Association between serum ferritin concentrations and depressive symptoms in Japanese municipal employees

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ABSTRACT

It remains unclear whether levels of body iron store are related to milder forms of depression, which are more common among apparently healthy people. We examined the association between serum ferritin concentrations and depressive symptoms among 312 men and 216 women working in two municipal offices in Japan. Depressive symptoms were assessed by using the Center for Epidemiologic Studies Depression (CES-D) scale. In men, increased prevalence of depressive symptoms (defined by using a cutoff value of ≥ 19) was significantly associated with decreased levels of serum ferritin. In age- and study-site-adjusted models, ORs (95% CIs) for depressive symptoms for men in first, second, third, and fourth quartiles of serum ferritin concentrations were 2.83 (1.01–7.94), 1.74 (0.87–3.49), 1.33 (0.71–2.47), and 1.00 (reference), respectively (p for trend = 0.02). In multivariate-adjusted model, ORs (95% CIs) in first, second, third, and fourth quartiles of serum ferritin concentrations were 2.88 (0.93–8.91), 1.91 (0.90–4.05), 1.28 (0.66–2.49), and 1.00 (reference), respectively (p for trend = 0.03). No significant association was detected in women. Our finding that men with lower levels of serum ferritin concentrations had a higher prevalence of depressive symptoms suggests that adverse psychological effects may be implicated in iron deficiency among middle-age Japanese workers.

1. Introduction

The relationship of iron to brain function, cognition, and behavior, including affective behavior, has been the subject of considerable interest during the past decades (Beard et al., 1993; Hunt and Penland, 1999). Iron deficiency anemia in infants is associated with disturbances in behavior related to alertness, responsiveness, unhappiness, fearfulness, and tension (Lozoff, 1988). More recently, alterations in iron metabolism have been suggested as potential pathological markers in patients with manifest depression (Penninx et al., 2003).

Serum ferritin plays an important role in the storage of intracellular iron and has been the subject of extensive reviews (Orino and Watanabe, 2008; Wang et al., 2010). Significantly lower serum ferritin has been reported in non-anemic women with untreated major endogenous depression than in healthy controls (Batalena et al., 1990). In contrast, increased levels of serum ferritin concentrations were positively associated with depressive symptoms

in studies conducted among inpatients admitted to the treatment resistant depression ward (Maes et al., 1996) and chronic hemodialysis patients with major depression (Huang and Lee, 2007). Roles of systemic, low-grade inflammation have been frequently used to explain the relationship (Maes et al., 1996; Huang and Lee, 2007). These findings, however, were observed in patients with severe forms of major depression. Whether milder forms of depressive symptoms, which are more common among apparently healthy people, are also linked with serum ferritin levels have not been widely examined.

Four studies, to our knowledge, have explored the relationship in general population (Hunt and Penland, 1999; Baune et al., 2006; Vahdat Shariatpanaahi et al., 2007; Baune et al., 2010), and findings from these existing studies have been inconsistent. Two studies did not find significant association (Hunt and Penland, 1999; Baune et al., 2006), and two other studies concluded that depression is associated with decreased levels of serum ferritin concentrations (Vahdat Shariatpanaahi et al., 2007; Baune et al., 2010). To date, no study has been conducted in Japan where the prevalence of depressive symptoms in general population is relatively high (Kaji et al., 2010). To address the gap in the literature, we conducted this study to examine the association between serum ferritin and depressive symptoms among Japanese municipal employees. We hypothesized that levels of serum ferritin concentrations would be significantly

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lower in individuals with depressive symptoms after controlling for potential confounding factors.

2. Materials and methods

2.1. Study subjects and procedures

The study procedure has been described in greater details elsewhere (Murakami et al., 2008; Nanri et al., 2010). In brief, the survey was conducted in July and November 2006 among employees working in two municipal offices in northeastern Kyushu, Japan. All full-time employees ($n = 601$) were invited to participate in this study, except for those on long sick or maternity leave. Out of those invited, 323 men and 224 women participated, yielding a response rate of 91.0%. We excluded 16 subjects with missing information on depression, serum ferritin, body mass index, alcohol drinking, and smoking status. We further excluded three subjects with a history of diseases that may affect serum ferritin levels (one with anemia and two with chronic liver disorder). Finally, 312 men and 216 women remained in the present study.

Participants were asked to fill in the survey questionnaires well before the day of health checkup. The questionnaires were then checked by research staff for completeness, and where necessary, clarifications were made by asking the subjects during the examination. We measured demographic characteristics, lifestyle, anthropometric, and biochemical markers according to the same survey protocol at both study sites. The Ethics Committee of the National Center for Global Health and Medicine approved the study protocol, and a written informed consent was obtained from each participant.

2.2. Depressive symptoms

Depressive symptoms were assessed by using a Japanese version (Shima et al., 1985) of the Center for Epidemiologic Studies Depression scale (CES-D) (Radloff, 1977). This scale consists of 20 questions addressing six symptoms of depression, including depressed mood, guilt or worthlessness, helplessness or hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance experienced during the preceding week. Each question is scored on a scale of 0 to 3 according to the frequency of the symptoms, and the total CES-D score ranges from 0 to 60. The criterion validity of the CES-D scale has been well established in Western (Radloff, 1977) and Japanese (Shima et al., 1985) subjects. We defined depressive symptoms as present when a subject had a CES-D score of ≥16. Other cutoff values for the definition were also used: ≥19 that has been recommended for use among Japanese workers and ≥23 indicative of severe depressive state (Wada et al., 2007).

