data. Am J Epidemiol 1985;122:904–14.
[11] Burke SN, Barnes CA. Neural plasticity in the ageing brain. Nat Rev 2006;7:30–40.

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[12] Burton EJ, McKeigh IG, Burn DJ, et al. Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls. Brain 2004;127:791–800.
[13] Camus V, Kraehenbuhl H, Preisig M, et al. Geriatric depression and vascular diseases: what are the links? J Affect Disord 2004;81:1–16.
[14] Carmelli D, Swan GE, Reed T, et al. Midlife cardiovascular risk factors and brain morphology in identical older male twins. Neurology 1999;52:1119–24.
[15] Chen P, Yu ES, Liu WT, et al. ADL dependence and medical conditions in Chinese older persons: a population-based survey in Shangai, China. J Am Geriatr Soc 1995;43(4):378–83.
[16] Convit A, Wolf OT, Tarshish C, et al. Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly. Proc Natl Acad Sci USA 2003;100:2019–22.
[17] Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol 2004;3:169–78.
[18] Craft S. Insulin resistance and cognitive impairment. Arch Neurol 2005;62:1043–4.
[19] Davison KK, Ford ES, Cogswell ME, et al. Percentage of body fat and body mass index are associated with mobility limitations in people aged 70 and older from NHANES III. JAGS 2002;50:1802–9.
[20] De La Torree JC. Alzheimer's disease is a vasocognopathy: a new term to describe its nature. Neurol Res 2004;26(5):517–24.
[21] De Leeuw FE, de Groot JC, Achten E, et al. Prevalence of cerebral white matter lesions in elderly people: a population-based magnetic resonance imaging study. The Rotterdam Scan Study. J Neurol Neurosurg Psychiatry 2001;70(1):9–14.
[22] Depp CA, Jeste DV. Definitions and predictors of successful aging: a comprehensive review of larger quantitative studies. Am J Geriatr Psychiatry 2006;14(1):6–20.
[23] Di Legge S, Piero VD, Altieri M, et al. Usefulness of primitive reflexes in demented and non-demented cerebrovascular patients in daily clinical practice. Eur Neurol 2002;45:104–10.
[24] Duncan BB, Schmidt MI, Polanczyk CA, et al. High mortality rates among Brazilian adult populations—an international comparison. Rev Assoc Med Br 1992;38:138–44 [Portuguese].
[25] Eguchi K, Kario K, Shimada K, et al. Greater impact of coexistence of hypertension and diabetes on silent cerebral infarcts. Stroke 2003:2471–4.
[26] Farkas E, De Jong G, Apro E, et al. Similar ultrastructural breakdown of cerebrocortical capillaries in Alzheimer's disease, Parkinson disease, and experimental hypertension. What is the functional link? Ann NY Acad Sci 2000;903:72–82.
[27] Ferrand J. Essai sur l'hémiplégie des veillards: les lacunes de désintégration cerébrale. Paris These, 1902 [French].
[28] Firbank M, O'Brien JT, Pakrasi S, et al. White matter hyperintensities and depression—preliminary results from the LADIS study. Int J Geriatr Psychiatry 2005;20:674–9.
[29] Folstein MF, et al. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatry Res 1975;12:189–98.
[30] Ford ES, Giles WH, Dietz WH, et al. Prevalence of the metabolic syndrome among US adults: findings from the third national health and nutrition examination survey. JAMA 2002;287:356–9.
[31] Fundação Instituto Brasileiro de Geografia e Estatistica (IBGE). (Portuguese) [On-line] available at: http://www.ibge.gov.br [accessed 30-11-2005].
[32] Furukawa S, Fujita T, Shimabukuro M, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest 2004:1752–61.
[33] Gardner JP, Li S, Srinivasan SR, et al. Rise in insulin resistance is associated with escalated telomere attrition. Circulation 2005;111: 2171–7.
[34] Geroldi C, Frisoni GB, Paolisso G, et al. Insulin resistance in cognitive impairment. The Inchanti study. J Am Geriatr Soc 2005;62: 1067–72.
