The Relationship Between Subjective Memory Complaints and Objective Memory Performance, Depression and Anxiety Levels in Patients Under 55 Years of Age

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SUMMARY

Objective: Psychiatric differential diagnosis is often ignored in young patients with memory complaints, even if no neurological or physical illnesses were evident. In this study, we aimed to determine the relationship between subjective memory complaints and objective memory impairment, depression and anxiety levels in young patients with memory complaints.

Method: The study was carried out with 56 patients under the age of 55 who applied to the psychiatry, neurology and internal medicine outpatient clinics with memory complaints and 55 healthy volunteers. All participants completed the Subjective Memory Complaints Questionnaire (SMCQ), the Montreal Cognitive Assessment (MoCA), the Auditory Verbal Learning Test (AVLT), the Benton Visual Memory Test (BVMT), the Digit Span Test (DST), the Verbal Fluency Test (VFT), the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI).

Results: Significant differences were observed in the scores of SMCQ, MoCA, AVLT, BVMT, DST, VFT, BDI and BAI in individuals with memory complaints compared to the controls, which could not be ascribed to any neurological or physical disease. Depression and anxiety levels were significantly higher than those of the control group.

Conclusion: Differential diagnosis of memory complaints has to be made in young patients. Subjective memory complaints may be indicative of depression and anxiety disorders. It is necessary to evaluate the cognitive impairment that may develop over time in young patients with subjective memory disturbances via longitudinal studies.

Keywords: Memory complaints, memory, depression, anxiety

INTRODUCTION

Memory is a cognitive process that comprises perception of information and its organisation, coding, storing and recall. The term forgetfulness, on the other hand, is a cognitive complaint expressing the perception of a subjective impairment, and corresponds to conditions of robust or impaired memory function evaluated by means of neuropsychological tests.

Memory complaints are often observed in elderly patients, suggesting demential diseases (Ponds et al. 1997). In our clinical practice, memory complaints are increasing among non-geriatric patients and the evaluation and differential diagnosis of cognitive disorders is gaining importance in these patients.

Subjective memory complaints (SMC) are complaints expressed by a person on his/her own observations of memory functions. SMC have been reported to occur in almost 50% of middle aged adults (Hurt et al. 2010). The relationship between SMC and objective memory impairment is controversial (Abdurlrab et al. 2008, Balash et al. 2010). It was concluded in a meta-analysis that the existence of

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SCM without another medical diagnosis doubles the risk of cognitive impairment, increases the risk of mild cognitive impairment (MCI) by 38.2%, and raises the risk of dementia by 42.8% (Mitchell 2008). In their six-year observational study Hessen et al. (2017) found that out of the 81 patients with SMC, 9% had MCI and 5% had dementia, and their SMC cases were mostly benign. Also, it was found that the initially low amyloid-β_{42} ($A\beta_{42}$) levels in the cerebrospinal fluid (CF) and development of amnesia in the first two years of SMC were the indicators of dementia. In cross-sectional studies particularly, there is either a weak or no relationship between SMC and objective memory impairment (Balash et al. 2010, Riedel-Heller et al. 1999). This may be due to the inadequacy of standard memory tests to detect mild memory impairment, as well as the effects of SMC on personality traits and psychiatric illnesses such as depression and anxiety disorders (Hanninen et al. 1994, Smith et al. 1996, Derouesne et al. 1999).

Depression is a disorder commonly involving SMC as one of its major components (Lahr et al. 2007). Depressive disorders are expected to be the second most common cause of worldwide labour force loss after ischemic heart disease by 2020 (Milchaud et al. 2001). These data suggest that major depression is an important public health problem that needs to be understood better (Aydemir et al. 2009, Landro et al., 2001, Porter et al. 2000). Presence of cognitive impairment alongside the emotional and physical symptoms of depression is well known, and the connection between depression and memory disorders has been shown by many studies (Ottowitz et al. 2002). Neuropsychological evaluations of depressed individuals have demonstrated deterioration of psychomotor speed, attention, memory and executive functions when compared to healthy controls (Zakzanis et al. 1998). Cognitive dysfunction in depression has been attributed to hippocampal volume reduction by the impaired hypothalamus-pituitary-adrenal axis, the increase in corticosteroid levels and the anterior cingulate gyrus dysfunction (Hammar and Ardal 2009).