2.3. Serum ferritin concentration

After an overnight fast, 7 mL of venous blood was drawn from each participant into a vacuum tube and then conveyed in a cooler box to a laboratory. The blood was centrifuged for 15 min, and the separated serum was divided into a maximum of six tubes (0.5 mL each) at $-20\,°C$ or $-80\,°C$ until the analyses were performed. We measured serum ferritin concentrations by using chemiluminescence immunoassay on the Bayer ADVIA Centaur at an external laboratory (Mitsubishi Chemical Medience Corp, Tokyo, Japan).

2.4. Other variables

Marital status, social status as defined by job position, and status of current smoking and alcohol drinking were self-reported in a lifestyle questionnaire. Occupational physical activity was divided into sedentary or active work according to job title; clerical jobs were classified as sedentary work, whereas other types of work including childcare work, school lunch cooking, and technical jobs were classified as active work (Ohta et al., 2007). Non-job physical activity was computed as the average metabolic equivalent-hours per week (Ainsworth et al., 1993) on the basis of self-reported usual frequency and duration of six different activities (walking, low-, moderate-, and high-intensity activities, gardening, and commuting to work). Body height was measured to the nearest 0.1 cm with the subject standing without shoes. Body weight in light indoor clothes was measured to the nearest 0.1 kg. Body mass index (BMI) was calculated as body weight (kg) divided by the square of body height (meters).

2.5. Statistical analyses

Differences in proportions and means of covariates between subjects with and without depressive symptoms and according to the quartiles of serum ferritin concentrations were assessed by using χ^2 test and t test or one-way analysis of variance (ANOVA), respectively. The association between depressive symptoms and serum ferritin concentrations was examined separately among men and women. In women, because serum ferritin concentrations considerably increases after menopause (Whitfield et al., 2003), we further analyzed the data separately for those aged <50 years and ≥50 years, with reference to data regarding the mean age of menopause in Japanese women (48.3 years old) (Amagai et al., 2006).

Multivariate logistic regression analyses were then used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) of depressive symptoms for the quartiles of serum ferritin concentrations, taking the highest quartile category as a reference. In the first model, we adjusted for age and study site. In the final models, we further adjusted for marital status, social status, occupational physical activity, non-job physical activity, BMI, current smoking, current alcohol drinking, and serum folate. Trend of the association was assessed by using multiple linear regression analyses with the ordinal numbers 0 to 3 assigned to the quartile categories of serum ferritin concentrations. In addition, we conducted multivariate linear regression analyses in which both serum ferritin concentrations and CES-D score were log-transformed and included as continuous variables. Two-sided p-values of less than 0.05 were regarded as statistically significant. All data analyses were performed with SPSS version 17.0 (SPSS Inc, Chicago, IL, USA).

3. Results

In total, 36.5% of men and 36.1% of women had a CES-D scale score of ≥16. The prevalence of those with a CES-D score of ≥19 and ≥23 was 26.0% and 14.4% for men and 26.4% and 14.4% for women, respectively. As shown in Table 1, men with depressive symptoms were significantly more likely to be unmarried and in lower social status. Women with depressive symptoms were significantly more likely to be engaged in sedentary work compared to those without depressive symptoms.

Mean values of serum ferritin concentrations were significantly higher in men (Mean = 163.9 μg/L, S.D. = 141.9) than in women (Mean = 49.7 μg/L, S.D. = 59.9) ($p<0.001$). In women, those aged 50 years or older had significantly higher levels of serum ferritin concentrations (Mean = 38.6 μg/L, S.D. = 50.7) compared to those aged younger than 50 years (Mean = 77.6 μg/L, S.D. = 71.8) ($p<0.001$). The comparisons of characteristics of subjects according to the quartiles of serum ferritin concentrations stratified by gender are shown in Table 2.

Table 3 presents the ORs (95% CIs) of depressive symptoms according to quartile categories of serum ferritin concentrations in age- and study-site-adjusted and multivariate-adjusted models stratified by gender. In men, the association between serum ferritin concentrations and prevalence of depressive symptoms remained statistically significant when the cutoff for CES-D of ≥19 was used even after adjustment for potential confounding variables, with multivariate adjusted ORs (95% CIs) in the first, second, third, and fourth quartiles of serum ferritin concentrations of 2.88 (0.93–8.91), 1.91 (0.90–4.05), 1.28 (0.66–2.49), and 1.00 (reference), respectively (p for trend = 0.03). However, we could not detect such association when the cutoff for CES-D of ≥16 and ≥23 were used with a p for trend in the multivariate-adjusted model of 0.21 and 0.91, respectively.

In women, no significant association was found between serum ferritin concentrations and prevalence of depressive symptoms defined by the three different cutoff values of CES-D, and U-shape relationships were observed (Table 3). Consistently, no significant difference was obtained even after exclusion of women aged 50 years and older in both the age- and study-site-adjusted and the multivariate-adjusted models. When the presence of depressive symptoms was defined as having CES-D score of ≥16, the multivariate-adjusted ORs (95% CIs) for depressive symptoms in first, second, third, and fourth quartiles of serum ferritin concentration were 0.79 (0.17–3.68), 0.82 (0.17–4.02), 0.62 (0.12–3.24), and 1.00 (reference), respectively (p for trend = 0.73). Similarly, no significant association was found when the cutoff for CES-D of ≥19 and ≥23 were used.

In multiple linear regression analyses including both serum ferritin and CES-D score as continuous variables, there was no significant association between them in both men ($\beta = -0.13$, $p = 0.09$) and women ($\beta = -0.05$, $p = 0.40$).

4. Discussion

This study examined the relationship between levels of serum ferritin concentrations and depressive symptoms in well-functioning people in Japan. To the best of our knowledge, this study is among a few studies to date that attempts to explore the link between serum