Gender-specific effects of subjective memory complaints with respect to cognitive impairment or depressive symptoms

Short title: Subjective memory complaints and gender

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Abstract

Aim

To investigate the association between subjective memory complaints (SMCs) and gender.

Methods

We researched the prevalence of SMCs in a sample of 394 participants who were at least 60 years of age (138 male and 256 female). We also administered the Mini-Mental State Examination (MMSE) and the Center for Epidemiologic Studies for Depression (CES-D) scale. A multiple logistic regression analysis, which included SMCs in association with the MMSE or CES-D scores and other confounding factors, was performed to determine the influence of gender on SMCs. A p-value<0.05 was considered statistically significant.

Results

The duration of education of male participants were significantly higher than those of female participants. MMSE scores for female participants were significantly higher than those for males. There was no significant difference in CES-D scores between male and female participants. Twenty-four male participants and seventy-two female participants

showed evidence of SMCs. The incidence of SMCs was more frequent in female participants than male participants.

In the entire participants, sex difference and CES-D score were significantly associated with SMCs. In male participants, MMSE score was independently and significantly associated with SMC. Both in female participants and the entire participants, CES-D score was independently and significantly associated with SMC.

Conclusion

SMCs varied by gender and were associated with the degree of cognitive impairment in male participants, while they were associated with depressive symptoms in female participants.

Keywords: dementia; gender; major depressive disorder; mild cognitive impairment; subjective memory complaints

Introduction

Many studies in clinical psychiatry have investigated the concept of subjective memory complaints (SMCs) and suggest that the understanding of these complaints is of great relevance.[1] Some studies indicate that the presence of any type of SMC may indicate objective memory impairment or be predictive of future dementia.[2-4] In particular, difficulties following a group conversation or finding one's way around familiar streets may be associated with severe memory impairment.[5]

Recent studies suggest that SMCs, in addition to being associated with dementia or cognitive impairment, are associated with depressive states or major depressive disorder (MDD). Fischer et al. (2008) studied the presence of SMCs among participants with and without MDD and reported that the subgroup of patients with MDD had significantly more subjective memory complaints;[6] however, there were no significant differences between the two groups with respect to objective neuropsychological assessments. The decline in the self-evaluation of patients with MDD or the inhibition of thought may cause them to have SMCs. Mowla et al. (2008) investigated the cognitive function of patients with MDD and revealed that there was no relationship between SMCs and objective memory performance. Therefore, the meaning of SMCs among patients with MDD in this study is questionable.[7]

In general, the prevalences of MDD, depressed mood and dementia, or cognitive impairment differ with gender. Previous studies have reported that females are more likely to develop MDD than males.[8-10] Gao et al. (1998) investigated the incidence of Alzheimer's disease and reported that the likelihood of females developing Alzheimer's disease relative to males is 1.56 (95% confidence interval, 1.16-2.10).[11] In addition, Pedro-Cuesta et al. (2009) showed that the prevalence of Alzheimer's disease and dementia was higher in females.[12]

Thus, we hypothesized that there would be gender differences associated with SMCs. However, no studies have specifically investigated this potential association. In this study, we investigated the association between the presence of SMCs, cognitive impairment and depressed mood in a community dwelling population and investigated the differential effect of gender on this association.

Methods

Participants

The study group consisted of 394 volunteers (more than 60 years old; 138 males and 256 females) who participated in the Iwaki Health Promotion Project in 2011. The participants were residents of Iwaki district, Hirosaki City, in northern Japan. Iwaki district is a stable community with a population of 12,220. The age and occupational distributions of this population are representative of a Japanese countryside community. Data collection for the present study and the project were approved by the Ethics Committee of Hirosaki University School of Medicine, and all subjects provided written informed consent prior to participating in the project. Demographic data (age, gender, and duration of education) and lifestyle factors (smoking and drinking) were obtained from self-questionnaires and interviews.

We excluded participants with an Mini-Mental State Examination (MMSE) score less than 24, because we investigated healthy subjects in the present study and a score less than 24 was defined as poor cognitive function.[13]

Assessments of cognitive function and SMCs

The Mini-Mental State Examination (MMSE) was given to all participants to measure their global cognitive status. This test assesses orientation to place and time, short-term memory, episodic long-term memory, subtraction, ability to construct a sentence, and oral language ability. The maximum score was set at 30, and poor cognition was defined as a score less than 24.[13]

Participants were asked the following question: “Have you been distressed by your forgetfulness?” SMCs were judged for each participant on the basis of their answer to this question.