SMC is also frequently observed in anxiety disorders that affect the daily life, social functioning and interpersonal relationships of the individual. Cognitive functions are affected in various forms according to the severity and content of the disorder in this group of diseases (Williams et al. 1997).

The purpose of this study was to determine the relationship of SMC with objective cognitive performance, depression and anxiety severity in patients of ≤ 55 years of age, consulting our neurology, internal medicine and psychiatric outpatient clinics with an increasing incidence of memory complaints, but without a history of psychiatric diagnosis and pharmacotherapy and any neurological or other physical illness to explain their complaint; and thereby make a contribution to appropriate treatment approach through differential diagnosis.

MATERIAL AND METHOD

Participants

The Clinical Research Ethics Committee of Faculty of Medicine, Marmara University approved the study with the protocol code of 09.2017.349. Study participants consisted of 56 outpatients under 55 years of age, consulting our neurology, internal diseases, and psychiatry polyclinics with memory complaints, but without a history of psychiatric consultation or drug use, or any neurological or internal disease to explain their complaints. The control group consisted of 55 healthy volunteers without any neurological, psychiatric or internal diseases. Each participant in the study group was examined and evaluated by the neurology and internal diseases polyclinics in order to eliminate any neurological and internal diseases that may underlie the complaint of forgetfulness. Individuals on psychoactive drugs and/or diagnosed with mental retardation were not included in the study.

Data Acquisiton

After selecting the patients and controls on the basis of the criteria for inclusion in the study, and obtaining their informed consent, the following tests were administered by our psychologist for the purposes of gathering data.

The socio-demographic data form: In accordance with the aims of the study, a questionnaire was used for acquiring clinical data including psychoactive substance use and disease history and socio-demographic data such as age, gender, education level, marital status, and employment.

Psychometric Scales

a. The Subjective Memory Complaints Questionnaire (SMCQ): This is a short, valid and reliable scale designed by Youn et al. (2009) as a two-way close ended questionnaire (yes/no) composed of 14 questions, with the first 4 (1-4) evaluating general memory and the remaining 10 (5-14) evaluating daily memory functions. The total score is calculated by adding the "yes" responses in it. Validity and reliability of the Turkish language version of the SMCQ was carried out by Özel-Kızıl et al. (2013).

b. The Beck Depression Inventory (BDI): This self-assessment scale, developed by Beck et al. (1961) to measure emotional, cognitive, somatic and motivational symptoms of depression, consists of 21 items each of which is scored between 0-3. The validity and reliability of the Turkish language version of BDI was conducted by Hisli (1988).

c. The Beck Anxiety Inventory (BAI): This is a 21-item scale of self-assessment scale developed by Beck et al. (1989) to determine the frequency of anxiety symptoms experienced by a person. Validity and reliability of the Turkish language version was conducted by Ulusoy et al. (1998).

Screening Tests

a. The Montreal Cognitive Assessment Scale (MoCA): This test is a screening scale developed to evaluate the initial stages of impairment in cognitive functions related to memory, visual-spatial skills, executive functions, attention, concentration, abstract thinking, orientation functions and language. (Nasreddine et al. 2005). Validity and reliability study for the Turkish language version of MoCa was conducted by Selekler et al. (2010) and Kaya et al. (2014).