[35] Guccione AG, Felson DT, Anderson JJ, et al. The effects of specifical medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 1993;84:351–8.
[36] Gustafson D, Rothenberg E, Bjorkelung C, et al. An 18-year follow-up of overweight and risk of Alzheimer's disease. Arch Intern Med 2003;163:1524–8.
[37] Hachinsk V. Preventable senility: a call for action against the vascular dementias. Lancet 1992;340:645–8.
[38] Hachinski VC, Lassen NA. Multi-infarct dementia: a cause of mental deterioration in the elderly. Lancet 1974:2207–10.
[39] Haslam DW, James WPT, et al. Obesity. Lancet 2005;366:1197–209.
[40] Hausdorff JM, Yogev G, Springer S, et al. Walking is more like catching than tapping: gait in the elderly as a complex cognitive task. Exp Brain Res 2005;164:541–8.
[42] Hickman S, Howieson DB, Dame A, et al. Longitudinal analysis of the effects of the aging process on neuropsychological test performance in the healthy young-old and oldest-old. Dev Neuropsychol 2000;17:323–37.
[43] Hyung-Min K, Kim BJ. Metabolic syndrome as an independent risk factor of silent brain infarction in healthy people. Stroke 2006;37:466–72.
[44] Ishii N, Nishihara Y, Imamura T. Why do frontal lobe symptoms predominate in vascular dementia with lacunes? Neurology 1986;36:340–5.
[45] James WPT, Leach RJ, Mhurch CN, et al. Overweight and obesity (high body mass index). Geneva, Switzerland: World Health Organization; 2004. p. 497–596.
[46] Jensen GL. Obesity and functional decline: epidemiology and geriatric consequences. Clin Geriatr Med 2005;21:677–87.
[47] Kahn R, Buse J, Ferrannini E, et al. The metabolic syndrome: time for a critical appraisal—joint statement from the American Diabetes Association and the European association for the Study of Diabetes. Diabetes Care 2005;28:2289–304.
[48] Kalaria R. Similarities between Alzheimer's disease and vascular dementia. J Neurol Sci 2002;203/204:29–34.
[49] Kalmijn S, Foley D, White L, et al. Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men: the Honolulu-Asia aging study. Arterioscler Thromb Vasc Biol 2000;20: 2255–60.
[50] Kario K, Matsuo T, Kobayashi BA, et al. Hyperinsulinemia and haemostatic abnormalities are associated with silent lacunar cerebral infarcts in elderly hypertensive subjects. J Am Coll Cardiol 2001;37:871–7.
[51] Kobayashi S, Okada K, Koide H, et al. Subcortical silent brain infarction as a risk factor for clinical stroke. Stroke 1997;28:1932–9.
[52] Koyano W, Shibata H, Nakazato K, et al. Measurement of competence: reliability and validity of the TMIG-index of competence. Arch Gerontol Geriatr 1991;13:103–16.
[53] Kumari M, Brunner E, Fuhrer R, et al. Minireview: mechanisms by which the metabolic syndrome and diabetes impair memory. J Gerontol A: Biol Sci Med Sci 2000;55:B228–32.
[54] Kuo H-K, Lipsitz LA. Cerebral white matter changes and geriatric syndromes: is there a link? J Gerontol: Biol Sci Med 2004:M818–26.
[55] Kuusisto J, Koivisto K, Mykkanen L, et al. Association between features of the insulin resistance and Alzheimer's disease independently of apolipoprotein E4 phenotype: crosssectional population-based study. BMJ 1997;315:1045–9.
[56] Kwon HM, Kim BJ, Lee SH, et al. Metabolic syndrome as an independent risk factor of silent brain infarction in healthy people. Stroke 2006;37:466–72.
[57] Laakso MP, Partanen K, Riekkinen P, et al. Hippocampal volumes in Alzheimer's disease, Parkinson's disease with and without dementia, and in vascular dementia: an MRI study. Neurology 1996;46:678–81.
[58] Lesser IM, Boone KB, Mehringer CM, et al. Am J Psychiatry. Cognition and white matter hyperintensities in older depressed patients 1996;153:1280–7.
[59] Lotufo PA. Stroke in Brazil: a neglected disease. Sao Paulo Med J 2005;123:3–4.