Assessment of depression

The Japanese version of the Center for Epidemiologic Studies for Depression (CES-D) scale was also administered to all participants to measure their depressive status.[14] The questionnaire has been widely used to measure depressive symptoms in community populations, and it is also used as a screening tool for depression.[15] The CES-D is a 20-item, self-report scale that focuses on depressive symptoms within the week prior to administration of the questionnaire. The maximum score is set at 60, and higher scores are associated with depression. CES-D scores of 16 or higher have

generally been thought to indicate clinically relevant depressive symptoms, including both minor or subthreshold depression and MDD.[16, 17]

Statistical analysis

Descriptive statistical analyses were performed to describe demographic and clinical variables. To compare how characteristics between groups differed by gender, the unpaired Student's t-test was used to analyze variables. A multiple logistic regression analysis of SMCs in association with MMSE score, CES-D score and other confounding factors (age, duration of education and MMSE or CES-D score) was performed. The data were analyzed using the SPSS software for Windows (Version 21). A p-value<0.05 was considered statistically significant.

Results

Participant characteristics

The demographic data and scores for the MMSE and CES-D are presented in Table 1. The mean ages of male and female participants were 68.8±6.7 and 68.7±6.1 years, respectively. The duration of education was 11.1±2.1 years for male participants and 10.5±1.9 years for female participants. The duration of education of male participants were significantly higher than those of female participants. The average MMSE score was 28.0±2.1 for male participants and 28.6±1.8 for female participants. The MMSE scores of female participants were significantly higher than those of male participants. The average CES-D score was 10.6±4.6 for male participants and 10.7±5.8 for female participants.

Twenty-four male participants (18.3%) and seventy-two female participants (29.2%) had SMCs. The rate of participants who reported SMCs was significantly higher in female participants than that in male participants.

The influence to subjective memory complaints

Multiple logistic regression analysis was performed for entire participants and each gender to assess the influence of MMSE and CES-D score on SMCs.

Table 2 provides details of multiple logistic regression analysis for SMCs in association with the MMSE and CES-D score and other confounding factors in the entire participants. In the entire participants, sex difference and CES-D score was significantly associated with SMCs.

Table 3 provides details of multiple logistic regression analysis for SMCs in association with the MMSE and CES-D score and other confounding factors in male participants. In male participants, only MMSE score was significantly associated with SMCs.

Table 4 provides details of multiple logistic regression analysis for SMCs in association with the MMSE and CES-D score and other confounding factors in female participants. In female participants, only CES-D score was significantly associated with SMCs

Discussion

The results of this study showed that SMCs are differentially associated with cognitive impairment or depressive symptoms on the basis of gender. In male participants, SMCs were associated with actual cognitive impairment, while in female participants, SMCs were associated with depressive states. This is the first study to show a gender difference with regard to the clinical meaning of SMCs. These findings indicate that when patients have SMCs, clinicians should pay more attention to cognitive impairment in males and depressive status in females. Odds ratios of the significant variables were relatively low, but sex showed the highest OR (1.870) in the entire participants. So we should particularly consider sex of the patients who have SMCs.

Previous studies have reported that SMCs are related to actual cognitive impairment.[3, 4] Clarnette et al. (2001) indicated that cognitive function, as assessed using MMSE scores, in subjects with SMCs (n=97) was significantly lower than that in controls (n=38).[3] In addition, Benito-Leon et al. (2010) investigated SMCs in a large sample (1073 vs. 1073) and reported that some measures of cognitive function were significantly different between groups, while other measures of cognitive function were not different between subjects with and without SMCs.[4] However there was no

information regarding the impact of gender on these differences. In this study, there was no significant association between SMCs and actual cognitive impairment in the sample population.

An association between SMCs and depressive mood has been reported in a previous small study.[6] Scores on several SMC measures, although not all measures, for depressed patients were significantly higher than those for controls. However, this study did not include a description of the effect of gender on this difference or the number of male and/or female subjects. In the present study, there was a significant association between SMCs and CES-D scores, not only in female participants but also in the entire sample population. This result may have been influenced by the fact that most of the subjects with SMCs in this study were female.

We are unable to explain why the meaning of SMCs differs by gender; however, gender differences in character or temperament may influence the results.[18] Males may objectively recognize their actual cognitive impairment and thus accurately report SMCs. On the other hand, females may interpret minor forgetfulness as severe symptoms of dementia and may become depressed, or females with depressive symptoms may be more likely to have SMCs than males.