Neuropsychological Tests

a. The Verbal Memory Processes Test (VMPT): Developed by Öktem (2011) for investigation of verbal learning and memory, the VMPT is a multi-factorial test firstly on the instantaneous memory; secondly on the process of learning or acquiring information; and thirdly on the processes of remembering or recalling. Remembering is evaluated in two ways, namely the delayed self-recall and the delayed recognising recall. The test consists of 15 unrelated vocabulary items, read to the participant with one-second interval after each word. When the reading is finished, the participant is asked to say the words he/she remembers which gives information about the instantaneous memory and the sustainable attention of the participant. The correct answers of the participant are written down as their Instantaneous Memory Score. Following the first trial, reading of the same list of words is repeated 9 times, and each time the participant is asked to say all the words he/she remembers which, on the other hand, gives clues about the ability of learning of the participant. This is followed by an interval of 30-40 minutes when the patient is asked to recall the words in the list; and the number of the words the patient can recall is taken as his/her size of self-recall in long term memory (LTM). The number of the words the patient says that are not in the list, on the other hand, is recorded as the size of misremembering in LTM. If the patient recognizes from a given choice some words that he/she couldn't recall by himself/herself during the self-recall process, this is called LTM recognition. The total number of the words written down through LTM self-recall and LTM recognition processes is taken as the size of LTM total recall.

b. The Benton Visual Memory Test (BVMT): This test developed by Benton (1974) evaluates the visual memory. It was translated by Aksel et al. (1972) into the Turkish language.

c. Number Extension Test (NET): This test is the 8th sub-test in the Weschler Memory Scale Enhanced Form (1987). This subtest consists of two sub-sections, the number sequences of which are read in increasing length. There are two separate trials, conducted for each length of the sequences. After presentation of each sequence, the patient is asked to repeat the staight sequence for a straight number score, and to repeat the sequence in reverse for an inverse number score. In this way, the simple and complex attention of the patient is measured. Validity and reliability study in the Turkish language was done by Karakaş (2004).

d. Verbal Fluency Test (VFT): Verbal fluency means speed and ease of verbal production. The purpose of this test is to assess the mental recall of the words that start with the letter given in the prescribed time or in the desired category. In this study, the letter fluency test standardized by Tumaç (1997) and the category fluency task sub-tests developed by Lezak (1995) were used.

Statistical Analysis

Descriptive statistics were used to define continuous variables (mean, standard deviation, minimum, median, maximum). The Student's t test was used for comparing two independent variables with normal distribution.; and the Mann-Whitney U test was used to compare two independent variables with non-normal distribution. The Chi-Square test or the Fisher's Exact test, when appropriate, were used to examine the relationship between categorical variables. Statistical significance level was determined by the p value of 0.05. Analyses were conducted on the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013).

RESULTS

Data on the mean age, gender and educational status of the study and control groups given in Table 1 show that these parameters did not differ significantly between the two groups.

Clinical Traits

All patients in the study group were examined by the psychiatrist who conducted this study. Diagnoses on these patients included depressive disorder (41.1%), adjustment disorder (17.8%) and anxiety disorder (16.1%), and appropriate treatments were started.

The participants in the study group did not have a history of psychiatric diagnosis or pharmacotherapy. The healthy volunteers included in the control group were not given psychiatric examination as they did not have any neurological, psychiatric or internal diseases, were not on treatment by the relevant polyclinics and had not used any psychiatric medication.

Comparison of the SMCQ scores of the study and control groups, given in Table 2, shows that the scores of the study

Table 1. Comparison of Age, Gender and Educational Status of the Study and Control Groups

		Study Group (n=56)	Control Group (n=55)	Z	P
Age		36.1±10.9	36.8±10.8	-0.283	0.777*
				x^2	
Gender	Female	41 (73.2%)	35 (63.6%)	1.179	0.312**
	Male	15 (26.8%)	20 (36.4%)		
Educational Status				2.438	0.495**
	Primary School	10 (17.9%)	15 (27.3%)		
	Middle School	6 (10.7%)	3 (5.5%)		
	High School	19 (33.9%)	20 (36.4%)		
	University	21 (37.5%)	17 (30.9%)		

* p>0.005 with Mann-Whitney, ** p>0.005 with Fisher's Exact.

group was significantly higher than those of the control group (p<0.001).