Please cite this article as: Matheus Roriz-Cruz et al., Cognitive impairment and frontal-subcortical geriatric syndrome are associated with metabolic syndrome in a stroke-free population, Neurobiology of Aging (2006), doi:10.1016/j.neurobiolaging.2006.07.013

[60] Luichsinger J, Tang M, SheaS, et al. Hyperinsulinemia and risk of Alzheimer disease. Neurology 2004;63:1187–92.
[61] Marie P. Des Foyers lacunaires de désintégration et de différents autres états cavitaires du cerveau. Rev Med 1901;21:281–98 [French].
[62] McLaren D. Is insulin resistance becoming a global epidemic? Nutrition 1997;13:64–6.
[63] Milionis HJ, Rizos MHJ, Goudevenos J, et al. Components of the Met.S and risk for first-ever acute ischemic non-embolic stroke in elderly subjects. Stroke 2005;36:1372–6.
[64] Monteiro CA. The nutrition transition in Brazil. Eur J Clin Nutr 1995;49:105–13.
[65] Morrison JH, Hof PR. Life and death of neurons in the aging brain. Science 1997;278:412–9.
[66] Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. Lancet 1997;349:1498–504.
[67] Murray CJL, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997;349:1436–42.
[68] National System of Health Information, Brazil. (Portuguese) [On-line] available at: http://tabnet.datasus.gov.br [accessed 8-11-2005].
[69] Ninomiya J, L'Italien F, Criqui MH, et al. Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. Circulation 2004;13:42–6.
[70] O'Brien J, Ames D, Schwietzer I, et al. White matter changes in depression and Alzheimer's disease: a review of magnetic resonance imaging studies. Int J Geriatr Psychiatry 1996;11:681–94.
[71] Olijhoek J, van der Graaf Y, Jan-Dirk B, et al. The metabolic syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm. Eur Heart J 2004;25:342–8.
[72] Osler W. The principle and practice of medicine. New York: D. Appleton; 1892.
[73] Otiniano ME, Du XL, Maldonado MR, et al. Effect of metabolic syndrome on heart attack and mortality in Mexican-American elderly persons: findings of a 7-year follow-up from the Hispanic established population for the epidemiological study of the elderly. J Gerontol A: Biol Sci Med Sci 2005;60:466–70.
[74] Palloni A, Pinto-Aguirre, Martha P. Demographic and health conditions of ageing in Latin America and the Caribbean. Int J Epidemiol 2002;31:762–71.
[75] Pantoni L, Basile AM, Pracucci G, et al. Impact of age-related cerebral white matter changes on the transition to disability: the LADIS study—rationale, design and methodology. Neuroepidemiology 2005;24(1–2):51–62.
[76] Pantoni L, Gracia JH. The significance of cerebral white matter abnormalities 100 years after Biswanger report. A review. Stroke 1995;26:1293–301.
[77] Perennou D, Decavel P, Manckoundia P, et al. Evaluation of balance in neurologic and geriatric disorders. Ann Readapt Med Phys 2005;48(6):317–35 [Francês].
[78] Petrella RJ, Lattanzio CN, Desmeray A, et al. Can adoption of regular exercise later in life prevent metabolic risk for cardiovascular disease? Diabetes Care 2005;28:694–701.