The MMSE scores of female participants showed significantly higher than those of male participants. The scores of MMSE subscale 1 (p=0.045) and 4 (p=0.020) of female participants were significantly higher than male participants. The lower subscale 1 indicates temporal orientation disturbance and the lower subscale 4 indicates attention and calculation disturbance. The difference of life style between male and female might lead to the difference of the score of subscale. In Japanese countryside community, male go to work every day and lifestyle the same as usual. Female do housework and have much chances to buy necessaries of life, so they have to calculate frequently and be careful on a date for the garbage days. Such habits might lead to the differences in the MMSE subscales but it is unclear whether these lead to SMCs.

MCI (mild cognitive impairment) is one of the most important themes in neuropsychiatric research that is related to dementia and depression. Modrego and Ferrandez reported that MDD increases the likelihood of the development of Alzheimer's disease in patients with MCI.[19] Although MDD is an independent risk factor for dementia,[20, 21] depressive symptoms are the prodromal symptoms of cognitive decline.[22, 23] Palmer et al. reported that among individuals with mild cognitive impairment no dementia (CIND), 11% remained stable and 25% improved compared to baseline after 3 years of follow-up;[24] in particular, the group demonstrating

improvement may have consisted of individuals with MDD who subsequently recovered from the condition. Therefore, the presence of MDD should be considered for patients who present with MCI.

There are some limitations to the current study. First, we used only one question ("Have you been distressed by forgetfulness?") to assess the presence of SMCs. Some studies have used a subjective memory complaints scale to evaluate the presence of SMCs;[2, 25, 26] however, the present study did not include an analysis of the quality of SMCs. Second, we studied a general, community-dwelling population. It is unclear whether our data are generalizable to patients visiting hospitals or clinics for SMCs. Further studies are needed to further clarify the influence of gender on subjective memory complaints in patients. Third, this study was conducted at only one site; therefore, our results could have been influenced by the culture of this region of Japan. Further research in other countries or of other races is needed to confirm our preliminary results. Forth, there is not information about the physical diseases and the impairment of activities of daily living. These could influence the cognitive function and lead to depressive symptoms, such information might change the results of present study.

In conclusion, this study showed that SMCs are differentially associated with cognitive impairment or depressive symptoms on the basis of gender. In male participants, SMCs were associated with actual cognitive impairment, while in female participants, SMCs were associated with depressive states. Further studies are needed to confirm our preliminary results.

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The authors declare that they have no competing interests.

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Table 1 Demographic characteristics of subjects

	Total (n=377)	Male (n=131)	Female (n=246)	P value
Age	68.7±6.3	68.8±6.7	68.7±6.1	0.868
Duration of Education (years)	10.7±2.0	11.1±2.1	10.5±1.9	0.012*
SMC	25.4% (n=96)	18.3% (n=24)	29.2% (n=72)	0.015*
MMSE	28.4±1.9	28.0±2.1	28.6±1.8	0.005**
CES-D	10.7±5.4	10.6±4.6	10.7±5.8	0.881

Values are mean ± SD. The student's unpaired t-test was used to evaluate the differences between Male participants and Female participants. * $p < 0.05$. ** $p < 0.01$

Table 2 Multiple logistic regression analysis for SMC in entire subjects

Variables	Regression coefficient (β)	Standard error	Odds ratio	95% Confidence interval	p value
Sex	0.626	0.284	1.870	1.071-3.267	0.028*
Age	0.010	0.021	1.010	0.969-1.054	0.627
Duration of Education (years)	-0.038	0.070	0.936	0.840-1.105	0.591
MMSE	-0.059	0.066	0.942	0.827-1.073	0.371
CES-D	0.084	0.025	1.088	1.036-1.143	0.001**

* $p < 0.05$. ** $p < 0.01$

Table 3 Multiple logistic regression analysis for SMC in male subjects

Variables	Regression coefficient (β)	Standard error	Odds ratio	95% Confidence interval	p value
Age	0.042	0.039	1.043	0.967-1.125	0.271
Duration of Education (years)	0.038	0.125	1.038	0.813-1.326	0.763
MMSE	-0.284	0.121	0.752	0.593-0.954	0.019*
CES-D	-0.001	0.058	0.999	0.891-1.120	0.987

* $p < 0.05$

Table 4 Multiple logistic regression analysis for SMC in female subjects

Variables	Regression coefficient (β)	Standard error	Odds ratio	95% Confidence interval	p value
Age	-0.011	0.026	0.989	0.939-1.041	0.665
Duration of Education (years)	-0.090	0.085	0.914	0.773-1.080	0.289
MMSE	0.065	0.086	1.067	0.901-1.264	0.453
CES-D	0.106	0.030	1.112	1.049-1.179	0.000**

**p < 0.01