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Association of insulin-like growth factor-1 with mild cognitive impairment and slow gait speed

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ABSTRACT

The decrease in serum insulin-like growth factor-1 (IGF-I) with aging is related to the neurobiological processes in Alzheimer's disease. IGF-1 mediates effects of physical exercise on the brain, and cognition has a common pathophysiology with physical function, particularly with gait. The aim of this study was to examine whether mild cognitive impairment (MCI) and slow gait are associated with the serum IGF-1 level. A population survey was conducted in 3355 participants (mean age, 71.4 years). Cognitive functions (attention, executive function, processing speed, visuospatial skill, and memory), gait speed, and demographic variables were measured. All cognitive functions and gait speed were associated with the IGF-1 level ($p < 0.001$). The association of IGF-1 with slow gait was weakened by adjustment for covariates, but MCI and the combination of MCI and slow gait were independently related to the IGF-1 level in multivariate analysis ($p < 0.05$). Our findings support the association of a low IGF-1 level with reduced cognitive function and gait speed, particularly with a combination of MCI and slow gait.

1. Introduction

Insulin-like growth factor-1 (IGF-1) is an important mediator of growth hormone effects in body growth and tissue remodeling (Nishijima et al., 2010) and contributes to the promotion of neuronal plasticity and skeletal muscle (Clegg et al., 2013; Florini et al., 1991; van Dam et al., 2000). IGF-1 also has protective effects on the neurobiological processes that are compromised by aging and Alzheimer's disease (AD), including those with potent neurotrophic and neuroprotective actions (Baker et al., 2012; de la Monte and Wands, 2005; Deak and Sonntag, 2012; Sonntag et al., 2005). A decrease in IGF-1 may be related to the pathology of AD because IGF-1 increases clearance of amyloid beta (Aβ) in the brain and upregulates Aβ carriers and transport of Aβ-carrier protein complexes (Carro et al., 2002, 2006). In humans, low levels of serum IGF-1 are a risk for AD and dementia (Watanabe et al., 2005; Westwood et al., 2014).

Mild cognitive impairment (MCI) is a prodromal status in the course of AD. Subjects with MCI have characteristics between healthy subjects and AD, including pathology, biomarkers, brain function, and cognitive function (Petersen, 2004, 2011). The common features of MCI, particularly in cases showing progression to AD, are higher levels of Aβ42 and tau, brain atrophy, and reduced cognitive function (Petersen, 2011). Subcutaneous injections of growth hormone–releasing hormone enhances the IGF-1 level and improves cognitive function in MCI subjects (Baker et al., 2012), but it is unclear whether lower levels of serum IGF-1 are a characteristic of MCI.

Cognitive impairment has a strong link with physical frailty, especially with slow gait linked with worsening of cognitive function. Slow gait has been associated with the cognitive decline (Mielke et al., 2013) and with accumulation of brain pathology related to AD at autopsy (Buchman et al., 2013), whereas longitudinal studies indicate that slow gait precedes MCI and dementia (Buracchio et al., 2010; Solfrizzi et al., 2013). Importantly, a combined status of slow gait and cognitive impairment increases the risk for dementia compared with each status alone (Waite et al., 2005). The mechanism of the association between physical and cognitive impairment was not examined, but IGF-1 may mediate this association.

The mechanism underlying the benefit of exercise on cognition is also thought to involve IGF-1 (Liu-Ambrose et al., 2012). Exercise-dependent stimulation of angiogenesis and neurogenesis seems to

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be regulated by IGF-1 (Cotman et al., 2007), whereas a peripheral increase in IGF-1 appears to be required for exercise-induced neurogenesis in the brain (Trejo et al., 2001). IGF-I is also an important modulator of muscle mass and function (Barbieri et al., 2003). Low IGF-I levels may also be associated with physical frailty represented by muscle weakness and slow gait speed (Cappola et al., 2001; Onder et al., 2006). Therefore, an improved understanding of the association of IGF-1 with physical and cognitive functioning may contribute to the clarification of mechanisms associated with aging.

The aim of this study was to examine the association between serum IGF-1 and MCI and to determine whether slow gait affects this association. We hypothesized that lower levels of serum IGF-1 are associated with reduced cognitive function and gait speed and that a combined status of MCI + slow gait speed would be sensitively associated with a lower IGF-1 level. Assessments of cognitive function require the use of a variety of cognitive domains (Albert et al., 2011) because there is some debate over which cognitive functions are related to IGF-1 levels (Dik et al., 2003; Sanders et al., 2014). In contrast, confirmed covariates in older adults, such as age and body mass index (BMI), are known to weaken the association between mobility and IGF-1 (Cappola et al., 2001; Kaplan et al., 2008; Sanders et al., 2014). Thus, we conducted a population survey in a large cohort with adjustment for covariates in multivariate analysis.