The BDI and BAI mean scores of the groups and their comparisons are given in Table 2. In the patient group depression levels were ranked as severe (10.7%), moderate (30.4%), mild (33.9%) and symptom-free (25%); while in the control group the rankings were mild (5.5%) and symptom-free (94.5%). In the study group the anxiety symptom severity were ranked as severe (23.2%), moderate (21.4%), mild (30.4%) and symptom-free (25%). Whereas the rankings were mild (3.6%) and symptom-free (96.4%) in the control group. The results indicate that the incidences of mild and severe depression and anxiety symptoms were higher in the study group.

Comparison of MoCA points between the study and control groups is given in Table 2. Although the MoCA points of both groups were higher than the threshold level, those of the study group was significantly lower than that of the control group (p=0.05).

The mean scores and statistical comparisons of the VMPT subtests of both groups are given in Table 2, showing that the instant memory score, learning score and the highest learning score of the study group were significantly lower than those of the control group (respectively, p<0.001, p=0.025 and p<0.001). Furthermore, the LTM scores of the study group for self recall, misremembering and recognition were found significantly lower (respectively, p=0.034, p=0.041 and p<0.001).

Mean scores and comparisons of the BVMT, Number Extension and Verbal Fluency Subtests of the two groups are given in Table 2. The total score on the BVMT, and scores on the subtests Inverse Number Range Test, Animal Naming Test and Naming with Letter K Test of the study group were significantly lower than those of the control group.

Table 2. Comparison of the Mean Scores of the Study and Control groups on the SMCQ, BDI, BAI, MoCA, VFT Subtests, BVMT and NET Subtests

	Study Group (n=56)	Control Group (n=55)	z[1]	P
SMCQ	11.9±3.8	1.4±1.2	-9.081	<0.001*
BDI	19.3±10.5	3.3±3.5	-8.039	<0.001*
BAI	16.1±10.7	2.1±2.1	-7.803	<0.001*
MoCA	24.8±3.1	26.4±2.5	-2.805	0.005*
VFT Instantaneous memory	5.7±1.4	6.7±0.8	-4.400	<0.001*
Learning score	114.2±14.9	120.6±14.3	-2.270[2]	0.025**
The highest learning	13.7±2.7	14.8±0.3	-4.369	<0.001*
LTM Self recall	12.9±1.9	13.9±0.8	-2.118	0.034*
LTM Misremembering	0.31±0.2	0.15±0.3	-2.08	0.041*
LTM Recognition	2.09±0.3	1.48±0.6	-5.896	<0.001*
LTM Total Recall	14.52±0.2	14.49±0.3	-0.28	0.692*
LTM Misrecognition	0.03±0.01	0.025±0.01	-0.78	0.506*
BMVT	12.6±1.5	14.2±0.9	-5.814	<0.001*
Straight Number Range Test	5.3±0.7	5.5±0.6	-1.529	0.126*
Inverse Number Range Test	4.4±0.9	5.2±0.6	-5,215	<0.001*
Animal Naming Test	18.4±6.2	22.2±2.6	-3.965	<0.001*
Naming with Letter K Test	13.7±4.6	20.2±4.7	-6.057	<0.001*

*p<0.05 with Mann-Whitney U; **p<0.05 with Student t test; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory: BMVT:Benton Visual Memory Test; LTM: Long term memory; MoCA: Montreal Cognitive Assessment Scale; SMCQ: Subjective Memory Complaints Questionnaire; VFT: Verbal Fluency Test.

