individuals for dementia, a particularly suitable population for preventive approaches. Longitudinal studies of case series have revealed an increased risk of AD in MCI subjects, with a conversion rate ranging from 7 to 20% per year (Johnson *et al.*, 1998; Wolf *et al.*, 1998; Pertersen *et al.*, 1999; Petersen *et al.*, 2005).

Most studies investigating the natural history of MCI have been conducted on samples of subjects recruited in specialized outpatient clinics such as memory clinics for AD. Such samples are highly selected, and it would be essential to identify high-risk subjects of dementia from community-based surveys to carry out early intervention. To our knowledge, one community-based prospective cohort study reported that an annual conversion rate was 8.3% for 5 years (Larrieu *et al.*, 2002). The incidence and outcome of MCI in the general population are still largely unknown.

Standardized memory examinations such as the Wechsler memory scale revised (WMS-R) can be used to identify subjects satisfying a strict definition of MCI (Flicker *et al.*, 1991; Petersen *et al.*, 1997). However, it may be very difficult to carry out such time-consuming examinations in community-based epidemiological surveys.

We extracted a group of mild memory impairment/no dementia (MMI/ND) with Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975; Mori *et al.*, 1985), based on the results of a population-based dementia study in Nakayama. The aim here is to report on a diagnostic system for MCI-like high-risk community dwellers by simple methods, which could be employed for community-based interventions and public health activities.

SUBJECTS

In the current study, we selected subjects who were participants in the first Nakayama study, and who satisfied the following criteria: (1) normal general cognitive function, with MMSE ≥ 24; (2) objective memory impairment, assessed by three-words recall in MMSE (delayed recall 0/3 or 1/3); (3) neuropsychiatric examination: absence of dementia or depression, diagnosed by geriatric neuropsychiatrists according to the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn, revised (DSM-III R) (American Psychiatric Association, 1987) criteria; (4) no ADL impairment. Subjects above mentioned could be defined as MMI/ND.

For comparison, 74 subjects who did not receive a diagnosis of dementia or MMI/ND at baseline were investigated with the same protocol in a 5-year follow-up. All subjects were hung in one randomly selected village (one of 43) in Nakayama town.

METHODS

Baseline assessment (The first Nakayama study)

Nakayama is a Japanese rural community adjacent to Matsuyama City, a metropolis on Shikokou Island. We selected this town because of its population size (5038 total residents, of whom 1438 were over 65 years of age), population stability (only 3.1% of people more than 65 years of age had moved elsewhere, including institutions, in the 3 years preceding the first survey), and active collaboration offered by family doctors.

The first Nakayama study included all residents over 65 years at home in the rural community of Nakayama town in Japan between January 1997 and March 1998 by means of a door-to-door survey with a three-phase design. Of 1438 inhabitants, 1162 (81.0%) completed the protocol. A more detailed description of the methods has been reported previously (Ikeda *et al.*, 2001; Ikeda *et al.*, 2004).

The screening interview (Phase 1) consisted of a semistructured questionnaire (questions on education, occupation, daily life activities, alcohol consumption, exposure and risk factor profile, previous disease, medication, sleep, and appetite), followed by the MMSE for participants and the short memory questionnaire (SMQ) (Koss *et al.*, 1993) for a family member of each participant. All subjects were examined by neuropsychiatrists. Participants were submitted to clinical evaluation according to the cut point of these tests for the presence of a cognitive disorder, based on previous studies (MMSE ≤ 23 and/or SMQ ≤ 39).

The clinical evaluation (Phase 2) included a semistructured interview of the participant's medical history; standard physical and neurological examination; severity evaluation using the clinical dementia rating scale (CDR) (Hughes *et al.*, 1982), and psychiatric evaluation using the neuropsychiatric inventory (NPI) (Cummings *et al.*, 1994). Based upon the results of these evaluation, participants were selected for diagnostic procedures (Phase 3).

Participants were asked to undergo cranial computed tomography (CT) and routine blood tests including serum vitamin B 12 and thyroid function tests. A final diagnosis was made based on combined information, using three diagnostic steps. The diagnosis of dementia was established using the DSM-III R criteria. MMI/ND subjects were selected from Phase 1.

Follow-up assessment and diagnosis

Five-year follow-up was conducted on all these individuals between April and December in 2003. A senior neuropsychiatrist administered MMSE to subjects, while a public health nurse interviewed Physical Self-Maintenance Scale (PSMS) and Instrumental Activities of Daily Living Scale (IADL) (Lawton and Brody, 1969) to a family member of each subject. Subjects hospitalized or entered institutions were included. Cranial CT was conducted on all subjects whose MMSE score had declined by more than 2 points since baseline (Mohs *et al.*, 2001).

The diagnosis of dementia was established according to the DSM-III R criteria. Finally, demented subjects were classified into subgroups by the cause of dementia. AD was defined according to the NINCDS-ADRDA criteria for probable AD (McKhann *et al.*, 1984), VaD was defined according to the NINDS-AIREN criteria (Roman *et al.*, 1993).

This survey was conducted after obtaining informed consent from all subjects or their relatives.

Statistics

The conversion rate was calculated using the person-year method (Beth and Robert, 2001).

RESULTS

The sample consisted of 104 subjects at baseline; 59 were women and 45 were men. The mean age was 75.5 ± 6.7 years (range, 65.1 to 90.2 years) for women and 73.6 ± 6.8 years (range, 65.1 to 101.4 years) for men.

Five years after the first Nakayama study, 14 subjects were dead, 13 had moved to other communities (mainly due to institutionalization), and six refused to participate in the follow-up investigation. Eleven (10.6%) subjects were diagnosed with AD (five men, six women), five (4.8%) were diagnosed with VaD (three men, two women), and six (5.8%) were diagnosed with dementia of other etiology. There were nine (8.7%) subjects who remained in MMI/ND. Furthermore, 40 (38.5%) subjects showed restored MMSE score (Table 1, Figure 1). In our survey, the conversion rate from MMI/ND to AD was 8.5% per 100 person-year and to dementia was 16.1% per 100 person-year for 5 years.

The comparison group consisted of 74 participants at baseline; 41 were women and 33 were men. The mean age was 75.4 ± 7.2 years (range, 65.1–89.2 years) for women and 73.2 ± 6.7 years (range, 65.1–92.4 years) for men. There were no significant differences in age or in gender ratio between the MMI/ND group and the comparison group. Of the 74 participants without dementia or MMI/ND at baseline, nine subjects had died, two moved to other communities, two subjects were diagnosed with VaD (one woman, one man), one was diagnosed with dementia of other etiology, one with MMI/ND, and none who developed AD (Table 1).

Table 1. As a result of 104 MMI/ND subjects and 74 control subjects in 5 years follow-up

	MMI/ND subjects	Free of dementia and MMI/ND subjects
	No. of samples	No. of samples
Died	14	9
Moved to other community	13	2
refused	6	0
AD	11	0
VaD	5	2
other type of dementia	6	1
MMI/ND	9	1
Free of dementia and MMI/ND	40	59

The Odds ratio for dementia was 5.2.

DISCUSSION

This is the first report of the five-year outcomes of MCI in a population-based study of dementia in Asia. Our survey differs from previous investigations in the following aspects. First, even in the screening interview, subjects were examined directly by a neuropsychiatrist, and, cranial CT was conducted on all subjects with any signs of dementia. Secondly, we have continued follow-up over five years in the Nakayama community after the first Nakayama investigation with a definite examination at 5 years.

The MCI group only has real value if the majority of people who develop dementia pass through this stage. Several studies have been undertaken to determine the natural course of MCI in attempts to estimate the 'conversion' rate to AD in this group (Petersen *et al.*, 2001). As expected from its concept, most longitudinal studies of case series revealed a much increased risk of AD in MCI subjects (Flicker *et al.*, 1991; Meyer *et al.*, 2002a; Meyer *et al.*, 2002b). MCI subjects may constitute a particularly suitable population for preventive approaches.

In previous clinic-based reports, MCI progresses to AD at a rate of 7 to 20% per year (Flicker *et al.*, 1991; Meyer *et al.*, 2002b; Tierney *et al.*, 1996). Standardized episodic memory examinations

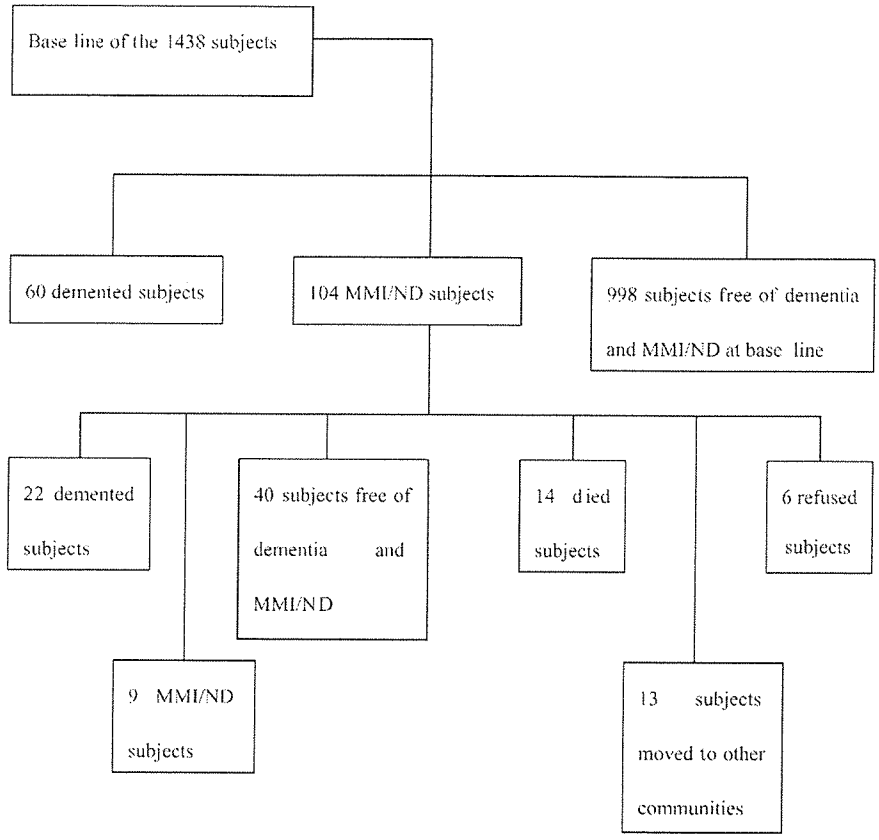

Figure 1. General design of the MMI/ND follow up study in Nakayama

(e.g. WMS-R) with comprehensive neuropsychological tests have been suggested to select a subject satisfying one strict definition of MCI. Therefore, measured cognitive function with MMSE, WMS-R, Wechsler Adult Intelligence Scale Revised (WAIS-R), Auditory Verbal Learning Test were adopted in those studies. The differences in these rates are probably related to the different instruments and cut-off limits chosen to define MCI across studies.

