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Leukocyte mitochondrial DNA (mtDNA) content is associated with depression in old women

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ABSTRACT

The purpose of this study was to investigate whether mitochondrial DNA (mtDNA) content of peripheral blood leukocyte is related to depression in community-dwelling old women. A total of 142 community-dwelling women, older than 60 years, were included in the study. The mtDNA copy number, which represents the mtDNA content, was measured using real-time PCR methods. Patients with depression defined as the subjects whose 15-question geriatric depression scale (GDS) score was ≥8 or who were taking anti-depressant medication. We also measured cognitive function, physical performances (gait speed, chair-stand times, tandem standing times) and metabolic parameters. The depression group had a significantly lower mtDNA copy number than the control group (71.5 vs. 107.3; interquartile range (IQR) = 42.7–116.0 vs. 51.7–202.1; $p = 0.028$). The Korean version of the mini mental state examination (K-MMSE) score and physical performance score were significantly lower in the depression group than in the control group ($p = 0.041$, and $p = 0.002$, respectively). After adjustment for confounding factors using multiple logistic regression analysis, mtDNA copy number was significantly related to depression ($p = 0.025$). We demonstrated that low leukocyte mtDNA content is related to depression in community dwelling old women. This finding suggests that mitochondrial dysfunction could be a mechanism of geriatric depression.

1. Introduction

Depression and suicide currently are serious social issues. Lifetime prevalence of depression is known to reach 10% around the world, and the rate of persons who has experienced mood episode once or more regardless of diagnosis of major depression is reported to be 48% (Cassem, 1995). The WHO reported that depression ranked fourth among diseases provoking social and physical disability in 2001. According to 2007 Korea Health and Nutrition Examination Survey, 12.7% of adults had experienced depressive symptoms for over two weeks and the percentage increased with age to over 20% in those over 60 years old (Korea Center for Disease Control and Prevention, 2008).

Depression is hard to define with a single concept and the progress and response to treatment of depression varies widely. Although genetic factors, monoamine deficiency, stress and hypothalamus–pituitary–adrenal axis dysfunction have been reported as the cause of depression (Belmaker and Agam, 2008), its exact pathophysiologic mechanism has not yet been determined.

Mitochondria are intracellular organelles producing adenosine triphosphate (ATP) through oxidative phosphorylation under aerobic condition. Mitochondria also play a key role in biological activities of cells such as apoptosis and calcium ion control (Chan, 2006).

Several studies on the relationship between mitochondrial function and diseases have shown that mitochondrial dysfunction are related with aging and major diseases like type 2 diabetes, neurodegenerative disease, cardiovascular disease and cancer as well as genetic diseases with congenital abnormality of mtDNA (Johannsen and Ravussin, 2009).

The mtDNA content, which is measured by copy number, has been known as an index reflecting stability of mitochondrial genes and mitochondrial biogenesis (Clay Montier et al., 2009). In addition, a recent study reported that maintenance of mtDNA content is essential for mitochondrial function and cell growth (Jeng et al., 2008). The mtDNA-depletion was reported as a quantitative disorder of mtDNA, characterized by decreased muscle strength, hypotonia and developmental delay due to a congenital deficiency of mtDNA (Macmillan and Shoubridge, 1996). In addition, it has been reported in several clinical studies that the decrease of mtDNA content is related with type 2 diabetes (Lee et al., 1998), microalbuminuria (Lee et al., 2009), breast cancer

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(Fan et al., 2009), colon cancer (Lin et al., 2008), and renal cell carcinoma (Xing et al., 2008).

Synthesis, secretion and reabsorption of neurotransmitters such as serotonin and norepinephrine, which are closely related to depression, require an efficient supply of ATP (Brodin et al., 1999). Therefore, an association between mitochondrial function and depression can be supposed. In an animal model of depression induced by chronic artificial stress, it was reported that depression was related to the decrease of enzymes associated with mitochondrial electron transport system (Rezin et al., 2008), but there have been a few studies about the relationship between depression and mitochondrial function in humans. This study aimed to investigate the relationship between leukocyte mtDNA content and depression in old women.

2. Subjects and methods

2.1. Study subjects

This study conducted as a part of the Yonsei Aging Study (YAS) (Lee et al., 2010). YAS was designed as a survey to investigate the factors related to depression, cognitive function and physical performance in community dwelling old people in Korea. Among 200 YAS participants, this study included 142 old women, aged ≥60 years, who were recruited through public health centers located in the Yangpyung and Ilsan districts of South Korea in 2008. The subjects with dementia, stroke, serious cognitive dysfunction (MMSE score ≤ 10), and those who drank over 30 g of alcohol daily were excluded. This study was approved by the Institutional Review Board of Severance Hospital.

2.2. Assessment of clinical parameters

Subjects were questioned on lifestyle parameters, including cigarette smoking, alcohol consumption, physical activity and current medication. The subjects who drank alcohol once or more per week were classified as alcohol-drinking group and those taking analgesics regularly were the chronic pain group. The hypertension group was defined as subjects with high blood pressure (≥140/90 mm Hg) or taking antihypertensive medication. Heart disease included ischemic heart disease, heart failure and arrhythmia.