Table 3. Correlation Analysis of the Relation Between the Depression/ Anxiety Symptoms, the Subjective Memory Complaints and the Cognitive Functions of the Study Group

		BDI r (p)	BAI r (p)
SMCQ		0.319 (0.018)*	0.308 (0.022)
MoCA		-0.248 (0.066)	-0.041 (0.766)
VMPT	Instant memory	-0.188 (0.165)	-0.092 (0.500)
	Learning score	-0.116 (0.396)*	0.127 (0.352)
	The highest learning	-0.261 (0.052)	0.117 (0.392)
LTM Total recall		-0.028 (0.840)	0.024 (0.861)
Benton Visual Memory Test		-0.110 (0.422)	0.078 (0.567)
Straight Number Range Test		-0.301 (0.024)	-0.086 (0.526)
Inverse Number Range Test		-0.283 (0.035)	-0.247 (0.066)
Animal Naming Test		-0.294 (0.028)	-0.283 (0.035)
Naming with Letter K Test		-0.307 (0.021)*	-0.270 (0.044)

Spearman's rho p, *Pearson p, BDI: Beck Depression Inventory; BAE: Beck Anxiety Inventory; SMCQ: Subjective Memory Complaints Questionnaire; MoCA: Montreal Cognitive Assessment Scale ; LTM: Long Term Memory.

In the patient group, we observed a mildly positive correlation between the symptom severity of depression and SMCQ score, and mildly negative correlations between the symptom severity of depression and the scores on the Straight Number Range Test, Inverse Number Range Test, Animal Naming Test and Naming with Letter K Test. Also, mild positive correlations between the anxiety symptoms of the study group and the tests on Animal Naming and Naming with Letter K were determined. The relationships between the depression and anxiety symptoms of the study group, and their SMC and cognitive functions are presented in Table 3.

DISCUSSION

As expected, it was determined in this study that the incidence of SCM in patients of less than 55 years of age without any neurological or internal diseases to explain their memory complaints and/or a history of psychiatric diagnosis or pharmacotherapy, was significantly higher as compared to the control group. Also, depression and anxiety levels were higher in the study group; and the tests carried out to evaluate objective memory impairment indicated deterioration in this group when compared to the control group.

SMC cases have been increasing in our clinical practice. Inconsistencies exist in the results of cross-sectional studies on the relationships between subjective memory disorders and objective memory disorders (Lenehan et al. 2012). It has been suggested that SMC and its disorders appear many years before the development of dementia. It was argued that a 'subjective memory impairment' period that started about 20 years ahead was the basis of mild cognitive impairment (MCI) resulting in Alzheimer's disease (Reisberg et al. 2008). In the case-control and cross-sectional studies by Balash et al. (2009) with 341 patients, a clear relationship between memory performance and SMC was frequently undemonstrable. However, depression and anxiety scores were higher in patients with SMC, suggesting mild depressive and anxiety disorder in these patients.

A 24-month observation study demonstrated that SMC was associated more with depression and anxiety than cognitive impairment (Yates et al. 2017). Other studies have reported that depression or psychiatric comorbidity increased SMC; and that SMC predicts demential progress only in the presence of determinants such as BOS amyloid and tau anomaly, positive amyloid PET scanning and/ or APOE-4 allele trait (Molinuevo et al. 2017; Buckley et al. 2015; Horn et al. 2018; Garcia-Ptacek et al. 2016). In our study, using the MoCA, which was developed to evaluate the early stage cognitive impairment in patients with SMC, demonstrated statistically significant lowering of the MoCA mean score of the study group. The VFT, designed for multifactorial investigation of verbal learning and memory, and which facilitates their diagnosis and differential diagnosis, was used in the study. It was found that the control group scores on all the VFT subtests, with the exception of those on LTM total recall and LTM misrecognition, were significantly higher. The study and control groups were investigated by means of the VFT to measure verbal fluency, the BVMT to test visual memory, and the NET to measure simple and complex attention. In all three tests, the mean scores of the control group were significantly higher than those of the patient group. In our study a significant relationship was found between SMC and deterioration of performance on objective memory tests, in agreement with other reports in the literature.