To our knowledge, there are a few community-based prospective cohort studies, following a community-dwelling MCI elderly people for several years (Larrieu *et al.*, 2002; Tuokko *et al.*, 2003; Gangluli *et al.*, 2004). In one of these studies (Larrieu *et al.*, 2002), comprehensive test batteries for an evaluation of global mental status (MMSE), visual memory (Benton's Visual Retention Test), verbal fluency (Isaacs Set Test), visuospatial attention (Zazzo's Cancellation Test), and simple logical reasoning and attention (Wechsler's Digit Symbol Test) were adopted. The conversion rate from MCI to AD was 8.3% per 100 person-year for 5 years (Larrieu *et al.*, 2002). This conversion rate is compatible with our result.

It may be difficult to administer comprehensive tasks in ordinal epidemiological surveys. It takes not only money and time (more than 1 h) but is also a large burden for any substantial size participants, particularly the very old. Therefore, it is an unsuitable method for extracting a high-risk group to AD in public health. There is an increasing need for brief but efficient cognitive screening instruments suitable for detecting MCI from normal aging individuals (Loewenstein *et al.*, 2000). Such screening tests would lighten the burden on patients and physicians, economize medical resources, and provide opportunities for dementia prevention and treatment when there is evidence that effective interventions exist (Bland and Newman, 2001). In the current study, we used MMSE to select subjects who present MMI/ND. We measured general cognitive performances with total score of MMSE and evaluated

memory impairment with three-words recall in MMSE. The MMSE total score was used to screen subjects and select them for neuropsychiatric evaluation/diagnosis, and then a subset of the MMSE (three-word recall) was used to further classify them as MMI/ND. Neuropsychiatric examinations were independent of the MMSE results. MMSE is a widely used and well validated instrument for assessing global cognitive function (Xu *et al.*, 2002), and used as screening instrument for cognitive decline or cognitive impairment in population-based studies as well as in clinical practice. MMSE is easily administered with a short operation time, thus it is suitable for use in the community.

We do not use standardized memory tests except for MMSE three-word recall to detect prodromal dementia cases. Therefore, subjects are not strictly defined as MCI, although they show apparent deficits in memory without dementia. Some previous reports have stated that MCI could not be distinguished from normal aging by simple examination (O'Connor *et al.*, 1991; Devanand *et al.*, 1997). However, the conversion rate of MMI/ND in this study was almost the same as a previous community-based MCI study with strict memory examinations (Larrieu *et al.*, 2002). In this study, we do not check for subjective memory complaints preferably corroborated by informants, which are considered characteristic of MCI based on strict criteria (Petersen *et al.*, 1997). The observations by knowledgeable informants regarding an individual's cognitive abilities in everyday functioning have been shown to be sensitive and reliable for MCI detection (Carr *et al.*, 2000; Morris *et al.*, 2001). However, it is difficult to carry out informant-based scales as screening tools, because considerable dwellers live alone in modern Japanese society and in many Western societies.

Although the population examined here is reasonably stable, over 10% had moved to other communities during the first year period including those who needed institutional care. In Japan a new system of long term care insurance (i.e. kaigo hoken) was implemented in 2000 which may have been an influence in this movement and could be a limitation.

As a consequence of global aging of the human population, the occurrence of cognitive impairment and dementia is rapidly becoming a significant burden for medical care and public health systems. Primary and secondary prevention of dementia through population-level interventions could reduce age associated risk. Reliable identification of high-risk individuals for dementia is vitally important to test effects of early therapeutic interventions. If community interactions are to be developed at the individual level, practical and simple methods will be needed for identification of those at risk of 'conversion' at low cost. MMI/ND selected by our method might be a possible candidate for trials of preventive intervention on public health. MMI/ND might be a promising therapeutic target and an important target for screening and possible early intervention.

ACKNOWLEDGMENT

The authors would like to thank the officials of the Nakayama home health care support center, especially Ms Kaori Iimori and Ms Michiko Nishimura. This work was supported in part by Grant-in-aid for Scientific Research (C) from Japan Society for the Promotion of Science to MI.

REFERENCES

American Psychiatric Association. 1987. *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn, rev. American Psychiatric Association: Washington, DC.

Beth D, Robert GT. 2001. *Basic and Clinical Biostatistics (Lange Medical Books)*, 3rd edn. McGraw-Hill: New York.

Bozoki A, Giordani B, Heidebrink JL, Berent S, Foster NL. 2001. Mild cognitive impairments predict dementia in nondemented elderly patients with memory loss. *Arch Neurol* **58**: 411–416.

Bland RC, Newman SC. 2001. Mild dementia or cognitive impairment: the Modified Mini-Mental State Examination (3MS) as a screen for dementia. *Can J Psychiatry* **46**: 506–510.

Carr DB, Gray S, Baty J, Morris JC. 2000. The value of informant vs. individual's complaints of memory impairment in early dementia. *Neurology* **55**: 1724–1726.

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. 1994. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* **44**: 2308–2314.

Devanand DP, Folz M, Gorlyn M, Moeller JR, Stern Y. 1997. Questionable dementia: clinical course and predictors of outcome. *J Am Geriatr Soc* **45**: 321–328.

Dresser R. 2000. Weighing the benefits of new Alzheimer's treatments. *Science* **289**: 869.

Flicker C, Ferris SH, Reisberg B. 1991. Mild cognitive impairment in the elderly: predictors of dementia. *Neurology* **41**: 1006–1009.

Folstein MF, Folstein SE, McHugh PR. 1975. 'Mini-Mental State'. A practical method for grading the cognitive state of patients for clinician. *J Psychiat Res* **12**: 189–198.

Ganguli M, Dodge HH, Changyu S, DeKosky ST. 2004. Mild cognitive impairment, amnestic type: an epidemiologic study. *Neurology* **63**: 115–121.

Graham JE, Rockwood K, Beattie BL, *et al.* 1997. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet* **349**: 1793–1796.

Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. 1982. A new clinical scale for the staging of dementia. *Br J Psychiatry* **140**: 566–572.

Ikeda M, Fukuhara R, Shigenobu K, *et al.* 2004. Dementia associated mental and behavioural deisturbances in elderly people

in the community: findings from the first Nakayama study. *J Neurol Neurosurg Psychiatry* **75**: 146–148.
Ikeda M, Hokoishi K, Maki N, *et al.* 2001. Increased prevalence of vascular dementia in Japan: a community-based epidemiological study. *Neurology* **57**: 839–844.
Janus C, Pearson J, McLaurin J, *et al.* 2000. A beta peptide immunization reduces behavioral impairment and plaques in a model of Alzheimer's disease. *Nature* **408**: 979–982.
Johnson KA, Jones K, Holman BL, *et al.* 1998. Preclinical prediction of Alzheimer's disease using SPECT. *Neurology* **50**: 1563–1571.
Koss E, Patterson MB, Ownby R, Stuckey JC, Whitehouse PJ. 1993. Memory evaluation in Alzheimer's disease: caregiver's appraisals and objective testing. *Arch Neurol* **50**: 92–97.
Kral VA. 1962. Senescent forgetfulness; Benign and malignant. *J Can Med Assoc* **86**: 257–260.
Larrieu S, Letenneur L, Orgogozo JM, *et al.* 2002. Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. *Neurology* **59**: 1594–1599.
Lawton MP, Brody EM. 1969. Assessment of older people: self maintaining and instrumental activities of daily living. *Gerontologist* **9**: 179–186.
Loewenstein DA, Barker WW, Harwood DG, *et al.* 2000. Utility of a modified Mini-Mental State Examination with extended delayed recall in screening for mild cognitive impairment and dementia among community dwelling elders. *Int J Geriatr Psychiatry* **15**: 434–504.
Mckhann G, Drachman D, Fostein F, Katzman R, Price D, Stadlan EM. 1984. 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 of Alzheimer's disease. *Neurology* **34**: 939–944.
Meyer JS, Xu G, Thornby J, Chowdhury M, Quach M. 2002a. Is mild cognitive impairment prodromal for vascular dementia like Alzheimer's disease? *Stroke* **33**: 1981–1985.
Meyer JS, Xu G, Thornby J, Chowdhury M, Quach M. 2002b. Longitudinal analysis of abnormal domains comprising mild cognitive impairment (MCI) during aging. *J Neuro Sci* **201**: 19–25.
Mohs RC, Doody RS, Morris JC, *et al.* and the 312 Study Group. 2001. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology* **57**: 481–488.
Mori E, Mitani Y, Yamadori A. 1985. Useffulness of a Japanese version of the Mini-Mental State Test in neurological patients [in Japanese]. *Jap J Neuropsychol* **1**: 82–90.
Morris JC, Storandt M, Miller JP, *et al.* 2001. Mild cognitive impairment represents early-stage Alzheimer disease. *Arch Neurol* **58**: 397–405.
O'Connor DW, Pollitt PA, Hyde JB, Miller ND, Fellowes JL. 1991. Clinical issues relating to the diagnosis of mild dementia in a British community survey. *Arch Neurol* **48**: 530–534.
Petersen RC, Smith GE, Waring SC, Ivnik RJ, Kokmen E, Tangelos EG. 1997. Aging, memory, and mild cognitive impairment. *Int Psychogeriatr* **9**: 65–69.
Petersen RC, Smith GE, Waring SC, Ivnik RJ, Targalos EG, Kokmen E. 1999. Mild cognitive impairment-clinical characterization and outcome. *Arch Neurol* **56**: 303–308.
Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. 2001. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* **8**: 1133–1142.
Petersen RC, Thomas RG, Grundman M, *et al.* 2005. Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment. *N Engl J Med* **352**: 2439–2441.
Roman GC, Tatemichi TK, Erkinjuntti T, *et al.* 1993. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* **43**: 250–260.
Sherwin BB. 2000. Mild cognitive impairment: potential pharmacological treatment options. *J Am Geriatr Soc* **48**: 431–441.
Tierney MC, Szalai JP, Snow WG, *et al.* 1996. Prediction of probable Alzheimer's desease in memory-impaired patients: a prospective longitudinal study. *Neurology* **46**: 661–665.
Tuokko H, Frerichs R, Graham J, *et al.* 2003. Five-year follow-up of cognitive impairment with no dementia. *Arch Neurol* **60**: 577–582.
Wolf H, Grunwald M, Ecke GM, *et al.* 1998. The prognosis of mild cognitive impairment in the elderly. *J Neural Transm* **54**: 31–50.
Xu G, Meyer JS, Thornby J, Chowdhury M, Quach M. 2002. Screening for mild cognitive impairment (MCI) utilizing combined mini-mental-cognitive capacity examinations for identifying. *Int J Geriatr Psychiatry* **17**: 1027–1033.