[79] Plaschke K. Aspects of ageing in chronic cerebral oligaemia. Mechanisms of degeneration and compensation in rat models. J Neural Transm 2005;112:393–413.
[80] Podsiadlo D, Richardson S. The timed "Up and Go": a test of basic functional mobility for frail elderly persons. JAGS 1991;39:142–3.
[81] Prins ND, van Dijk EJ, der Heijer T, et al. Cerebral small-vessel disease and decline in information processing speed, executive function and memory. Brain 2005;128:2034–41.
[82] Pugh KG, Lipsitz LA. The microvascular frontal-subcortical syndrome of aging. Neurobiol Aging 2002;23:421–31.
[83] Rao R, Jackson S, Howard R, et al. Primitive reflexes in cerebrovascular disease: a community study of older people with stroke and carotid stenosis. Int J Geriatr Psychiatr 1999;14:964–72.
[84] Rasgon NL, Kenna HA. Insulin resistance in depressive disorders and Alzheimer's disease: revising the missing link hypothesis. Neurobiol Aging 2005;26(Suppl. 1):23–7.
[85] Roberts EL, Chich CP. Age-related alterations in energy metabolism contribute to the increased vulnerability of the aging brain to anoxic damage. Brain Res 1995;678:83–90.
[86] Rowe J, Kahn RL. Human aging: usual and successful. Science 1987;237:143–9.
[87] Saposnik G, Caplan LR, Gonzalez LA, et al. Stroke in South America: a systematic review of incidence, prevalence, and stroke subtypes. Stroke 2003:2103–7.
[88] Snowdon DA, Greiner LH, Mortimer JA, et al. Brain infarction and the clinical expression of Alzheimer's disease. The Nun Study. J Am Med Assoc 1997;277:813–7.
[89] Tinnetti ME, de Leon CFM, Doucette JT, et al. Fear of falling and fall-related efficacy in relationship to functioning among community-dwelling elders. J Gerontol 1990;45:239–43.
[90] Touboul PJ, Labreuche J, Vicaut E, et al. Carotid intima-media thickness, plaques, and Framingham risk score as independent determinants of stroke risk. Stroke 2005:1741–5.
[91] Trindade IS, Heineck G, Machado JR, et al. Prevalence of arterial hypertension in the population of Passo Fundo (Brazil) metropolitan area. Arq Bras Cardiol 1998;71:127–30 [Portuguese].
[92] Vanneste JAL. Diagnosis and management of normal-pressure hydrocephalus. J Neurol 2000;247:5–14.
[93] Veemer SE, Koudstaal PJ, Oudkerk M, et al. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke 2002:21–5.
[94] Verguese J, Lipton RB, Hall CB, et al. Abnormality of gait as a predictor of non-Alzheimer's dementia. N Engl J Med 2002;347:1761–8.
[95] Watson GS, Craft S. The role of insulin resistance in the pathogenesis of Alzheimer's disease. Implications for treatment. CNS Drugs 2003;17:27–45.
[96] Wolff SP, Jiang ZY, Hunt JV. Protein glycation and oxidative stress in diabetes mellitus and ageing. Free Radic Biol Med 1991;10:339–52.
[97] World Health Organization. Research protocol for measuring the prevalence of neurological disorders in developing countries. Neurosciences Program, Geneva: WHO; 1981.
[98] Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. J Am Med Assoc 2004;292:2237–42.
[99] Zunker P. Hyperinsulinism and cerebral microangiopathy. Stroke 1996;27:219–23.