It is difficult to state at this stage whether this result is related to the depression-anxiety levels of the study group or the initiator of a cognitive disease which may present in the future. However, inclusion of investigations such as the BOS amyloid and tau bio-determiners that are thought to appear before demential progress, and the positive results in amyloid PET scanning, APOE-4 allele traits with low BOS $A\beta_{42}$ levels, has increased the predictive power of our study. It is thought that the detection by magnetic resonance imaging (MRI) of atrophy in medial temporal structures such as the hippocampus is a diagnostic determiner of demential progress in the MCI stage that occurs prior to cognitive complaints (Frisoni et al. 2010, Teipel et al. 2013). MRI was used in this study on the patient group but the results were not quantitatively evaluated for medial temporal lobe atrophy (MTA) and small vessel disease which decreases the power of our study for predicting dementia.

In the study for the development of VMPT by Öktem (1992), scores on the learning process were found to be lower in the 84 patients diagnosed with depression as compared to those of the normal control group, demonstrating that

memory problems develop secondarily to the impairment of attention in depression. Severity of depression was found to correlate with the extent of impairments of visual memory, visual motor monitoring, focused attention and verbal fluency skills (Demir et al. 2000). It has been argued that individuals with anxiety disorders focus attention, at the initial stage of processing information, on the content that is threatening, causing it to gain priority; but, that at the later stage of detailed processing of the information, distancing of attention from the threatening content leads to complication in recalling the information. This results in impairment of objective evaluation of the information and makes adaptation harder (Williams et al. 1997) In parallel with these studies, when comparing the depression and anxiety levels of the groups in our study, we found the depression and anxiety levels of the study group to be significantly higher than in the control group. In line with the literature, correlation analysis of the relationship of depression with SCM and cognitive functions has shown us the deterioration in simple and complex attention, verbal fluency and the pace and ease of verbal production. These cognitive functions also deteriorate in anxiety disorders and the SCM is exacerbated with the increase in the severity of anxiety and depression symptoms. Despite detecting deterioration in the verbal memory field with depressive symptoms, probably due to secondary memory deterioration, a relationship was not demonstrated between depression and anxiety severity and the results of general memory tests. Hence, we claim that this result of our study is related more to depression and anxiety symptoms than SMC as the initiator of dementia in the population under the age of 55.

Derouesne et al. (1999) found the memory complaints to be psychological symptoms in both the 183 elderly and 77 young patient groups consulting the hospital memory clinic with SMC complaints not based on any known psychiatric or neurological diseases. Incidence of depressive symptoms was found to be 24.1% among 946 participating patients without a history of neurological or psychiatric diseases or the use of any psychiatric medicine (Gino et al. 2010). In our study, 75% of the participants were diagnosed with psychiatric diseases with most of them consulting the neurology and internal diseases clinics. These data revealed to us that a significant number of the outpatients consulting the hospital with memory complaints are not assessed through differential diagnosis for psychiatric disease.

Limitations of the Study

One of the limitations of this study is not having used a tool such as the SCID to ensure the absence of psychiatric disease in the control group which may have been missed and would decrease the reliability of the comparison between the study and the control groups. In order to detect the initial phase of cognitive impairment we used in this study the Turkish language version of MoCA which had been tested for validity and reliability on patients over 65 year of age. Having patients ≤ 55 years of age as the participants of our study may affect the validity and reliability of this test. Not having standardized the Benton Visual Memory Test and the Verbal Fluency Test in the Turkish language are other limitations of the study. All the patients in our study group were examined by the neurology and internal diseases clinics, and the ones who had neurological or internal diseases that could have explained the complaints of forgetfulness were excluded from the study. However, the tests that were used in these two clinics for the diagnosis of any such relevant disease were not standardised. Finally, the patients were not examined with MRI for medial temporal atrophy and small vessel disease.

CONCLUSION

Patients with SMC frequently consult not only the psychiatry but also the neurology and internal medicine outpatient clinics where the diagnosis of psychiatric symptoms are often missed and the patients are not referred to the psychiatry units for treatment. Patients with SMC should be examined for depression and anxiety on the basis of differential diagnosis to be given guidance for treatment and planned follow up to detect possible mild cognitive dysfunction and dementia development.

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