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Subjective memory complaints, neuropsychological performance and psychiatric variables in memory clinic attendees: a 3-year follow-up study

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Abstract

The aims were to evaluate the cognitive performance and clinical diagnosis in patients (< 75 years) seeking help for subjective memory complaints, to determine the prevalence of certain psychiatric symptoms and to conduct follow-up examinations. At baseline 41% showed normal cognitive performance (subjective memory impairment; SMI), 37% fulfilled criteria for mild cognitive impairment (MCI) and 22% were classified as dementia. There were significant associations between the three groups and experiences of psychosocial stress and feelings of anxiety. The proportion of psychosocial stress was significantly higher in SMI vs. MCI and SMI vs. dementia. Feelings of anxiety was significantly higher in SMI vs. MCI. At the three-year follow-up, 88% of the SMI patients remained stable SMI and 60% of the MCI patients remained stable. There was a significant reduction of psychosocial stress and moderate reduction of feelings of anxiety among the SMI patients. The findings indicate that the risk of patients with SMI developing dementia is small within a three year span. We propose that subjective memory complaints might be influenced by the presence of psychosocial stress and feelings of anxiety disturbing the memory processes and interfering with the patients' evaluation of their memory function.

Keywords: subjective memory impairment, mild cognitive impairment, psychosocial stress, depressed mood, feelings of anxiety, neuropsychological tests

1. Introduction

Subjective memory complaints are very common in the elderly but are also reported among middle-aged and young old patients. The complaints of poor memory might be associated with benign changes of healthy aging (DeCarli, 2003). However, memory complaints may also be associated with other conditions, especially MCI and dementia as well as depression and anxiety (Reisberg and Gauthier, 2008). The relationship between subjective memory complaints and objective performance in neuropsychological tests has been investigated (Jonker et al., 2000; Elfgren et al., 2003; Guarch et al., 2004; Lautenschlager et al., 2005; Vestberg et al., 2007, 2009; Gallassi et al., 2008). Some studies have found an association between subjective memory impairment and poor performance in memory tests, whereas others have failed to do so. It has been shown that the relationship between subjective memory complaints occurring in a sample drawn

from the general population reporting the everyday irritation of minor forgetfulness is not the same as in a study recruiting subjects who seek help at a memory clinic (Jonker et al., 2000; Elberling et al., 2002; Mitchell, 2008). The evaluation of memory complaints in relation to objective test performance requires knowledge about how the choice of the sample affects the results.

Several studies have shown that depression and other psychiatric conditions such as anxiety and psychosocial stress may affect both the patients' perception of their own performance as well as their objective memory performance (Smith et al., 1996; Jonker et al., 2000; Comijs et al., 2002; Elfgren et al., 2003; Jorm et al., 2004). There are important and complex interrelationships between psychiatric conditions and cognitive impairment. In a study by Sinforiani et al. (2007) it was found that subjects with cognitive complaints but whose neuropsychological evaluation was within normal range were younger and presented higher scores of anxiety and depression. So far, there are only a few follow-up studies of patients with subjective memory complaints without objective memory impairment evaluating the influence of psychiatric variables. A recent study by Glodzik-Sobanska et al. (2007) has shown that the presence of subjective memory complaints was a predictor of future cognitive decline. Some subjects did however present as "unstable" over time fluctuating between decline and normal cognitive performance. These "unstable" subjects had a high intensity of memory complaints and more affective symptoms. A tentative conclusion from these findings is that the presence of even low levels of affective symptoms may have prognostic relevance and even treatment consequences in subjects with memory complaints (Reisberg and Gauthier, 2008).

In the current study the primary aim was to evaluate the cognitive performance, clinical diagnosis and duration of memory problems in patients (< 75 years) seeking help for their subjective memory impairment at an outpatient memory clinic. The second aim was to determine the prevalence of certain psychiatric conditions (experiences of psychosocial stress, feelings of anxiety and depressed mood), which might influence the memory performance or the experience of memory deficits. A third aim was to conduct follow-up examinations after three years.