Please cite this article as: Matheus Roriz-Cruz et al., Cognitive impairment and frontal-subcortical geriatric syndrome are associated with metabolic syndrome in a stroke-free population, Neurobiology of Aging (2006), doi:10.1016/j.neurobiolaging.2006.07.013.

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

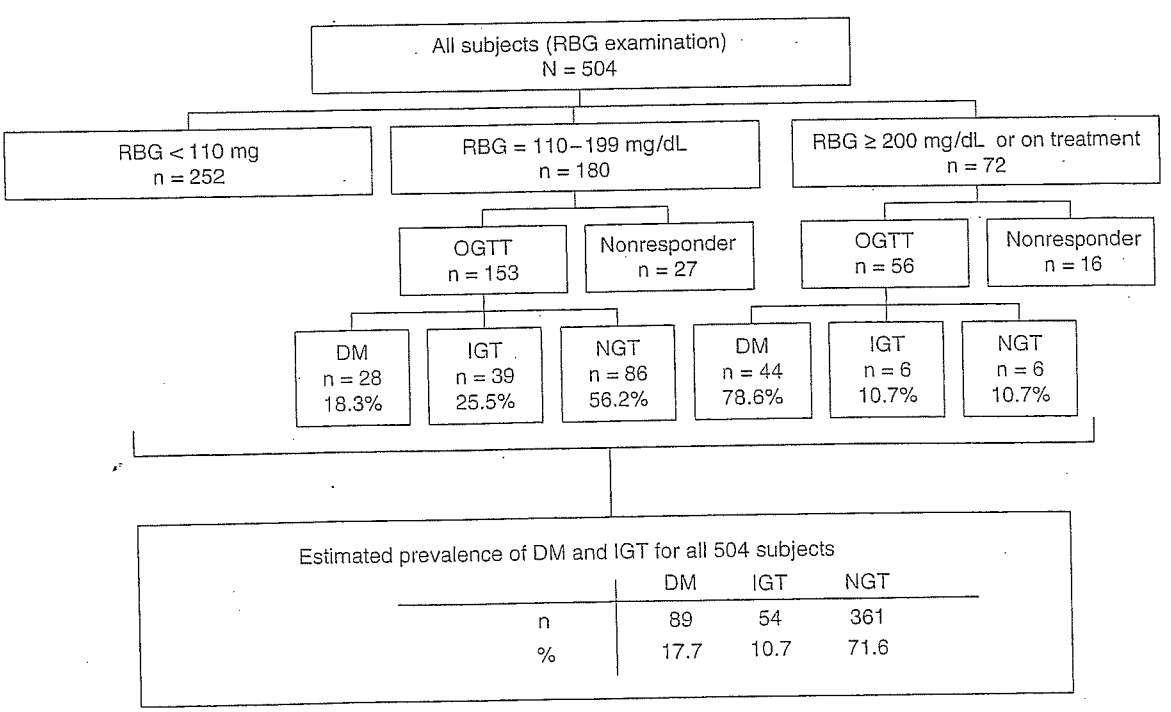

Figure 1. Estimated prevalence of diabetes mellitus (DM) and impaired glucose tolerance (IGT) in community-dwelling older people in Laos using 75-g oral glucose tolerance test (OGTT). OGTT was performed on 209 subjects, 82.9% of all people in the district noted with high random blood glucose (RBG) (≥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

Financial Disclosure

Kiyohito Okumiya received funding for Project 4–2 of the Research Institute for Humanity and Nature from the Japanese Ministry of Education, Science and Culture. The study was also supported by the overseas grant-in-aid of the Ministry of Health, Labor and Welfare, Japan.

Author Contributions: Kentaro Suzuki, Kiyohito Okumiya, Masayuki Ishine, Tiengkham Pongvongsa Boungnong Boupha, and Kozo Matsubayashi conceived and designed the project. All authors participated in the medical survey in Laos. Kentaro Suzuki, Kiyohito Okumiya, and Kozo Matsubayashi were engaged in analysis and interpretation of data and preparation of the manuscript.

Sponsor's Role: None.

REFERENCES

1. Wild S, Roglic G, Green A et al. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–1053.
2. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: Prevalence, numerical estimates, and projections. Diabetes Care 1998;21:1414–1431.
3. Tan CE, Emmanuel SC, Tan BY et al. Prevalence of diabetes in the cardiovascular risk factors. The 1992 Singapore National Health Survey. Diabetes Care 1999;22:241–247.
4. Aekplakorn W, Stolk RP, Neal B et al. The prevalence and management of diabetes in Thai adults: The international collaborative study of cardiovascular disease in Asia. Diabetes Care 2003;26:2758–2763.
5. King H, Keuky L, Seng S et al. Diabetes and associated disorders in Cambodia: Two epidemiological surveys. Lancet 2005;366:1633–1639.
6. Okumiya K, Ishine M, Wada T et al. Comprehensive geriatric assessment for community-dwelling elderly in Asia compared with those in Japan. IV. Savannakhet, Laos. Geriatr Gerontol Int 2005;5:159–167.
7. Ishine M, Wada T, Sakagami T et al. Comprehensive geriatric assessment for community-dwelling elderly in Asia compared with those in Japan. III. Phuto in Vietnam. Geriatr Gerontol Int 2005;5:115–121.
8. Wada T, Ishine M, Okumiya K et al. Comprehensive geriatric assessment for community-dwelling elderly in Asia compared with those in Japan. V. West Java, Indonesia. Geriatr Gerontol Int 2005;5:168–175.
9. Wada T, Okumiya K, Suzuki K et al. Comprehensive geriatric assessment for community-dwelling elderly in Asia compared with those in Japan. VI. Maubin in Myanmar. Geriatr Gerontol Int 2005;5:276–285.
10. Caballero B. A nutritional paradox—underweight and obesity in developing countries. N Engl J Med 2005;352:1514–1516.