Original Research Article

Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2006;21:74–80
DOI: 10.1159/000090139

Accepted after revision: September 3, 2005
Published online: December 6, 2005

Initial Symptoms in Frontotemporal Dementia and Semantic Dementia Compared with Alzheimer's Disease

Shunichiro Shinagawa[a,b] Manabu Ikeda[a] Ryuji Fukuhara[a]
Hirotaka Tanabe[a]

[a]Department of Neuropsychiatry, Ehime University School of Medicine, Ehime, and [b]Department of Psychiatry, Jikei University School of Medicine, Tokyo, Japan

Key Words
Frontotemporal dementia · Semantic dementia · Alzheimer's disease

Abstract
Background: Despite many reports about cognitive decline and behavioral changes in patients with frontotemporal lobar degeneration (FTLD), there have been very few systematic studies of initial symptoms of frontotemporal dementia (FTD) and semantic dementia (SD). ***Objective:*** It was the aim of this study to investigate FTD and SD and to establish whether they are characterized by different initial symptoms. ***Methods:*** Three groups of patients were studied: FTD (n = 36), SD (n = 17) and age-matched Alzheimer's disease (AD) patients (n = 52). Information on initial symptoms was obtained from caregivers. Symptoms were classified into 22 distinct categories from the following domains, based on previous studies of symptoms of FTLD: (1) change in social behavior, affection, and daily activities, (2) cognitive decline, (3) language impairments, and (4) other abnormal symptoms. ***Results:*** Change in social behavior, affection, and daily activities was significantly more common in patients with FTD; on the other hand, language impairments were significantly more common in patients with SD as initial symptoms. Apathy and stereotypic behaviors were the most common initial symptoms among patients with FTD, while anomia, paraphasia, and impairment in word comprehension were the most common initial symptoms among patients with SD. Memory disturbance was the most common initial symptom among patients with AD. ***Conclusions:*** Behavioral and psychiatric symptoms are predominant initial symptoms in FTD, while language symptoms are predominant initial symptoms in SD. In addition to the assessment of current symptoms, the assessment of initial symptoms is useful for differential diagnosis in patients with FTD, SD and AD.

Introduction

Currently, frontotemporal lobar degeneration (FTLD) is the preferred term used to describe primary cerebral degeneration involving the frontal and/or temporal lobes associated with non-Alzheimer's pathology [1, 2]. It is the second most common form of primary dementia in the presenium and associated with a high degree of caregiver

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1420–8008/06/0212–0074$23.50/0

Accessible online at:
www.karger.com/dem

Manabu Ikeda, MD, PhD
Department of Neuropsychiatry
Ehime University School of Medicine
Shitsukawa, Toon-city, Ehime, 791-0295 (Japan)
Tel. +81 89 960 5315, Fax +81 89 960 5317, E-Mail mikeda@m.ehime-u.ac.jp

burden as it produces changes in personality, behavior, and communication abilities [3]. FTLD gives rise to three different clinical syndromes determined by the distribution of atrophy within the frontal and temporal lobes, i.e. frontotemporal dementia (FTD), semantic dementia (SD), and progressive non-fluent aphasia (PNFA).

Patients with FTD may experience disorders predominantly related to behavior, including loss of insight, disinhibition, apathy, mood changes, mental rigidity, stereotypic behavior, and eating behaviors [4–7]. SD, by contrast, is a form of dementia in which progressive loss of conceptual knowledge about words and objects are the main symptoms [8–10]. Although the semantic deficit is the main clinical feature, changes in behavior and personality are also present [5, 6, 11, 12]. When the concept of FTLD was proposed, it was suggested that some overlap in symptomatology between SD and FTD would be anticipated with disease progression [1]. Recent reports, however, have highlighted that some symptoms commonly occur in these subtypes at an early stage of the disease [5, 7].

Despite many reports about behavioral changes and cognitive decline in patients with FTLD, there have been very few systematic studies of the initial symptoms of FTLD. From a clinical point of view, it is important to investigate the initial symptoms of FTLD for the following reasons. First, there is a possibility to gather knowledge about the prodromal state of FTLD, just like the mild cognitive impairment state in Alzheimer's disease (AD). Second, behavioral features in the presenium are often misdiagnosed as psychiatric disorders such as schizophrenia or mood disorder. This misdiagnosis has led to the under-recognition of FTD, and hence, to underestimation of its prevalence [1]. Third, cognitive decline in the presenium is frequently misdiagnosed as AD. Although the concept of SD has recently become more widely appreciated, loss of semantic memory for words or objects in SD is still difficult to understand for many physicians and caregivers [1]. Cases of SD with semantic memory impairment are erroneously diagnosed as AD because the unique symptoms are considered to be ordinary forgetfulness. Fourth, because both patients with FTD and SD present behavioral changes at an early stage of the disease, it might be generally difficult to distinguish these subtypes according to their behavioral symptoms.

From a therapeutic point of view, it is important to distinguish AD from FTLD at an early stage of the disease, particularly with the advent of cholinesterase inhibitors for the treatment of AD [13]. There is also the possibility that serotonin selective reuptake inhibitors may be beneficial in reducing behavioral symptoms in FTLD [14]. This new therapeutic strategy could reduce the burden of care for patients with FTLD.

The main aims of this study were twofold: (1) to investigate initial symptoms of FTD and SD, and (2) to establish the nature by which the initial symptoms of FTD and SD differ among each other and from AD.

Methods

After a complete description of the study to all patients or their caregivers, written informed consent was obtained.

Patients

Patients were recruited from the Higher Brain Function Clinic of the Department of Neuropsychiatry, Ehime University Hospital, between June 1999 and August 2004, and were seen by a senior neuropsychiatrist. All patients underwent both physical and neurological examinations. Patients underwent magnetic resonance imaging (MRI) and HMPAO-SPECT, together with the usual battery of screening blood tests including vitamin B_{12} and thyroid function. We also used a standard psychiatric evaluation to exclude major functional psychiatric disorders such as schizophrenia and mood disorder. Patients with a history of significant head trauma and alcoholism were excluded. Patients were assessed with a comprehensive battery of neuropsychological and neuropsychiatric tests, including the mini-mental state examination (MMSE) [15], digit span test, verbal fluency test, Raven's Coloured Progressive Matrices [16], clinical dementia rating (CDR) [17], and neuropsychiatric inventory (NPI) [18, 19] at the first visit. Patients were rated on the NPI for assessment of behavioral features. Caregivers were asked if the behavior had been present during the previous month. In aphasic patients, the language function was evaluated by the Japanese Standard Language Test of Aphasia [20] within 2 months from the first visit. Two patients could not complete MMSE because of their behavioral symptoms, and 1 patient could not complete NPI at the first visit.

Three groups of patients were involved in this study: FTD (n = 36), SD (n = 17) and AD patients (n = 52). All patients in the FTD and SD groups fulfilled the recent consensus criteria for FTLD, which recognizes the subtypes of FTD, SD, and PNFA [2]. Patients with PNFA were excluded because they were too few (n = 4) to enable meaningful comparisons with the other groups. There was no family history in all subtypes of FTLD patients, as in most Japanese cases of FTLD [3]. All patients with FTD showed either frontal atrophy on MRI and/or frontal lobe hypoperfusion on HMPAO-SPECT [21]. All brain MRI images of SD patients showed focal atrophy involving the polar and inferolateral regions of the temporal lobe [22, 23]. Fifty-two patients with AD, matched for age and MMSE score at first consultation and education, were also selected. Patients with AD satisfied probable AD criteria according to the criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [24]. Brain MRI showed either a mild degree of medial temporal lobes or diffuse atrophy.

Table 1. Demographic variables of the three patient groups

	FTD (n = 36)	SD (n = 17)	AD (n = 52)
Sex, male/female	17/19	6/11	15/37
Age at consultation, years	68.8 ± 9.1 (49–85)	64.9 ± 7.8 (52–81)	66.1 ± 7.3 (56–85)
Duration from initial symptom appearance to consultation, months	36.0 ± 24.0 (3–117)	39.6 ± 16.8 (12–78)	37 ± 34.3 (1–162)
CDR grade, 0.5/1/2/3	13/8/13/2	8/4/5/0	13/21/13/5
MMSE score	19.0 ± 9.0	17.5 ± 10.0	18.7 ± 6.1
NPI score	21.6 ± 14.1	19.5 ± 16.4	16.2 ± 13.7

Data are given as number of patients or means ± SD; figures in parentheses indicate range.

Assessment of Initial Symptoms

We routinely and systematically gathered information about initial symptoms from caregivers. Caregivers were asked to recall the onset of the illness to permit demarcation of the period of illness. It was emphasized that the 'initial symptom' was the first change the caregiver noticed and should reflect a substantive change from the patient's premorbid state, rather than a longstanding character trait. After having recorded the content as described by caregivers, all symptoms were categorized into the following domains, which relate to components from the FTLD diagnostic criteria [2, 25], NPI [18, 19], and previous studies regarding the symptoms of FTLD [5–7, 12]:

(1) Change in social behavior, affection, and daily activities: loss of social awareness (lack of social tact, misdemeanors), loss of personal awareness (neglect of personal hygiene and grooming), disinhibition (unrestrained sexuality, violent behavior), apathy or social withdrawal or aspontaneity, stereotypic behavior (stereotypic movement, stereotypic speaking, stereotypic daily routines, obsessive-compulsive behavior), mental rigidity and inflexibility, depression or anxiety, irritability or aggression, delusion or hallucination, abnormal eating and oral behaviors (overeating, altered food preference, food fads, mouthing of inedible objects), and decline in daily activities not caused by a specific symptom.

(2) Cognitive decline except language impairments: memory disturbance, deficits in visuospatial function, disorientation (time or date), disturbance of attention or distractibility, and prosopagnosia.

(3) Language impairments: reduction of speech, paraphasia, anomia or impairment in word naming, and impairment in word comprehension.

(4) Other abnormal symptoms: physical symptoms, not otherwise classified.

The examining clinician confirmed the context in which each symptom occurred, together with the caregiver, to avoid misclassification. For example, if a caregiver mentioned that the patient had begun to speak the same phrases repeatedly, further clarification was sought to ascertain whether this represented repetitive questioning in the context of a memory disorder versus stereotypic catch-phrase usage. Likewise, if a caregiver reported that the patient's language had become rough and/or blunt, the caregiver was asked to elaborate so that the clinician could decide whether this referred to crude speech due to lack of social awareness versus the usage of generic terms due to aphasia. When the caregiver reported multiple symptoms as first changes, all symptoms were classified as initial symptoms (maximum three symptoms).

Data Analysis

Data analyses were carried out using the SPSS-PC software package. Statistical differences between the three groups were assessed by the Kruskal-Wallis test for non-parametric variables, as well as the χ^2 test with post hoc Fisher's exact test for nominal variables.

Results

The demographic characteristics of the three groups including sex, age at consultation, duration from initial symptom appearance until consultation, CDR grade, MMSE score, and NPI score are summarized in table 1. There were no significant differences between the three groups in sex, education, age at consultation, and duration from initial symptom appearance until consultation. There were also no significant differences in the severity of dementia according to CDR and the total score of MMSE, as well as the total severity of psychiatric symptoms according to the total score of NPI at the first visit.