2. Patients and methods

2.1. Patients

Patients with subjective memory complaints, examined at the out-patient Memory clinic, University Hospital of Lund, Sweden, were recruited. The majority of the patients attending this Memory clinic are above 75 years but in the current study the focus was to examine patients younger than 75 years. The patients were either referred by their GP or attended of their own accord. Inclusion criteria were: (1) presence of memory complaints, (2) age between 35-75 years. Exclusion criteria were: (1) a previous diagnosis of organic dementia or other neurodegenerative brain disorder, (2) ongoing anti-dementia pharmacological treatment, (3) a prior history of stroke, (4) post-traumatic stress disorder, (5) long-term solvent exposure, long-term drug or alcohol abuse, (6) psychosis, bipolar disorder, significant depression or generalized anxiety disorder, (7) traumatic brain injury. Seventy-eight patients fulfilled the criteria. Nineteen of the 78 patients declined to participate resulting in a group of 59 (25 men, 34 women; age range, 35-73 years; mean age, 59.6±8.2 years (±S.D.). After three years, 43 patients were re-evaluated with the same neuropsychiatric and neuropsychological examinations as used at baseline. One patient had withdrawn consent and two were missing due to severe somatic disease. The patients diagnosed with dementia at baseline (n = 13) were followed clinically but not re-evaluated within the current study. There was one interim visit between baseline and the three year follow-up, however, not reported in this study.

The study was approved by the Research Ethical Committee and written consent was obtained from all participants.

2.2. Neuropsychiatric examination

The neuropsychiatric examinations were conducted by experienced psychiatrists (UP, LG). The assessments included a clinical interview with the patient, a standardized psychiatric assessment including the mini-mental state examination (MMSE), a physical/neurological examination and routine electrocardiogram (Folstein et al., 1975). The presence of depressive symptoms was rated in accordance with the Montgomery-Asberg depression scale (MADRS; Montgomery and Asberg, 1979). In the clinical interview the psychiatrists ascertained the presence of depressed mood and/or feelings of anxiety. Subjects were judged as having depressed mood if the ratings according to MADRS≥ 7 and/or if they reported “feeling sad” regularly

over the last month and/or if the clinical interview indicated sadness (Snaith et al., 1986). Feelings of anxiety were based on the patient's own report as well as clinical signs. Furthermore, the presence of psychosocial stress at work and/or at home was recorded if the patient reported experiences of daily stress over the last three months.

2.3. Neuropsychological examination

All subjects were evaluated using eight neuropsychological tests chosen from the Betula study, Sweden (Nilsson et al., 1997). The Betula study is a prospective cohort study on memory, health and aging. Verbal functions were examined through a multiple-choice vocabulary test and two tests of verbal fluency (the Betula study). Four tests of verbal episodic memory were used: test a) free immediate recall of 16 imperative sentences that were read aloud for the patients to follow and to memorize, test b) 16 similar sentences, also read aloud but with visible text which then had to be memorized. Delayed cued recall of nouns from the previously learned and performed sentences (test c and d) was tested after 30-40 minutes (the Betula study). Visuo-spatial construction ability was examined using block design (the Betula study; Wechsler, 1992). Besides the Betula tests, there was a test of visual episodic memory, the immediate recall of Rey complex figure test (RCFT; Meyers and Meyers, 1995). The neuropsychological test results for the Betula tests were compared with the age scaled normative data from the Betula study (Nilsson et al., 1997). The data used was from the first wave of 1000 subjects of the Betula study. The test result of the RCFT test was compared with the normative standard groups given in the manual (Meyers and Meyers, 1995).

2.4. Diagnostic procedure

Based on the neuropsychiatric and neuropsychological examinations, the patients were classified into three groups: patients with no significant memory deficits on the neuropsychological testing hereafter referred to as patients with SMI, patients with MCI and patients with a dementia disorder. The patients were classified into the SMI and the MCI groups on the basis of the neuropsychological test results. The operational criteria for SMI were (1) subjective memory complaint, (2) no significant deficits in any of the tests of episodic memory, verbal function or visuospatial construction ability. The criteria for MCI were (1) subjective memory complaint, (2)

impaired memory function documented by the results of the neuropsychological memory tests, the scores of which should be 1.5 S.D. or more, below age and estimated premorbid level of intellectual function. The premorbid level, as determined by a neuropsychologist's judgment, was based on the results of the test of vocabulary and on the years of education of the patient, (3) preserved general cognitive abilities, allowing for some cognitive impairment but diagnosed as no dementia by the psychiatrist, (4) essentially normal activities of daily living as determined by a clinical interview with the patient, and (5) not sufficiently impaired, cognitively and functionally, to meet either the DSM IV criteria for dementia or the criteria for Alzheimer's disease (AD), established by NINCDS-ADRDA (McKhann et al., 1984; APA, 1994). The MCI criteria included two clinical subtypes of MCI: (1) Amnestic MCI (aMCI) with objective memory impairment and absence of other cognitive disorders, (2) Multiple domains MCI (mdMCI) with objective memory impairment and a slight impairment in other cognitive domains (Petersen, 2004). Patients with a dementia disorder were diagnosed according to DSM IV criteria for dementia, NINCDS-ADRDA and consensus criteria for frontotemporal dementia (McKhann et al., 1984; APA, 1994; Brun et al., 1994). The diagnostic procedure also incorporated a standard battery of screening blood tests, CT or MRI scans, EEG and single photon emission computed tomography (SPECT).