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-

Coke, Dr. Richard Camicioli, Dr. D'Arcy Duggan, Ms. Bonnie Launhardt, Ms. Debbie Gordon, and Ms. Bernice Magee: study concept and design, preparation of manuscript. Dr. Bruce Fisher: study concept and design. Ms. Marilou Hervas-Malo: analysis and interpretation of data.

Sponsor's Role: None.

REFERENCES

1. Fick DM, Agostini JV, Inouye SK. Delirium superimposed on dementia. A systematic review. J Am Geriatr Soc 2002;50:1723–1732.
2. Williams MA, Campbell EB, Raynor WJ et al. Predictors of acute confusional states in hospitalized elderly patients. Res Nurse Health 1985;8:31–40.
3. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. JAMA 1990;263:1097–1101.
4. Rockwood K. Acute confusion in elderly medical patients. J Am Geriatr Soc 1989;37:150–154.
5. Rockwood K, Cosway S, Carver D et al. The risk of dementia and death after delirium. Age Ageing 1999;28:551–556.
6. Borson S, Scanlan J, Brush M et al. The Mini-Cog: A cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. Int J Geriatr Psychiatry 2000;15:1021–1027.
7. Borson S, Scanlan JM, Chen P et al. The Mini-Cog as a screen for dementia: Validation in a population-base sample. J Am Geriatr Soc 2003;51:1451–1454.
8. Wind AW, Schellevis FG, Van Staveren G et al. Limitations of the Mini-Mental State Examination in diagnosing dementia in general practice. Int J Geriatr Psychiatry 1997;12:101–108.
9. Scanlan JM, Borson S. The Mini-Cog: Receiver operating characteristics with expert and naive raters. Int J Geriatr Psychiatry 2001;16:216–222.
10. Inouye SK, van Dyck C, Alessi C et al. Clarifying confusion: The confusion assessment method. Ann Intern Med 1990;113:941–948.

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.

necessities, prepare a meal, pay bills, handle banking matters); (2) intellectual activities (4 items: the ability to fill out forms, read newspapers, and read books or magazines and interest in television programs or news articles on health-related matters); and (3) social roles (4 items: the ability to visit friends, give advice to relatives and friends, visit someone in the hospital, and initiate a conversation with younger people).[4] The 15-item Geriatric Depression Scale (GDS-15) was used to screen the subjects for depression. Quantitative subjective QOL was assessed using a 100-mm visual analog scale (the worst QOL being on the left end of the scale and the best on the right) with the following five items: subjective sense of health, relationship with family, relationship with friends, financial satisfaction, and subjective happiness.[5,6]

Table 1 shows ADL scores, mean GDS-15 scores, the prevalence of depression (GDS cut-off = 10), the number of subjects taking antidepressive drugs, and QOL scores of subjects with and without HI. Scores on all ADL items (including basic ADLs, instrumental ADLs, intellectual ADLs, social roles, and the TMIG Index), mean GDS scores, and all quantitative QOL scores were significantly lower in elderly subjects with HI than those without. Moreover, the rate of depression as assessed according to the GDS was higher in those with HI than those without.

These findings in community-dwelling older people in Japan coincide with the findings reported in two other studies.[2,7] It is therefore suggested that the close association between HI and ADLs, depression, and QOL in older people is a universal phenomenon. Moreover, in addition to HI, other sensory functions might also be related to ADLs, depression, and QOL in older people. In conclusion, these findings suggest that more attention should be paid to routine evaluation of sensory impairment during comprehensive geriatric assessment and to trying to improve such impairment where possible.

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ACKNOWLEDGMENTS

Financial Disclosure: None.