The initial symptoms of the three groups are summarized in table 2. Thirty-six patients with FTD showed a total of 64 initial symptoms, with an average of 1.8 initial symptoms per patient. 'Change in social behavior, affection, and daily activities' occurred as initial symptoms in 62.5% of all patients with FTD, 'cognitive decline' involving distractibility in 18.8%, and 'language impairments' in 14.1% of FTD patients. Seventeen patients with SD showed a total of 24 initial symptoms, with an aver-

Table 2. Frequency of initial symptoms (%) in FTD, SD and AD

	FTD	SD	AD	p value	
Number of initial symptoms per 1 patient	1.8	1.4	1.4	NS	
Change in social behavior, affection, and daily activities	62.5	20.8	19.2	0.000	FTD>SD FTD>AD
Loss of social awareness	7.8	0.0	0.0	0.022	FTD>AD
Loss of personal awareness	3.1	4.2	0.0	NS	
Disinhibition	6.3	0.0	1.4	NS	
Apathy or social withdrawal of aspontaneity	14.1	4.2	2.7	0.0043	FTD>AD
Stereotypic behavior	12.5	4.2	0.0	0.002	FTD>AD
Mental rigidity and inflexibility	3.1	0.0	0.0	NS	
Depression or anxiety	1.6	0.0	2.7	NS	
Irritability or aggression	3.1	4.2	4.1	NS	
Delusion or hallucination	0.0	0.0	5.5	NS	
Abnormal eating and oral behaviors	3.1	0.0	0.0	NS	
Decline in daily activities not reduced to a specific symptom	7.8	4.2	2.7	NS	
Cognitive decline	18.8	16.7	74.0	0.000	AD>FTD AD>SD
Memory disturbance	9.4	8.3	61.6	0.000	AD>FTD AD>SD
Deficits in visuospatial function	0.0	4.2	6.8	NS	
Disorientation (time/date)	0.0	0.0	4.1	NS	
Disturbance of attention or distractibility	7.8	0.0	1.4	NS	
Prosopagnosia	1.6	4.2	0.0	NS	
Language impairments	14.1	62.5	2.7	0.000	SD>FTD SD>AD FTD>AD
Reduction in speech	3.1	4.2	0.0	NS	
Anomia or impairment in word naming	7.8	25.0	2.7	0.004	SD>AD
Paraphasia	1.6	16.7	0.0	0.001	SD>FTD SD>AD
Impairment in word comprehension	1.6	16.7	0.0	0.001	SD>FTD SD>AD
Other abnormal symptoms	4.7	0.0	4.1	NS	
Physical symptoms	3.1	0.0	2.7	NS	
Not otherwise classified	1.6	0.0	1.4	NS	

age of 1.4 initial symptoms per patient. 'Language impairments' occurred as initial symptom in 62.5% of all SD patients, 'change in social behavior, affection, and daily activities' in 20.8%, and 'cognitive decline' in 16.7% of SD patients. Fifty-two patients with AD showed a total of 73 initial symptoms, with an average number of 1.4 initial symptoms per patient. 'Cognitive decline' occurred as initial symptom in 74.0% of AD patients, 'change in social behavior, affection, and daily activities' in 19.2%, and 'language impairments' in 2.7% of AD patients.

The domain of 'change in social behavior, affection, and daily activities' was significantly more common in patients with FTD than in patients with SD and AD ($p < 0.01$), and 'language impairments' was significantly more common in patients with SD than in patients with FTD and AD ($p < 0.01$). Apathy and stereotypic behaviors were the most common initial symptoms in patients with FTD, while anomia, paraphasia, and impairment in word comprehension were the most common initial symptoms in patients with SD. In patients with AD, memory disturbance was the most common initial symptom.

There was no significant difference between FTLD and AD groups in the frequency of other items, such as disinhibition, depression or anxiety, irritability or aggression, delusion or hallucination, disorientation, disturbance of attention or distractibility, or reduction in speech.

Discussion

Clear and significant differences existed in initial symptoms between FTD and SD compared with AD. The most common initial features of FTD patients were 'change in social behavior, affection, and daily activities',

while the most common initial feature of SD patients was 'language impairments'. The most common initial feature of AD patients was 'cognitive decline', with 61% of all initial symptoms begin memory disturbance. By contrast, the frequency of cognitive deficits in patients with FTD and SD was low and we found no significant differences between these two groups. This result is consistent with many other studies that have found memory disturbance in AD usually precedes other cognitive deficits [26–28]. Lindau et al. [29] reported that memory disturbance was the first symptom of 76% of AD patients, whereas only 2% of FTD patients presented with memory disturbance.

There are 8 patients with FTLD whose caregivers reported memory disturbances as their initial symptom; nevertheless, 4 of them scored more than 2 points on the 'recall of three words' item at the MMSE when performed at the first visit. In contrast, AD patients who typically present with memory disturbance do not score well on this item [30, 31]. Therefore, it is unclear whether these FTLD patients who scored more than 2 points on the 'recall of three words' item at the MMSE genuinely had memory disturbance at their onset. Caregivers may have mistaken apathy or aphasia in FTLD for memory disturbance. These might be factors of misdiagnosis for FTLD patients at the examination.

Apathy and stereotypic behavior were remarkably more common initial symptoms in FTD compared with AD; on the other hand, anomia, paraphasia, and impairment in word comprehension were remarkably more common initial symptoms in SD compared with AD. Some recent reports mentioned that changes in behavior commonly occur in both FTD and SD at an early stage of the disease [6, 7]. Indeed, in our study, there was no significant difference in the severity of psychiatric symptoms according to the total NPI score between patients with FTD and SD at the time of the first visit, which in both groups was on average 3 years after initial symptom appearance. However, there was a significant difference in the quality of initial symptoms between these groups. This result suggests that in SD, isolated language impairment is the initial feature and that, subsequently, there is a gradual development of behavioral changes. This result may also suggest that anatomical heterogeneity between FTD and SD led to distinctive initial symptoms.

There were 6 patients with FTLD (5 patients with FTD and 1 patient with SD) whose initial symptoms were classified as 'decline in daily activities not caused by a specific symptom'. For example, those whose cooking ability deteriorated without any specific reason were categorized in this group. Such declines in daily activities may be due to a variety of symptoms which are connected with one another, for instance, mental rigidity and inflexibility, apathy, disturbance of attention, or distractibility. The number of initial symptoms per patient was higher in patients with FTD than in other groups, although this was not statistically significant. The possible reasons for these various symptoms in patients with FTD are the following. First, several different neural circuits of the frontal lobe may be impaired at the same time even at a very early stage [32]. Second, all symptoms which seemed to be different may be manifestations of one common factor.

We could find no significant differences between the three groups in the frequency of disinhibition, irritability or aggression, abnormal eating behavior, disturbance of attention, or distractibility. Although these symptoms are very common in patients with FTD [1, 2, 7] and included in clinical diagnostic criteria of FTD [2, 25] as the core or supportive symptoms, these symptoms might not occur frequently in the very early stage. We could not find a significant difference between the three groups in the frequency of visuospatial dysfunction and disorientation either, although these are very common symptoms in AD.

We also investigated the sensitivity and specificity for each symptom of the three patient groups. Memory disturbance achieved 87% sensitivity and 85% specificity for the classification of AD and FTLD groups. Memory disturbance might be an overwhelming initial symptom in AD and useful for differential diagnosis. On the other hand, anomia achieved 35% sensitivity and 92% specificity for the differentiation between the SD group and the other two patient groups, although it was a most popular initial symptom in the SD group. This may be because SD patients present various language impairments as initial symptoms, such as anomia, paraphasia, and impairment in word comprehension. The whole language impairments achieved 71% sensitivity and 89% specificity for the differentiation between the SD group and the other two patient groups. Apathy achieved 25% sensitivity and 92% specificity for the differentiation between the FTD group and the other two patient groups, although it was a most frequent initial symptom in the FTD group. This may be because FTD patients develop plural behavioral symptoms as initial symptoms, as described previously. This variety of symptoms is a characteristic of FTD patients, as is also described in diagnostic criteria. It is plausible that they present low sensitivity for only one symptom, even if it is a most frequent symptom.

In this study, we clinically diagnosed FTD and SD groups according to the consensus criteria for FTLD [2]. We did not perform lumbar puncture and could not discuss abnormal tau deposits. Recent researches have revealed that FTD patients consist of pathological heterogeneous groups including Pick's disease with or without Pick bodies, FTD and parkinsonism linked to chromosome 17, dementia lacking distinctive histology, corticobasal degeneration, and motor neuron disease [33, 34]. They have also demonstrated that clinical assessments fail to discriminate between either types of pathology. We need a longitudinal follow-up to observe a symptomatic change with progression. Further studies of clinicopathological correlation are required.

There are a few methodological issues that should be taken into consideration to fully appreciate our results. First, as this study is based on a retrospective recall of caregivers, it can be claimed that the informants' memories may have been inaccurate [35]. However, it seems implausible that the ability of caregivers of FTLD patients to remember initial symptoms would be different from that of caregivers of AD patients. Furthermore, using a clinical interview to obtain a medical history is the usual way of diagnosing dementia, so any possible bias introduced by the current methods are likely to be similar in routine clinical practice. Second, there is a possibility that the initial symptoms for which there was an overlap between FTD, SD and AD (for example, irritability or aggression) may be qualitatively different. Snowden et al. [6] have described possible differences in the quality of symptoms found in FTD and SD, although their study did not concern initial symptoms. Therefore, we cannot exclude the possibility that our study categorized different qualities of symptoms as same symptoms. Furthermore, it is difficult to standardize the severity of dementia between subgroups of FTLD and AD. Although we used CDR for determination of dementia severity, it is not specifically designed for FTLD. Third, as the investigation items of initial symptoms are related to items of clinical diagnostic criteria, it can be claimed that initial symptoms and diagnostic criteria seem circular. However, psychiatric symptoms and behavioral features were assessed during the month prior to the first visit using NPI [18, 19] for diagnosis. Likewise, language symptoms of aphasic patients were assessed within 2 months from the first visit, using the Standard Language Test of Aphasia [20]. Therefore, we believe that clinical diagnosis at the examination and information about initial symptoms may be basically independent.

Many studies have attempted to address the issue of differential diagnosis of early-stage FTLD and AD, including brain imaging and neuropsychological testing [27, 36–38]. However, there are many inconsistencies and it often remains difficult to make a clear diagnosis in the early stage of the disease. We think that initial symptoms should be taken into account in the assessment of patients with dementia as their evaluation may helpfully contribute to the differential diagnosis of FTD, SD and AD.

Acknowledgements

We want to thank Dr. Peter J. Nestor for his helpful comments on an earlier version of this paper. The present study was supported in part by a research grant from the Ministry of Health, Labor and Welfare.

References

1 Snowden JS, Neary D, Mann DMA: Fronto-Temporal Lobar Degeneration: Fronto-Temporal Dementia, Progressive Aphasia, Semantic Dementia. New York, Churchill Livingstone, 1996.

