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ALTERATIONS IN COGNITIVE FUNCTION DURING THE MENOPAUSAL TRANSITION

To the Editor: The physiological and psychological changes associated with menopause have remained a major psychosocial stressor for women throughout the ages, but many of the neuropsychological changes have not been well characterized.

The present study evaluates cognitive function in a large group of women aged 40 to 54 who were enrolled in the Kinmen Women-Health Investigation (KIWI).[1] Kinmen is a 176-km^2 island located 154 miles (248 km) west of Taiwan and 25 miles (41 km) east of mainland China. It consists of four townships with a total population of 51,060 (1998). The people in Kinmen are Han Chinese, and most are involved in farming activities. The details of the KIWI have been described elsewhere.[1]

Of the 1,270 subjects in the final analysis, 77 (6%) were current or past hormone replacement therapy (HRT) users. The 1,173 women who never used HRT had a significantly lower education level than HRT users (P = .004). The distribution of menopausal status of women who never used HRT was premenopausal, 694 (58%); perimenopausal, 323 (27%); and postmenopausal, 176 (15%). The premenopausal period was defined as regular menstruation. A woman was considered perimenopausal if her menstrual cycles had been irregular or her last menstrual bleeding occurred more than 3 and 12 or fewer months before the study. Women who had not menstruated within the previous 12 months were categorized as postmenopausal. Women with surgically induced menopause were excluded from this study.

Each subject received a 45-minute battery of neuropsychological tests consisting of: the Wechsler Adult Intelligence Scale-Revised (WAIS-R),[2] Digit Span Subtest (forward and backward), the continuous recognition paradigm of Kimura (CRP),[3] the Trail Making Test (TMT) parts A and B,[4] verbal fluency,[5] and the Rey Auditory-Verbal Learning Test (RAVLT).[6] The menopause-related symptom checklist modified from the Kupperman index[7] and the Hospital Anxiety and Depression Scale (HADS)[8,9] were also administered to each subject.

Table 1 lists the results of the neuropsychological tests by menopausal status group for the non-HRT users. Univariately, all cognitive functions except the CRP significantly declined with the progression of menopausal status ($P < .0001$, except for verbal fluency $P = .008$). Pairwise comparisons further suggested that most of the differences derived from a comparison between the postmenopausal group and the other two groups.

The univariate analysis also indicated that age and education were two important factors that were significantly associated with cognitive function. However, the HADS scores did not demonstrate an association with any of the cognition tests.

Similar results were obtained in the multivariate analysis. With menopausal status, age, education, and HADS score in the model, education and age were significantly related to most cognitive functions. Education was a sig-

Table 1. Results of Neuropsychological Testing for Pre-, Peri-, and Postmenopausal Women

Neuropsychological Test	Premenopause (n = 694)	Perimenopause (n = 323)	Postmenopause (n = 176)	Total (n = 1,193)
Forward Digit Span†‖#	9.95 ± 2.59	9.66 ± 2.71	8.47 ± 2.58	9.65 ± 2.67**
Backward Digit Span†‖#	3.88 ± 2.35	3.53 ± 2.14	2.69 ± 1.92	3.61 ± 2.27**
Continuous Recognition Paradigm of Kimura†	69.94 ± 6.40	69.2 ± 6.20	69.01 ± 5.95	69.60 ± 6.29
Trail Making Test A‡‖#	65.14 ± 34.87	75.25 ± 43.51	95.51 ± 50.18	72.31 ± 41.19**
Trail Making Test B‡‖#¶	105.64 ± 50.40	109.82 ± 43.96	132.61 ± 52.94	110.27 ± 49.90**
Verbal fluency†‖	14.92 ± 4.12	14.54 ± 3.98	13.88 ± 3.85	14.66 ± 4.06*
Rey Auditory Verbal Learning Test†‖#	10.74 ± 2.57	10.46 ± 2.78	9.73 ± 2.77	10.51 ± 2.68**

Note: Statistical analysis by generalized linear model with appropriate distributions; $P \leq .01$ was considered to be statistically significant.
†Poisson regression.
‡Gamma distribution means were used for pairwise comparison.
Significant results are designated as follows: ‖pre- versus postmenopause, #peri- versus postmenopause, ¶pre- versus perimenopause, $**P < .001$, $*P < .01$.

nificant covariate for all cognition tests ($P < .0001$) except for the CRP ($P = .12$). The higher the education level, the better the cognitive function. Age was a significant covariate for the backward digit span ($P < .001$), CRP ($P = .004$), and TMT part B ($P < .0001$). Cognitive function declined significantly with age.