2. Material and methods

2.1. Participants

Subjects eligible for this study were participants in the population-based cohort of the Obu Study of Health Promotion for the Elderly (OSHPE), which was conducted from August 2011 to February 2012. Inclusion criteria for the OSHPE required each participant to be 65 years or older at the time of examination and to reside in Obu city; a total of 15,974 individuals were eligible for participation. Before recruitment, 1661 people were excluded because they had participated in other similar studies, were hospitalized or in residential care, or were certified at levels 3–5 to require support or care by the Japanese public long-term care insurance system. Recruitment was conducted via a letter sent to 14,313 individuals, and 5104 of these individuals participated in the OSHPE. In the present study, we included participants who were independent for basic activities of daily living, as confirmed by interview, and not certified by long-term care insurance, and were cognitively normal (no objective cognitive impairment and Mini-Mental State Examination [MMSE] score >23, Folstein et al., 1975) or met the criteria for MCI. MCI criteria followed those established and revised by Petersen (2004); in particular, subjects satisfied the following conditions: subjective memory complaints, objective cognitive impairment, no dementia, and independent in activity of daily living. No dementia was defined as not meeting clinical criteria for dementia, and intact global cognitive function was defined as an MMSE score >23 (Folstein et al., 1975). Cognitive function was also assessed in multiple domains using the National Center for Geriatrics and Gerontology Functional Assessment Tool (Makizako et al., 2013), and objective cognitive impairment was defined as having a cognitive function of >1.5 standard deviation lower than the normal data (Shimada et al., 2013a). Subjects were classified into subtypes of amnestic MCI (aMCI) and nonamnestic MCI (naMCI). Those with objective cognitive impairment in memory were defined as aMCI and others were defined as naMCI, based on the published criteria (Petersen, 2004). Participants were excluded based on a history of cerebrovascular disease, Parkinson disease, depression or dementia, or an MMSE score of ≤23 (Folstein et al., 1975). Finally, 3355 participants were judged to be eligible for the study and completed all assessments, including blood tests. The Ethics Committee of the National Center for Geriatrics and Gerontology approved this study.

2.2. Gait speed

Gait speed was measured as an indicator of motor function. Participants were asked to walk on a straight walkway of 6.6 m in length on a flat floor under their usual gait speed. Gait duration was measured using a stopwatch over a 2.4-m distance between marks at 2.1 and 4.5 m from the start of the walkway, and the mean gait speed (minute per second) was calculated. The measurement protocol of using a stopwatch has been validated elsewhere (Peters et al., 2013). The cutoff value (1.0 m/s) for a slow gait speed was based on the threshold value for discrimination of functional decline found in a previous study (Shimada et al., 2013b).

2.3. Cognitive function

Cognitive function was assessed using the National Center for Geriatrics and Gerontology Functional Assessment Tool (Makizako et al., 2013). The test consists of tasks to assess memory, processing speed, attention and executive function, and visuospatial cognition (Figure Selection Task). Memory was assessed using word and story tests. Both tests have 2 sessions (an immediate session and a delayed session). Processing speed was assessed using a tablet version of the Symbol-Digit Substitution Task (Makizako et al., 2013), based on the Symbol-Digit Modality Test (Shum et al., 1990). The score is the number of correct answers chosen within 90 seconds. Attention and executive functions were evaluated using a tablet version of the Trail-Making Test Part A (TMT-A) and Part B (TMT-B, 15 stimuli) (Makizako et al., 2013). The amount of time taken to complete each task was recorded. In the Figure Selection Task, participants were required to select the same figure from 3 choices shown at the bottom of the display (Makizako et al., 2013). This task consists of 9 questions and 1 point is given for each correctly selected figure, with the score being the number of correct answers (0–9). Better performance is represented by lower values on the TMT-A and TMT-B and higher values on the other tests.

2.4. IGF-1

To obtain serum, whole blood samples were allowed to coagulate at room temperature for 30 minutes and then centrifuged at room temperature for 15 minutes at 1000 × *g*. The collected serum was stored in polypropylene tubes at −80 °C until assayed. IGF-1 was quantitatively determined using an IGF-1 Immunoradiometric assay "Daiichi" (TFB Inc, Tokyo, Japan). Measurements were performed in duplicate and averaged to give a value in nanograms per milliliter. The assay was performed by SRL Inc (Tokyo, Japan).

2.5. Demographic and lifestyle data

Demographic data were collected for age, sex, BMI (weight/height^2), educational history, and medication use in a face-to-face interview. Information on lifestyle was also obtained, and sleep quality was assessed using the question "How would you rate your sleepiness in daytime?" on a 4-point scale ranging from "never," "very little," and "sometimes" to "almost always". Subjects who answered never or very little were judged to have good quality of sleep. Depressive symptoms were evaluated using the 15-item Geriatric Depression Scale (Yesavage, 1988). The total amount of time spent walking in a day was used to assess physical activity using a subscale of the International Physical Activity Questionnaire (Murase et al., 2003).