2 Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF: Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998;51:1546–1554.

3 Ikeda M, Ishikawa T, Tanabe H: Epidemiology of frontotemporal lobar degeneration. Dement Geriatr Cogn Disord 2004;17:265–268.

4 Gregory CA, Hodges JR: Frontotemporal dementia: use of consensus criteria and prevalence of psychiatric features. Neuropsychiatry Neuropsychol Behav Neurol 1996;9:145–153.

5 Bozeat S, Gregory CA, Ralph MA, Hodges JR: Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? J Neurol Neurosurg Psychiatry 2000;69:178–186.

6 Snowden JS, Bathgate D, Varma A, Blackshaw A, Gibbons ZC, Neary D: Distinct behavioural profiles in frontotemporal dementia and semantic dementia. J Neurol Neurosurg Psychiatry 2001;70:323–332.

7 Ikeda M, Brown J, Holland AJ, Fukuhara R, Hodges JR: Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. J Neurol Neurosurg Psychiatry 2002;73:371–376.

8 Snowden JS, Goulding PJ, Neary D: Semantic dementia: a form of circumscribed cerebral atrophy. Behav Neurol 1989;2:167–182.

9 Hodges JR, Patterson K, Oxbury S, Funnell E: Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. Brain 1992;115:1783–1806.

10 Snowden JS: Semantic dysfunction in frontotemporal lobar degeneration. Dement Geriatr Cogn Disord 1999;10(suppl 1):33–36.

11 Edwards-Lee T, Miller BL, Benson DF, Cummings JL, Russell GL, Boone K, Mena I: The temporal lobe variant of frontotemporal dementia. Neurology 1996;46:2023.
12 Shigenobu K, Ikeda M, Fukuhara R, Maki N, Hokoishi K, Nebu A, Yasuoka T, Komori K, Tanabe H: The Stereotypy Rating Inventory for frontotemporal lobar degeneration. Psychiatry Res 2002;110:175–187.
13 Cummings JL: Cholinesterase inhibitors: a new class of psychotropic compounds. Am J Psychiatry 2000;157:4–15.
14 Ikeda M, Tanabe H: Reducing the burden of care in dementia through the amelioration of BPSD by drug therapy. Expert Rev Neurother 2004;4:921–922.
15 Folstein MF, Folstein SE, McHugh PR: Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
16 Raven JC, Court JH, Raven J: Manual for Raven's Coloured Progressive Matrices. Oxford, Oxfords Psychologists Press, 1990.
17 Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL: A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566–572.
18 Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J: The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–2314.
19 Hirono N, Mori E, Ikejiri Y, Imamura T, Shimomura T, Hashimoto M, Yamashita H, Ikeda M: Japanese version of the Neuropsychiatric Inventory – A scoring system for neuropsychiatric disturbance in dementia patients. No To Shinkei 1997;49:266–271.
20 SLTA Committe: Standard Language Test of Aphasia Manual. Tokyo, Shinkou Igaku Shuppan-sha, 1997.
21 Miller BL, Gearhart R: Neuroimaging in the diagnosis of frontotemporal dementia. Dement Geriatr Cogn Disord 1999;10(suppl 1):71–74.
22 Chan D, Fox NC, Scahill RI, Crum WR, Whitwell JL, Leschziner G, Rossor AM, Stevens JM, Cipolotti L, Rossor MN: Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. Ann Neurol 2001;49:433–442.
23 Galton CJ, Patterson K, Graham K, Lambon-Ralph MA, Williams G, Antoun N, Sahakian BJ, Hodges JR: Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. Neurology 2001;57:216–225.
24 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.
25 The Lund and Manchester Groups: Clinical and neuropathological criteria for frontotemporal dementia. J Neurol Neurosurg Psychiatry 1994;57:416–418.
26 Cummings JL, Benson DF: Dementia of the Alzheimer type. An inventory of diagnostic clinical features. J Am Geriatr Soc 1986;34:12–19.
27 Welsh KA, Butters N, Hughes JP, Mohs RC, Heyman A: Detection and staging of dementia in Alzheimer's disease. Use of the neuropsychological measures developed for the Consortium to Establish a Registry for Alzheimer's Disease. Arch Neurol 1992;49:448–452.
28 Gregory CA, Orrell M, Sahakian B, Hodges JR: Can frontotemporal dementia and Alzheimer's disease be differentiated using a brief battery of tests? Int J Geriatr Psychiatry 1997;12:375–383.
29 Lindau M, Almkvist O, Kushi J, Boone K, Johansson SE, Wahlund LO, Cummings JL, Miller BL: First symptoms – Frontotemporal dementia versus Alzheimer's disease. Dement Geriatr Cogn Disord 2000;11:286–293.
30 Galasko D, Klauber MR, Hofstetter CR, Salmon DP, Lasker B, Thal LJ: The Mini-Mental State Examination in the early diagnosis of Alzheimer's disease. Arch Neurol 1990;47:49–52.
31 Loewenstein DA, Barker WW, Harwood DG, Luis C, Acevedo A, Rodriguez I, Duara R: Utility of a modified Mini-Mental State Examination with extended delayed recall in screening for mild cognitive impairment and dementia among community dwelling elders. Int J Geriatr Psychiatry 2000;15:434–440.
32 Cummings JL: Frontal-subcortical circuits and human behavior. Arch Neurol 1993;50:873–880.
33 Hodges JR, Davies RR, Xuereb JH, Casey B, Broe M, Bak TH, Kril JJ, Halliday GM: Clinicopathological correlates in frontotemporal dementia. Ann Neurol 2004;56:399–406.
34 McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ: Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol 2001;58:1803–1809.
35 Oppenheim G: The earliest signs of Alzheimer's disease. J Geriatr Psychiatry Neurol 1994;7:116–120.
36 Gregory CA, Serra-Mestres J, Hodges JR: Early diagnosis of the frontal variant of frontotemporal dementia: how sensitive are standard neuroimaging and neuropsychologic tests? Neuropsychiatry Neuropsychol Behav Neurol 1999;12:128–135.
37 Mathuranath PS, Nestor PJ, Berrios GE, Rakowicz W, Hodges JR: A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. Neurology 2000;55:1613–1620.
38 Kertesz A, Nadkarni N, Davidson W, Thomas AW: The Frontal Behavioral Inventory in the differential diagnosis of frontotemporal dementia. J Int Neuropsychol Soc 2000;6:460–468.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Neuroscience Letters 383 (2005) 115–120
Neuroscience Letters
www.elsevier.com/locate/neulet

Heart rate variability under acute simulated microgravity during daytime waking state and nocturnal sleep: Comparison of horizontal and 6° head-down bed rest

Koh Mizuno [a,*], Yuichi Inoue [b], Hideki Tanaka [a,c], Yoko Komada [a], Hidetomo Saito [d], Kazuo Mishima [d], Shuichiro Shirakawa [a]

[a] *Geriatric Mental Health, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kohnodai 1-7-3, Ichikawa, Chiba 272-0827, Japan*
[b] *Japan Somnology Center, Neuropsychatric Research Institute, Tokyo 151-0051, Japan*
[c] *Department of Clinical Psychology, Hiroshima International University, Hiroshima 724-0695, Japan*
[d] *Department of Psychiatry, Akita University, Akita 010-8543, Japan*

Received 4 November 2004; received in revised form 28 March 2005; accepted 29 March 2005

Abstract

This study examined the acute effect of cephalad fluid shift under simulated microgravity on heart rate variability (HRV) during both daytime waking state and nocturnal sleep. Seven healthy male volunteers (21–31 years) underwent a series of experiments involving 6° head-down bed rest (HD) for 3 days. A control experiment on the same subjects was conducted under horizontal bed rest (HZ) in the same series. HRV from electrocardiogram signals was periodically calculated by the MemCalc method during daytime on the first and second days of both conditions. Nocturnal sleep on the first night of bed rest was monitored by polysomnography. HRV during stage 2 sleep and REM sleep were assessed in the former and latter halves of the sleep period time. Nocturnal sleep architecture under both conditions was normal, but a slight decrease in stage 4 sleep and an increase in the number of arousals occurred under HD. On both the first and second days, HRV during the daytime did not differ between HZ and HD. In contrast, high frequency components in HRV during sleep stage 2 were significantly higher in the latter half of sleep under HD than under HZ, although there were no differences in the ratio of low frequency to high frequency components during both stage 2 and the REM stage between the conditions. These results suggest that the acute effect of the cephalad fluid shift on cardiac autonomic nervous activity might be affected by the sleep/wake state modulating the dominance between sympathetic and parasympathetic nervous activity.

Keywords: 6° Head-down bed rest; Autonomic nervous activity; Sleep; Awake

Change in autonomic nervous activity in space is a well-known physiological process. This phenomenon is related to orthostatic intolerance in a considerable number of astronauts after they return to earth [3]. It is known to be mediated by the acute cephalad fluid shift, which induces hypovolemia; this, in turn, affects the reflex control of the cardiovascular system [19,20]. Specific changes in basal autonomic nervous activity have been reported under actual and simulated microgravity by direct measurements of muscle sympathetic nerve activity [10,18] and by employing indirect indices derived from heart rate and blood pressure [14,15,25].

The frequency domain analysis of heart rate variability (HRV), which is a non-invasive measurement for estimating cardiac autonomic tone with less distress to the subject [1,24], has been applied to various experiments in the field of space medicine. In these studies, decreased high frequency power (HF) of HRV in subjects who are awake, which suggests decreased vagal tone, has been demonstrated during and after actual [21] and simulated [6,14,15,25] microgravity exposure. Although it has been reported that HRV during sleep

* Corresponding author. Tel.: +81 22 728 6000x113; fax: +81 22 728 6040.
E-mail address: mizuno@k.e-mail.ne.jp (K. Mizuno).

0304-3940/$ – see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2005.03.058

dramatically varies according to the sleep stage [9,29] and that it demonstrates clinical implications relevant to myocardial infarction [30], panic disorder [31], and insomnia [2], only one study has examined HRV in each stage of nocturnal sleep under microgravity [13]. In that study, the changes in HRV that occurred during sleep aboard the spaceship were not conclusive because of the individual differences among the subjects and, unfortunately, no result regarding autonomic nervous activity during daytime was presented. Therefore, it is unclear whether there are any differences in the responses in cardiac autonomic nervous activity under microgravity during the states of daytime waking and nocturnal sleep.

The purpose of the present study was to examine HRV under acute simulated microgravity during both daytime waking and nocturnal sleep. In order to sort the values of HRV according to sleep stage, polysomnographic sleep recording was conducted. To determine the effect of the cephalad fluid shift itself, two experimental runs with similar time schedules were conducted to compare HRV; one experiment involved 6° head-down bed rest (HD) for simulated microgravity, and the other experiment involved horizontal bed rest (HZ) as a control.