Of all neuropsychological tests, education was the only factor that influenced the forward digit span, TMT part A, verbal fluency, and RAVLT, based on the results of the linear model. The backward digit span and TMT part B results were associated with age and education. After adjusting for age and education, menopausal status had no effect on cognitive function except for the TMT part A. No significance was found for the effect of the HADS score on any cognitive function.

Multivariate analysis of HRT effects in perimenopausal and postmenopausal women showed that, after adjusting for menopausal status, age, education, presence of menopausal symptoms, HADS score, and HRT usage (never used, used <6 months, used ≥6 months), HRT only affected backward digit span ($P = .001$). Those using HRT for at least 6 months had the highest backward digit span score, followed by those using HRT for less than 6 months and then by the nonusers. The overall significant difference was attributed to the pairwise difference between nonusers and those who used HRT for less than 6 months; the adjusted relative risk was 1.38 (1.15–1.67).

In this community sample population, we found that most of the cognitive functions had significantly decreased from the pre- to the postmenopausal stage. The difference disappeared after adjusting for age and education, except for the TMT part A. We also demonstrated that HRT might help in the performance of the backward digit span of the WAIS-R.

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PERIVENTRICULAR WHITE MATTER LESIONS AND SLEEP ALTERATION IN OLDER PEOPLE

To the Editor: Sleep disorder, difficulty falling asleep (DFA) or early morning awakening (EMA) and not being able to fall asleep again, is common in older people. Older people without neurological deficits often have silent brain infarction (SBI) or white matter lesions (WMLs) identified using brain magnetic resonance imaging (MRI).[1,2] Case studies have suggested that there are sleep alterations in patients with brain infarction,[3] but little evidence exists that specific brain lesions cause sleep disorder. We therefore investigated the relationship between sleep disorder and brain MRI findings such as SBI and WMLs in older people.

Participants were 168 community-dwelling retired older people who were residents in the rural community of Onagawa, Miyagi, Japan. All participants were healthy volunteers and living independently at home without apparent history of stroke, malignancy, chronic renal failure, ischemic heart disease, or chronic obstructive pulmonary disease. Older people with depression and dementia were excluded from this study. Exclusion criteria were a score greater than 4 on the Geriatric Depression Scale or less than 24 on the Mini-Mental State Examination. Each participant gave written informed consent. All participants were asked whether they usually had a sleep disorder of DFA or EMA and were asked their usual total hours of sleep during the night, the usual time they went to bed, and the usual time they woke up. Awakening before 5:00 a.m., whether the participants complained of insomnia or not, was defined as AB-5. If a participant complained of both DFA and EMA, the one that caused the predominant disturbance was recorded. All participants underwent brain MRI examination. Brain infarcts were defined as lesions with abnormal signal in a vascular distribution and no mass effects. It was also defined as low intensity in the T1 images, high intensity in the T2 images, and internal low intensity and peripheral high intensity in the fluid-attenuated inversion recovery (FLAIR) images with a size greater than 3 mm. WMLs were specified as high signal-intensity area on both FLAIR and T2 images but isointense with normal brain parenchyma on T1 images. When the largest diameter of the WMLs was adjacent to the ventricle, they were defined as periventricular WMLs, otherwise as subcortical WMLs. The severity of WMLs was graded according to the criteria of Fazekas et al.[4] Periventricular WMLs were rated semiquantitatively as 0 (none), 1 (pencil-thin lining), or 2 (smooth halo) for three