Fasting blood glucose, total cholesterol, triglyceride, high density lipoprotein (HDL)-cholesterol, cortisol and dehydroepiandrosterone-sulfate (DHEA-S) were measured by using an ADVIA 1650 chemistry system (Siemens Medical Solution, Tarrytown, NY). The diabetes group was defined as those with a history of diabetes or fasting blood sugar ≥ 126 mg/dl. The dyslipidemia group was defined as those taking lipid lowering agents or those with a total cholesterol > 240 mg/dl, triglyceride > 200 mg/dl or HDL-cholesterol < 40 mg/dl.

2.3. Depression and cognitive function assessment

Depression was assessed with the short-form GDS consisting of 15 questions. The 30 question GDS was invented by Yesavage et al. (1982–1983). As the 30 question GDS took much time to assess the elderly, a shortened GDS with 15 questions was introduced. It was reported to closely correlate with the 30 question GDS (Alden et al., 1989), and have a similar sensitivity and specificity for screening for depression (Lesher and Berryhill, 1994). According to results of a study on validity of Korean version of the shortened GDS, we used points 8 as a cut-off value (Cho et al., 1999). The depression questionnaire was carried out by two experienced medical staff who were fully educated on the GDS. Cognitive function was evaluated with K-MMSE.

2.4. Evaluation of physical performance

To evaluate gait speed, the time it took to walk 6 m at a usual pace was measured, and to assess muscle strength of lower limbs, the chair-stand test was performed. Balance was evaluated by tandem standing test. The subjects were divided into four groups according to performance level of each item and they scored from 1 (worst performance) to 4 (best performance). The sum of the three components was used as the final physical performance score.

2.5. Measurement of leukocyte mtDNA content

DNA from peripheral leukocyte was extracted from 1 ml of whole blood with the QIAamp Tissue Kit 250 (Qiagen Inc., Valencia, CA). The relative mtDNA copy number was measured by real-time polymerase chain reaction (QPCR) through simultaneous measurement of a nuclear gene (β-globin) and a mitochondrial gene (ND1) (Wong and Cortopassi, 2002). This process was carried out by using the Light Cycler-Fast Start DNA Master SYBR Green I kit, supplied by Roche Molecular Biochemicals (Pleasanton, CA). Forward and reverse primers of β-globin were: 5′-GAAGAGC-CAAGGACAGGTAC-3′ and 5′-CAACTTCATCCACGTTCACC-3′, respectively and forward and reverse primers of mitochondrial ND1 gene were: 5′-AACATACCCATGGCCAACCT-3′ and 5′-AGCGAAGGGTTG-TAGTAGCCC-3′, respectively. After denaturation at 95 °C for 300 s, DNA samples were treated at 95 °C for 0.1 s, at 58 °C for 6 s and at 72 °C for 18 s and this process was repeated 40 times. The number of PCR cycle reaching 20 ng of DNA content was defined as the threshold cycle number (Ct), and mtDNA copy number was calculated with the following equation: relative copy number = $2^{\Delta Ct}$ ($\Delta Ct = Ct_{\beta\text{-globin}} - Ct_{ND1}$).

2.6. Statistical analysis

Subjects with GDS score ≥ 8 or on anti-depression medication were classified as the depression group and the others were the control group. Clinical characteristics of the two groups were compared with *t*-test or Wilcoxon rank sum test for continuous variables and χ^2–test or Fisher exact test for categorical variables. To determine an independent relationship between leukocyte mtDNA content and depression, multiple logistic regression analysis was performed. All statistical analysis was conducted with SAS 9.1 statistics package (SAS Institute Inc., Cary, NC, USA).

3. Results

The mean age of the subjects was 74.7 ± 5.88 years. The median of leukocyte mtDNA copy number was 92.4 (IQR = 44.3–188.1), and 39.4% of the total subjects were included in the depression group. Around 14% of the subjects took analgesics due to chronic pain (Table 1).

Leukocyte mtDNA copy number of the depression group was significantly lower than that of the control group (71.5 vs. 107.3, IQR = 42.7–116.0 vs. 51.7–202.1, $p = 0.028$). In addition, the depression group had a higher waist circumference (WC) compared to the control group (90.6 ± 8.39 vs. 86.8 ± 8.18, $p = 0.008$). The K-MMSE score of the depression group was lower than that of the control group and the physical performance of the depression group was also significantly poorer than the control group ($p = 0.041$ and $p = 0.002$, respectively). The depression group showed higher serum cortisol level (9.5 ± 3.45 vs. 8.9 ± 3.22), lower DHEA-S level (31.2 vs. 41.0, IQR = 21.6–55.3 vs. 20.7–65.4) and higher prevalence of diabetes and chronic pain, but there was no statistical significance (Table 2).

As leukocyte mtDNA copy number did not show a normal distribution, the log transformed mtDNA copy number