Author Contributions: Masayuki Ishine: study design and preparation of the letter. Kiyohito Okumiya: analysis and interpretation of the data. Kozo Matsubayashi: acquisition and input of the data.

Sponsor's Role: None.

REFERENCES

1. Cruickshanks KJ, Wiley TL, Tweed TS et al. Prevalence of hearing loss in older adults in Beaver Dam. Wisconsin Epidemiological Hearing Loss Study. Am J Epidemiol 1998;148:879–976.
2. Abrams ET, Barnet JM, Hoth A et al. The relationship between hearing impairment and depression in older veterans. J Am Geriatr Soc 2006;54:1475–1477.
3. Matsubayashi K, Okumiya K, Wada T et al. Secular improvement in self-care independence of old people living in community in Kahoku, Japan. Lancet 1996;347:60.
4. Koyano W, Hashimoto M, Fukawa T et al. Functional capacity of the elderly: Measurement by the TMIG Index of Competence [in Japanese]. Nippon Koshu Eisei Zasshi 1993;40:468–474.
5. Matsubayashi K, Okumiya K, Osaki Y et al. Quality of life of old people in the community. Lancet 1997;350:1521–1522.
6. Morrison DP. The Crichton Visual Analogue Scale for the assessment of behavior in the elderly. Acta Psychiatr Scand 1983;68:408–413.
7. Carabellese C, Appollonio I, Rozzini RA et al. Sensory impairment and quality of life in a community elderly population. J Am Geriatr Soc 1993;41:401–407.

後期高齢者の地域健康管理の課題 ②国際的観点から －特にアジアの点描－

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はじめに

21世紀において、社会の高齢化が問題となるのは先進諸国のみではない。図1に示すように、2000年ごろを境に、サブサハラ以南のアフリカを除く世界中の地域で、急速な人口の高齢化が始まっている[1)]。アジアの全域でも人口の高齢化が始まり、2050年には、日本に次いで、シンガポール、韓国、タイ、中国といった比較的裕福と考えられるアジアの国々が高齢社会(Aged Society)となり、その他のアジアでは貧しいとされるインドネシア、ベトナム、ラオス、ミャンマーでさえも高齢化社会(Aging Society)を迎えることが予測されている。

先進諸国で発達した近代医学は、細菌学の進歩と衣食住環境の整備を通じて、まず感染症の克服に成功した。経済力に裏打ちされた先進医療の進歩によって、急性期疾患の救命率は飛躍的に増大し、その結果として、先進諸国はかつて人類史上類をみない速度で平均寿命を延ばし「長寿」を実現した。しかし、この高齢社会は必然的に、虚弱高齢者(frail elderly)や要介護者をもたらし、これらの慢性疾患をかかえながら地域で生活している高齢者に対する医学的対応のありかたが21世紀医学に問われている。

先進諸国は豊かな社会を実現してから高齢化が進んだのに対して、途上国では豊かになる前に高齢化を迎えざるを得ない。しかも、途上国では欧米諸国がすでに克服し去った感染症がいまだに重大な課題として残されている。さらに、保健福祉に振り向けられる財源は豊かではない。アジアの保健福祉問題は、「感染症」「高齢化」「乏しい財源」という“triple burden”をかかえている。しかし、途上国のそれぞれは、高齢化というグローバリゼーションの趨勢(すうせい)を受け入れながらも、その地域固有のLocal Knowledgeを活かしつつ改変し、能動的に対処しようとしている。

以下、アジアの国々の高齢者の実態を点描してみたい。

家族と共同体による高齢者介護 －西ジャワの事例－

現在、高齢化率5%であるインドネシアの西ジャワでは、要介護高齢者が入院することはまずない。ほとんどの高齢者は家庭で過ごしている。図2は93歳の女性で、約10年間寝たきりである。食事の介助、見守り、体位交換、清拭などの身体介護は、家族だけではなく、村人たちが交代であたっている。この