The experimental protocol was approved by the ethics committee of the National Space Development Agency of Japan. Seven healthy male volunteers (age, 26 ± 4.5 years; height, 173 ± 6.9 cm; weight, 70 ± 11.0 kg) participated in the study after receiving a thorough explanation of the protocol and providing written informed consent.

A series of experiments that involved 3 days of bed rest were conducted twice on the same subjects; one experiment involved an HD, and the other involved an HZ. A 5-day interval was set between each experimental run, and the order of HD or HZ was counterbalanced across the subjects. From 1 week before through to the end of the experiment, the subjects maintained a similar sleep schedule without a daytime nap; this schedule was confirmed by Actigraphic recordings [7].

The subjects came to the bed rest laboratory 2 days prior to the beginning of each bed rest experiment. The first 2 days in the laboratory were used as an ambulatory control period, wherein the subjects performed several familiarization sessions for the planned measurements during bed rest. On the third day, after breakfast and evacuation, the subjects started HZ at around 09:30. During the HD session, 20 min after the start of horizontal bed rest, the bed position was fixed at 6° head-down position until 18:00 on the fifth day. With regard to the HZ condition, the same experimental procedure was conducted, maintaining the horizontal bed position until the end of the bed rest period.

During the bed rest period, the subjects were requested to lie down on the bed in the position specified, except during evacuation, which they were requested to carry out within 15 min after breakfast. The scheduled time for sleep was from 00:00 to 08:00, during which room illumination was lowered to 10 lx. Napping was prohibited during the daytime (from 08:00 to 24:00) and the illumination measured at the level of the subjects' face was controlled at 1000 lx during this period. However, during the bed rest period, the subjects were allowed to read, talk, or watch television, which was placed at their bedside, when they had no scheduled experimental measurement. The subjects were continuously observed, either directly or by video monitoring, throughout the bed rest period to ensure that they did not take a nap or sit up during daytime. Breakfast, lunch, and dinner without spicy foodstuffs or caffeine were provided at 08:30, 13:00, and 19:30, respectively, while daily water intake was controlled at 20 ml/kg body weight per day. The subjects were requested to drink an equal amount of water every 2 h from 10:30 to 22:30.

After complete voiding at 08:00 on the day before bed rest, urine was collected until 24:00 on the second day of bed rest. Urine volume during the daytime (from 08:00 to 24:00; 16 h) and during the night (from 24:00 to 08:00; 8 h) was separately measured on each day.

Polysomnographic sleep monitoring was performed when the subjects stayed in the bed rest laboratory. Digital sleep recordings were performed with a Polymate system (TEAC, Tokyo, Japan) with electrode placements at C3, F3, and O1, left and right outer canthi, and submentally. The sleep recordings obtained on the first night under the bed rest condition were scored in 20-s epochs according to standardized scoring criteria [27].

Throughout the subjects' stay, the R–R intervals of the electrocardiogram were continuously monitored using an activetracer, model AC-301 (GMS, Tokyo, Japan) with a sampling rate of 1 kHz. Power spectrum analysis of HRV was performed by the MemCalc method [28] using a commercial software (MemCalc/Win, Suwa Trust, Tokyo, Japan), developed for analyzing data files transferred from an activetracer. Heart rate (HR) and the power spectrum bands consisting of high frequency (HF: 0.15–0.40 Hz) and low frequency (LF: 0.04–0.15 Hz) components [1] were computed every minute. HF, reflecting respiratory-induced cardiac sinus arrhythmias, was identified as an index of cardiac vagal activity [1,24]. The ratio of low frequency to high frequency components (LF/HF) was then calculated as an index of sympathovagal balance [1,24]. The data sampled after 18:30 on the second day of bed rest was rejected because measurements and treatments for the other purpose were started from 19:00.

Regarding data analysis during daytime, the average values of HR, HF, and LF/HF for 30 min were periodically calculated. The periods over which data was averaged, six times each on both the first and second days, are shown in Fig. 1. The 30-min period after meals was excluded from the data-averaging period. Due to scheduling constraints, the data-averaging period was reduced to 20 min after 08:05 on the second day of bed rest. Subjects maintained a supine position during these periods.

With regard to the data on the first night of bed rest, the values were sorted according to sleep stage. Since it has been reported that HF and LF/HF differ across sleep stages [9,29], we chose the values only when three consecutive 20-s sleep

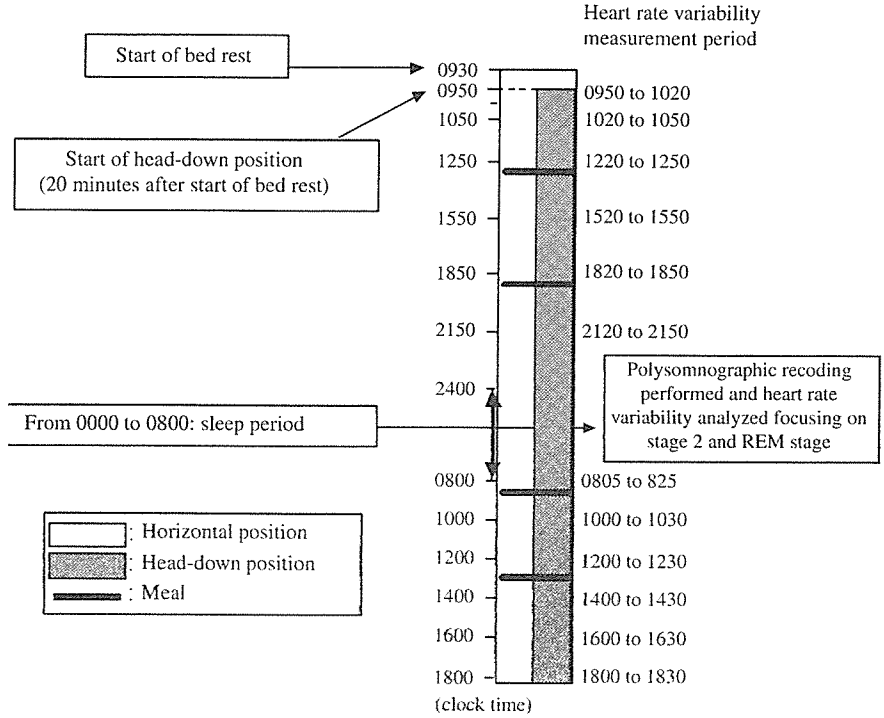

Fig. 1. Time schedule and heart rate variability measurement period for the first and the second days under each bed rest condition.

epochs were included in stage 2 and the REM stage, which commonly appears during both the early and the latter portions of the sleep period time (SPT). Based on these values, average values of HF and LF/HF during each of sleep stage 2 and the REM stage were calculated during the entire SPT and in the former and latter halves of the SPT, respectively.

All the values are expressed as mean ± S.E. A two-tailed paired *t*-test was used to compare urine volume and sleep parameters between HD and HZ. Analysis for HF and LF/HF during the daytime was separately conducted on both the first and the second days of bed rest by employing a two-way ANOVA (bed rest condition × time) for repeated measures. Average values of HF and LF/HF during each of sleep stage 2 and the REM stage obtained during the entire SPT and in the former and latter halves of the SPT were compared between HD and HZ using the Wilcoxon matched-pairs signed-ranks test. Statistical significance was defined as $P < 0.05$.

Urine volume during daytime was observed to increase on the first day under both bed rest conditions (HZ: 2127 ± 112 ml; HD: 2039 ± 125 ml) as compared to conditions prior to bed rest (HZ: 1111 ± 78 ml; HD: 1497 ± 195 ml) and on the second day of bed rest (HZ: 1331 ± 101 ml; HD: 1419 ± 149 ml). However, no significant difference in urine volume was observed between HZ and HD.

Sleep parameters measured on the first night of bed rest are shown in Table 1. Sleep parameters calculated for the entire

Table 1
Comparison of sleep parameters between horizontal and 6° head-down bed rest

	Results over entire TIB		Former half of SPT		Latter half of SPT	
	HZ	HD	HZ	HD	HZ	HD
TST (min)	441.5 ± 6.9	444.1 ± 3.0	223.7 ± 4.2	225.1 ± 3.0	222.5 ± 3.1	222.2 ± 2.5
SEI (%)	92.0 ± 1.4	92.6 ± 0.6	–	–	–	–
Sleep latency (min)	18.1 ± 6.5	11.4 ± 2.9	–	–	–	–
Stage REM (%)	26.8 ± 4.9	21.1 ± 2.0	17.6 ± 1.8	17.3 ± 2.2	27.6 ± 2.6	24.9 ± 3.3
Stage 1 (%)	14.0 ± 2.2	15.3 ± 1.6	11.4 ± 1.5	15.2 ± 1.7	164 ± 3.1	15.4 ± 2.3
Stage 2 (%)	46.5 ± 4. 7	47.9 ± 3.6	45.5 ± 4.9	44.8 ± 5.5	47.2 ± 4.5	50.9 ± 2.2
Stage 3 (%)	9.4 ± 1.1	8.7 ± 0.9	14.5 ± 1.5	14.6 ± 1.8	4.1 ± 1.4	2. 8 ± 1.1
Stage 4 (%)	3.6 ± 1.1	2.0 ± 0.7*	7.0 ± 2.1	3.7 ± 1.4*	0.2 ± 0.2	0.2 ± 0.1
WASO (%)	3.4 ± 0.9	4.5 ± 0.4	3.2 ± 1.0	3.9 ± 0.8	3. 6 ± 1. 2	5.1 ± 1.3
MT (%)	1.0 ± 0.3	0.6 ± 0.2	0.9 ± 0.3	0.5 ± 0.2	0.9 ± 0.4	0.6 ± 0.2
Number of arousals	21.7 ± 3.9	30.7 ± 3.3*	8.9 ± 1.5	14.4 ± 1.7	12.9 ± 2.9	16.3 ± 3.0

Values are expressed as mean ± S.E. TIB: Time in bed; SPT: sleep period time; TST: total sleep time; SEI: sleep efficiency index; WASO: wake after sleep onset; MT: movement time; HZ: horizontal bed rest; HD; 6° head-down bed rest.
* $P < 0.05$.

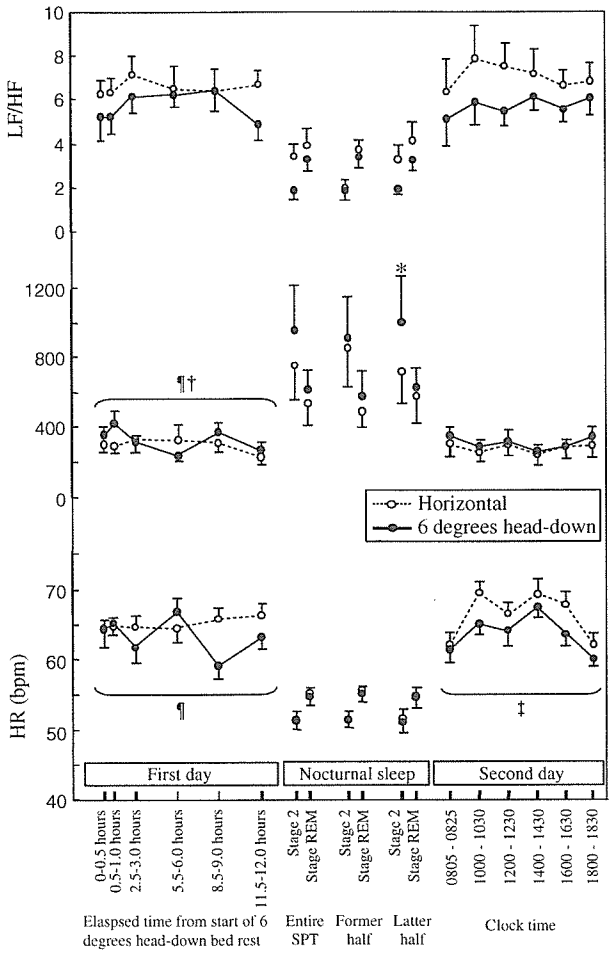

Fig. 2. Changes in HR, HF, and LF/HF during the initial 2 days under both bed rest conditions, including values during stage 2 and REM stage in former and latter halves of sleep period time. *: $P<0.05$ using Wilcoxon matched-pairs signed-ranks test; ¶: significant interaction of time × bed rest condition ($P<0.05$) using repeated measure ANOVA; †: significant effect of time ($P<0.01$) using repeated measure ANOVA; ‡: significant effect of time ($P<0.001$) using repeated measure ANOVA.

night showed no significant difference between HZ and HD, except for a slight but significant decrease in the percentage of stage 4 sleep and an increase in the number of arousals under HD. In each of the former half and latter halves of SPT, although there was no significant difference in the sleep parameters in the latter half, the percentage of stage 4 sleep in the former half was significantly lower under HD than that under HZ.

The values of HR, HF, and LF/HF throughout the initial 2 days of bed rest, including the data sampled during stage 2 sleep and the REM stage on the first night, are illustrated in Fig. 2. Under both bed rest conditions, the values of HF were apparently higher during nocturnal sleep, whereas the values of HR and LF/HF were apparently higher during daytime periods when subjects were awake. There was no significant effect of time and bed rest condition on HF and LF/HF during the daytime, except for HF on the first day, which revealed a significant effect of time ($F(1,5)=3.468$, $P<0.01$), and an interaction of time with bed rest condition ($F(1,5)=3.088$, $P<0.05$). On the first day, the values of HR under HD showed a larger fluctuation compared to those under HZ, and a significant interaction of time × bed rest condition ($F(1,5)=2.529$, $P<0.05$) was detected. On the second day, the values of HR under both bed rest conditions changed similarly through the daytime. These HR values showed lower values at 08:05 and 18:00, and a significant effect of time ($F(1,5)=11.498$, $P<0.001$) was detected.

During the entire SPT, although LF/HF did not show any statistical differences during both stage 2 sleep and the REM stage, HF during stage 2 sleep showed a tendency to increase under HD than under HZ ($P=0.063$). In the former half of SPT, HF and LF/HF during both stage 2 sleep and the REM stage showed no difference between the bed rest conditions. On the other hand, HF increased significantly ($P<0.05$) in the latter half of the SPT; LF/HF tended to decrease ($P=0.091$) during stage 2 sleep under HD as compared to under HZ. No difference in HF and LF/HF was observed during the REM stage in the latter half of the SPT. There was no difference in HR between the two conditions during both sleep stages during any period of the night.

The present study is the first report to examine HRV during both the daytime waking state and polysomnographically determined nocturnal sleep under microgravity. The primary findings of this study are that the difference in HRV between HZ and HD, as a sole effect of the acute cephalad fluid shift, was an increased HF during stage 2 NREM sleep under HD, but not during REM sleep and the daytime waking state. Previous studies have demonstrated that HF during the daytime waking state consistently decreased after long-term exposure to simulated or actual microgravity in cases of 14 and 15 days of 6° head-down bed rest [6,14,15] and 16 days of space flight [21]. In contrast, the results of acute responses in HRV within 2 days under 6° head-down bed rest have been reported to be inconsistent [14,15,17,25]. The present daytime findings were in agreement with the reports demonstrating unchanged HF under acute simulated microgravity [14,17]. As a larger fluctuation in HR observed on the first day under HD might reflect possible changes in cardiac autonomic activity induced by cephalad fluid shift, HRV under acute microgravity does not appear to be definitive.

As it has been shown that respiration has a major influence on HRV [16], Migeotte et al. [21] confirmed that the influence of respiration on HRV under actual microgravity was similar to that observed in a supine position on earth. In the present study, we made no attempt to artificially control the subjects' respiration when HRV was analyzed. However, Prisk et al. [26] reported that the respiration rate in wake subjects in the horizontal supine position and during 6° head-down bed rest was similar. Regarding the respiration rate during nocturnal sleep, although there has been no study to examine the effect of positional difference, it has been reported that the variations in respiration rate during nocturnal sleep are within a small range, which is unlikely to affect HRV [29]. Therefore, we could not assume any specific influence of respiration

on HRV values between HZ and HD during either daytime waking or nocturnal sleep.

Previous reports examining sleep architecture during actual space missions [8,23] or during 6° head-down bed rest [22] have demonstrated disturbed sleep characterized by poor subjective sleep quality, decreased total sleep time, and an increase in intermittent awakenings. As these studies examined nocturnal sleep several days after the onset of microgravity exposure, the present study is the first report to evaluate sleep architecture on the first night of 6° head-down bed rest. In contrast to previous reports, sleep architecture on the first night under HD was identified as being normal [5], despite a slight decrease in stage 4 sleep and an increase in the number of arousals. Since we carefully controlled the experimental environment (light/dark cycle, illumination, and food and water intake) and the subjects' behavior (no daytime nap under bed rest conditions and stable sleep/wake schedule during the experimental period), the present results suggest that 6° head-down bed rest itself has only a little effect on nocturnal sleep on the first night of bed rest.

The only comparable study evaluating HRV in each sleep stage was conducted on four astronauts aboard the Russian Mir space station [13]. In that study, although no significant effect of space flight on HRV was observed, an increase in HF during NREM sleep under microgravity was suggested by the statistical analysis, which incorporated their pre-flight resting HR as a covariate factor. The present study evaluated HRV during both the daytime waking state and nocturnal sleep under 6° head-down bed rest, and a significant increase in HF during stage 2 sleep was observed in the latter half of SPT, which was in line with the results described above [13]. The results suggest that changes in HRV under acute microgravity might be affected by the sleep/wake state. As can be seen in Fig. 2, which shows higher HR and LF/HF during daytime and higher HF during nocturnal sleep, cardiac autonomic nervous activity is sympathetic dominant during the daytime and vagal dominant during nocturnal sleep [11]. During these characteristic changes in cardiac autonomic nervous activity, the acute effects of the cephalad fluid shift might appear as increased HF during stage 2 sleep when the basal vagal tone is higher than that during daytime waking state and REM sleep [9,11,29]. Interestingly, a significant increase in HF under HD was observed only in the latter half of SPT. The reason for no significant increase in HF under HD in the former half of SPT was unclear. As acute responses in HRV under 6° head-down bed rest have been reported to be inconsistent in wake subjects [14,15,17,25], a possible interaction of elapsed time from the start of bed rest with the effect of the sleep/wake state might have induced the present results.

In spite of a significant increase in HF during stage 2 sleep under HD, HR showed no difference between HZ and HD. As HR is recognized as the net results of opposing sympathetic and vagal activities on the sinus node [12], these two autonomic activities during sleep were suggested to vary somewhat independently [4]. In fact, HR was reported to significantly correlate with LF/HF, but not with HF, during nocturnal sleep in healthy young subjects [4]. Therefore, although increased vagal activity during stage 2 sleep under HD could be suggested, the net results of sympathovagal balance, which are shown by HR and LF/HF, did not differ between HZ and HD.

In conclusion, nocturnal sleep architecture measured on the first night of bed rest was within the normal range in the 6° head-down position. In response to acute simulated microgravity exposure, the difference in HRV between HZ and HD was observed as an increase in HF during stage 2 sleep under HD, but not during REM sleep and the daytime waking state. These results suggest that the acute effect of microgravity on autonomic nervous activity might be influenced by its basal activity level modulated according to the sleep/wake state. In the case of actual space flight, other factors such as space motion sickness, excitement, and/or disturbed sleep may possibly act on the basal alteration of autonomic nervous activity induced by the cephalad fluid shift.

Acknowledgments

This study was carried out as a part of "Ground-based Research Announcement for Space Utilization" promoted by the Japan Space Forum. We greatly appreciate the valuable technical support and safety advice provided by Masamichi Sudo, Takuma Tozawa, Hiroyoshi Adachi, Nakamori Suganuma, Yasuhiro Sagami, and Yukio Ono.

References

[1] G.G. Berntson, J.T. Bigger Jr., D.L. Eckberg, P. Grossman, P.G. Kaufmann, M. Malik, H.N. Nagaraja, S.W. Porges, J.P. Saul, P.H. Stone, M.W. van der Molen, Heart rate variability: origins, methods, and interpretive caveats, Psychophysiology 34 (1997) 623–648.

[2] M.H. Bonnet, D.L. Arand, Heart rate variability in insomniacs and matched normal sleepers, Psychosom. Med. 60 (1998) 610–615.

[3] J.C. Buckey Jr., L.D. Lane, B.D. Levine, D.E. Watenpaugh, S.J. Wright, W.E. Moore, F.A. Gaffney, C.G. Blomqvist, Orthostatic intolerance after spaceflight, J. Appl. Physiol. 81 (1996) 7–18.

[4] H.J. Burgess, P.D. Penev, R. Schneider, E. VanCauter, Estimating cardiac autonomic activity during sleep: impedance cardiography, spectral analysis, and Poincare plots, Clin. Neurophysiol. 115 (2004) 19–28.

[5] M.A. Carskadon, W.C. Dement, Normal human sleep: an overview, in: M.H. Kryger, T. Roth, W.C. Dement (Eds.), Principles and Practice of Sleep Medicine,, Saunders Company, Philadelphia, 2000, pp. 15–25.

[6] G. Crandall, K.A. Engelke, J.A. Pawelczyk, P.B. Raven, V.A. Convertino, Power spectral and time based analysis of heart rate variability following 15 days head-down bed rest, Aviat Space Environ. Med. 65 (1994) 1105–1109.

[7] R.J. Cole, D.F. Kripke, W. Gruen, D.J. Mullaney, J.C. Gillin, Automatic sleep/wake identification from wrist activity, Sleep 15 (1992) 461–469.

[8] D.J. Dijk, D.F. Neri, J.K. Wyatt, J.M. Ronda, E. Riel, A. Ritz-De Cecco, R.J. Hughes, A.R. Elliott, G.K. Prisk, J.B. West, C.A. Czeisler, Sleep, performance, circadian rhythms, and light-dark cycles during two space shuttle flights, Am. J. Physiol. Regul. Integr. Comp. Physiol. 281 (2001) R1647–R1664.