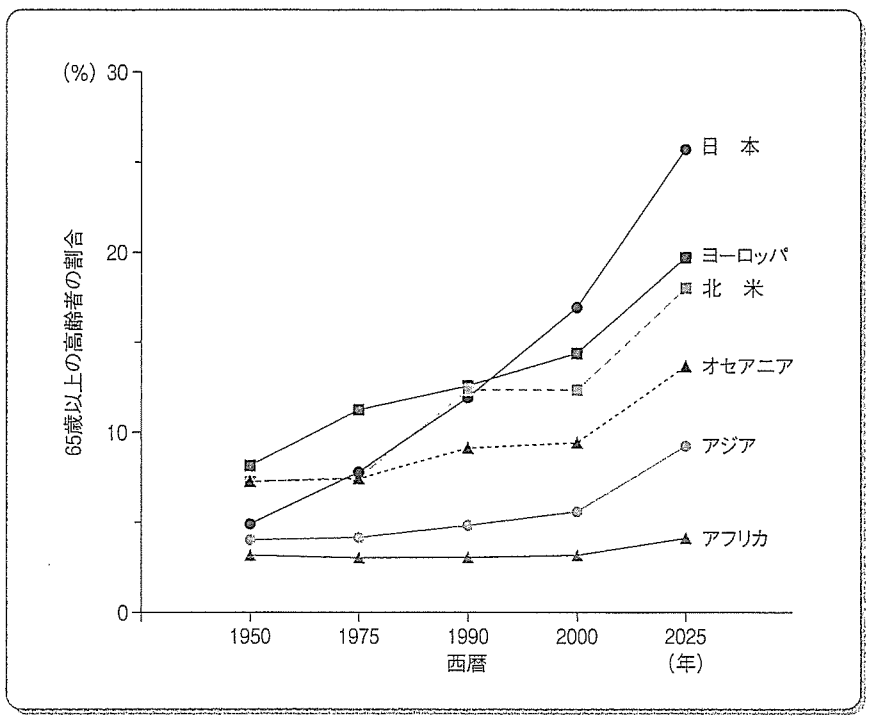

図1　65歳以上の高齢者の割合に関する国際比較

[文献1)より引用]

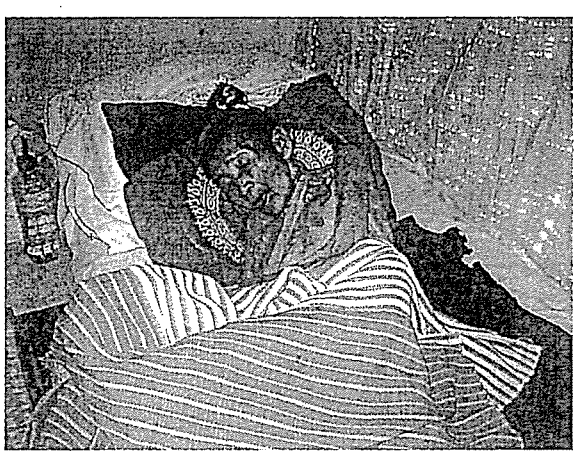

図2　西ジャワにおける93歳の要介護高齢者

村に医師はいない。駐在の看護助手が時折、訪問するが、格別な医療的処置はなされない。家族や村人は、介助しても食事が食べられる間は、この女性の生命力が続いているのであって、もし食事が摂れなくなったときにこの人の人生は終わる、という認識をもっている。また、都市部のジャカルタ近郊では、すでに貧困高齢者を対象とした私的なデイサービスが散見される。事業などで富をなした成功者が、私財をもって近隣の貧困高齢者を週に数回程度家に集め、食事、運動、コーランの祈り、団らんを供するものである。年に1〜2回、衣服も提供するという。イスラム世界では、社会の成功者が名をなし功を遂げたのちは、蓄えた私財をもって社会に奉仕するのがイスラムの教えにかなうという。このイスラム的宗教的伝統も、高齢者介護の一端を担っていることになる。

また、インドネシア全土には、母子保健のための保健ネットワーク“ポスヤンドウ”が広く張り巡らされているが、数年前からは高齢者のための保健組織“ポスビンドウ”が立ちあがり、まだ未整備ではあるものの、中央から徐々に地方に普及し始めている。