[9] S. Elsenbruch, M.J. Harnish, W.C. Orr, Heart rate variability during waking and sleep in healthy males and females, Sleep 22 (1999) 1067–1071.
[10] A.C. Ertl, A. Diedrich, I. Biaggioni, B.D. Levine, R.M. Robertson, J.F. Cox, J.H. Zuckerman, J.A. Pawelczyk, C.A. Ray, J.C. Buckey Jr., L.D. Lane, R. Shiavi, F.A. Gaffney, F. Costa, C. Holt, C.G. Blomqvist, D.L. Eckberg, F.J. Baisch, D. Robertson, Human muscle sympathetic nerve activity and plasma noradrenaline kinetics in space, J. Physiol. 538 (2002) 321–329.
[11] R. Furlan, S. Guzzetti, W. Crivellaro, S. Dassi, M. Tinelli, G. Baselli, S. Cerutti, F. Lombardi, M. Pagani, A. Malliani, Continuous 24-hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects, Circulation 81 (1990) 537–547.
[12] J.J. Goldberger, Sympathovagal balance: how should we measure it? Am. J. Physiol. 276 (1999) H1273–H1280.
[13] A. Gundel, J. Drescher, Y.A. Spatenko, V.V. Polyakov, Heart period and heart period variability during sleep on the MIR space station, J. Sleep Res. 8 (1999) 37–43.
[14] K. Hirayanagi, S. Iwase, A. Kamiya, T. Sasaki, T. Mano, K. Yajima, Functional changes in autonomic nervous system and baroreceptor reflex induced by 14 days of 6 degrees head-down bed rest, Eur. J. Appl. Physiol. 92 (2004) 160–167.
[15] K. Hirayanagi, A. Kamiya, S. Iwase, T. Mano, T. Sasaki, M. Oinuma, K. Yajima, Autonomic cardiovascular changes during and after 14 days of head-down bed rest, Auton. Neurosci. 110 (2004) 121–128.
[16] J.A. Hirsch, B. Bishop, Respiratory sinus arrhythmia in humans: how breathing pattern modulate heart rate, Am. J. Physiol. 241 (1981) H620–H629.
[17] R.L. Hughson, A. Maillet, G. Gauquelin, P. Arbeille, Y. Yamamoto, C. Gharib, Investigation of hormonal effects during 10-h head-down tilt on heart rate and blood pressure variability, J. Appl. Physiol. 78 (1995) 583–596.
[18] A. Kamiya, S. Iwase, D. Michikami, Q. Fu, T. Mano, K. Kitaichi, K. Takagi, Increased vasomotor sympathetic nerve activity and decreased plasma nitric oxide release after head-down bed rest in humans: disappearance of correlation between vasoconstrictor and vasodilator, Neurosci. Lett. 281 (2000) 21–24.
[19] T. Mano, Muscle sympathetic nerve activity in blood pressure control against gravitational stress, J. Cardiovasc. Pharmacol. 38 (Suppl. 1) (2001) S7–S11.
[20] T. Mano, S. Iwase, A. Kamiya, Sympathetic nerve responses in humans to short and long term simulation of microgravity, J. Gravit. Physiol. 5 (1998) 93–96.
[21] P.F. Migeotte, G.K. Prisk, M. Paiva, Microgravity alters respiratory sinus arrhythmia and short-term heart rate variability in humans, Am. J. Physiol. Heart Circ. Physiol. 284 (2003) H1995–H2006.
[22] T.H. Monk, D.J. Buysse, B.D. Billy, K.S. Kennedy, D.J. Kupfer, The effects on human sleep and circadian rhythms of 17 days continuous bedrest in the absence of daylight, Sleep 20 (1997) 858–864.
[23] T.H. Monk, D.J. Buysse, B.D. Billy, K.S. Kennedy, L.M. Willrich, Sleep and circadian rhythms in four orbiting astronauts, J. Biol. Rhythms 13 (1998) 188–201.
[24] M. Pagani, F. Lombardi, S. Guzzetti, O. Rimoldi, R. Furlan, P. Pizzinelli, G. Sandrone, G. Malfatto, S. Dell'Orto, E. Piccaluga, Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog, Circ. Res. 59 (1986) 178–193.
[25] A.R. Patwardhan, J.M. Evans, M. Berk, K.J. Grande, J.B. Charles, C.F. Knapp, Spectral indices of cardiovascular adaptations to short-term simulated microgravity exposure, Integr. Physiol. Behav. Sci. 30 (1995) 201–214.
[26] G.K. Prisk, J.M. Fine, A.R. Elliott, J.B. West, Effect of 6 degrees head-down tilt on cardiopulmonary function: comparison with microgravity, Aviat. Space Environ. Med. 73 (2002) 8–16.
[27] A. Rechtchaffen, A. Kales (Eds.), A manual of standardized terminology, techniques, and scoring system for sleep stages for human subjects, National Institute of Health (Publication No. 204), U.S. Government Printing Office, Washington, DC, 1968.
[28] Y. Sawada, N. Ohtomo, Y. Tanaka, G. Tanaka, K. Yamakoshi, S. Terachi, K. Shimamoto, M. Nakagawa, S. Satoh, S. Kuroda, O. Iimura, New technique for time series analysis combining the maximum entropy method and non-linear least squares method: its value in heart rate variability analysis, Med. Biol. Eng. Comput. 35 (1997) 318–322.
[29] J. Trinder, J. Kleiman, M. Carrington, S. Smith, S. Breen, N. Tan, Y. Kim, Autonomic activity during human sleep as a function of time and sleep stage, J. Sleep Res. 10 (2001) 253–264.
[30] E. Vanoli, P.B. Adamson, Ba-Lin, G.D. Pinna, R. Lazzara, W.C. Orr, Heart rate variability during specific sleep stages. A comparison of healthy subjects with patients after myocardial infarction, Circulation 91 (1995) 1918–1922.
[31] V.K. Yeragani, E. Sobolewski, G. Igel, C. Johnson, V.C. Jampala, J. Kay, N. Hillman, S. Yeragani, S. Vempati, Decreased heart-period variability in patients with panic disorder: a study of Holter ECG records, Psychiatr. Res. 20 (1998) 89–99.

Question
快適睡眠の工夫は？

快適睡眠の工夫について教えてください．

Answer

白川修一郎
（国立精神・神経センター精神保健研究所 老人精神保健研究室）

睡眠は複雑系の生命現象です．また，日常的な現象であり，生理的・心理的な影響を受けやすく，生活習慣によって大きく左右される側面をもつ現象です．快適睡眠確保のための基本的な工夫は，生活スタイルと睡眠環境の改善です．現在のところ理想的な睡眠薬は開発されておらず，薬剤により快適な睡眠が確保できるものではありません．睡眠は一生を通じての生命現象であり，睡眠健康の障害は心身の健康全般，脳機能，循環器系・免疫系機能，消化・代謝系機能，運動系機能の健全な働きを障害することもよく知られています．特に，人間の睡眠は，極度に発達した前頭葉機能を維持するために進化してきた特性をもっています．

快適な睡眠確保のための生活スタイルと睡眠環境の改善技術は，4分野に大別できます．不適切な要因が認められればその改善をはかります．分野別に，これまでの睡眠科学が明らかにした改善方策をそれぞれ列挙します．なお，生活スタイルの改善は習慣化が重要であり，中・長期的な視点で計画的に行うことが望ましいのです．

A）サーカディアンリズムの規則性の確保

サーカディアンリズムの規則性の改善は，快適睡眠確保のための第1にあげられる重要事項です．睡眠がサーカディアンリズムに強く影響されるという科学的事実は，多くの研究により明らかとなっています．

サーカディアンリズム

(1) 規則的な睡眠スケジュールと規則正しい食生活を守る．
(2) 軽度の有酸素運動を一定時間に行う．
(3) 朝，起床後2時間以内に太陽の光を30分以上あびる．

B）日中や就床前の良好な覚醒状態の確保

睡眠は覚醒と常に相互補完的な関係にあり，良質な覚醒は快適な睡眠を確保するための必要事項です．望ましい就床時刻に近い時点でのうたた寝や居眠りの混入は，主睡眠の入眠を妨害し，維持・安定性を障害します．また，日中の光環境が不十分な場合には，夜間メラトニン分泌が少なく，睡眠の維持を障害

「肥満と糖尿病」Vol. 4 No. 3 2005−521

その他

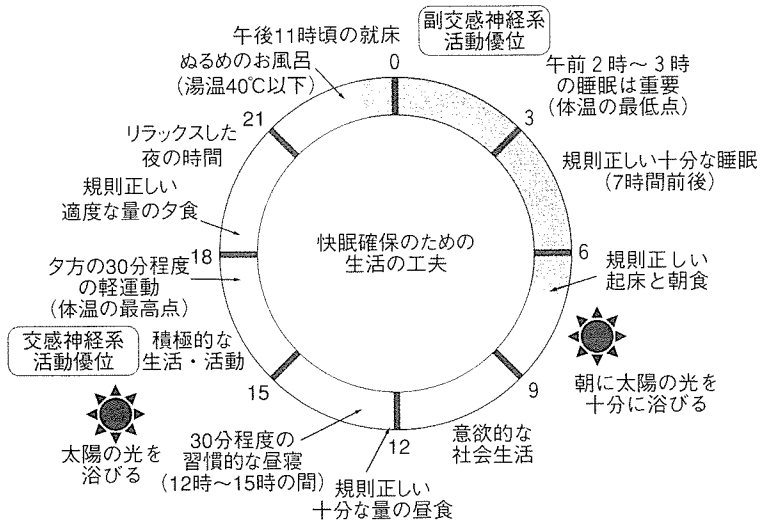

図　快眠確保のための生活上の工夫

しやすいことも判明しています.

(1)　日中はできるだけ意欲的な生活をこころがける.

(2)　高齢者では，習慣的入眠時刻から 15 時間前後に 30 分程度の短時間の昼寝をとる.

(3)　夕方に，30 分程度の軽運動を行う習慣をもつ.

(4)　夕食後は，居眠りをしたり仮眠をとることは避ける.

(5)　日中に 1 時間以上，外光をあびる.

C) 良好な睡眠環境の整備

良好な睡眠環境の選定基準の詳細については他誌を参照されたいが，原則は下記の 2 点に集約されます.

(1)　自分にあった寝具を選ぶ.

(2)　静かで暗く適度な室温，湿度の寝室環境を維持する.

D) 就床前のリラックスと睡眠への脳の準備

脳が興奮した状態，交感神経系活動が亢進した状態，深部体温の低下が不十分な状態では，円滑な入眠が阻害されやすいことが知られています.

(1)　就寝間近のお茶や多量のアルコールなどの摂取や喫煙を避ける.

(2)　就寝間近の激しい運動や心身を興奮させるものは避ける.