2.5. Statistical analysis

Statistical analyses were conducted using SPSS version 14.0. Dichotomous variables were analyzed using McNemar test, χ^2-test and Fisher exact test. Parametric ANOVA (with a post-hoc Bonferroni) was used to test differences regarding age, years of education, duration of memory complaints and scores on MMSE. Group comparisons for small subgroups (aMCI vs. mdMCI) were performed using Mann-Whitney U-test.

3. Results

3.1. Baseline; clinical diagnoses and psychiatric symptoms

At baseline 24 patients (41%) had no significant cognitive impairment and fulfilled the SMI criteria, while 22 patients (37%) fulfilled the MCI criteria. Thirteen patients (22%) were diagnosed as having a dementia disorder. The characteristics at baseline of the 59 patients are shown in Table 1. Their mean age was 56.6 (SMI),

61.3 (MCI) and 62.4 (dementia) years with no significant differences between the three groups. No significant differences between the groups were noted in terms of their level of education. The mean duration of memory problems varied from 29.5 to 41.5 months. The SMI patients reported the longest duration of memory problems, however there was no significant difference between the groups. The mean score of MMSE differed significantly in the patients with SMI 29.1 (range 26-30), MCI 27.9 (range 24-30) and the dementia patients with the lowest 22.2 (range 19-30). A family history of dementia was reported in 50 - 64% with no significant differences between the groups. The use of psychotropic medication was low and very similar in the three groups. The MCI patients were divided in the two subtypes aMCI (n = 13) and mdMCI (n = 9). These subgroups are relatively small and are not presented in table 1. There were no significant differences between aMCI and mdMCI regarding sex, age, education or duration of memory problems. However, there was a difference regarding the scores on the MMSE (aMCI: mean = 28.5 ± 1.0 vs. mdMCI: mean = 27.2 ± 1.5, p = 0.030).

The patient's psychiatric symptoms and signs at baseline are presented in Table 2. In the SMI group the prevalence of depressed mood was 33%, psychosocial stress 71%, while the prevalence of feelings of anxiety was 63%. In the MCI group the prevalence of depressed mood was 27%, psychosocial stress 18% and the prevalence of feelings of anxiety was 27%. The prevalence of depressed mood in the patients with dementia was 23%, psychosocial stress 0%, while the prevalence of feelings of anxiety was 58%. There were significant associations between the three groups and experiences of psychosocial stress and feelings of anxiety. The prevalence of psychosocial stress was significantly higher in SMI vs. MCI and SMI vs. dementia. The prevalence of feelings of anxiety was significantly higher in SMI vs. MCI. Given the small numbers of MCI patients reporting depressed mood, psychosocial stress and/or feelings of anxiety it was not feasible to compare the two subgroups aMCI and mdMCI.

3.2. The 3-year follow-up, clinical diagnoses and psychiatric symptoms

The patients with SMI and MCI diagnoses at baseline were re-examined at a 3-year follow-up visit. Out of the 24 patients with SMI at baseline there were 23 patients at the 3-year follow-up visit, one had withdrawn consent. Twenty-one (88%) remained stable SMI while 2 had converted to MCI. Of the 22 patients with MCI at

baseline, 13 (60%) remained stable MCI, one had improved (not fulfilling the MCI criteria), while six (27%) were diagnosed with a dementia disorder. There were two MCI patients missing due to severe somatic disease.

The evaluation of the psychiatric symptoms and signs at the three year follow-up for the patients who remained stable SMI (n = 21) showed that the prevalence of psychosocial stress was 14%, feelings of anxiety 33% while the prevalence of depressed mood was 19%. Comparisons of the prevalence of the psychiatric symptoms between baseline and follow-up (21 stable patients) showed that psychosocial stress was significantly reduced, from 71% to 14% ($p < 0.001$), while the prevalence of anxiety was moderately reduced (62% vs. 33%; $p = 0.035$) and depressed mood was only slightly reduced (33% vs. 19%). In the MCI group (consisting of the 13 stable patients) the prevalence of depressed mode was 14%, feelings of anxiety was 46% while none of the patients reported psychosocial stress. Since the MCI group was reduced from 22 to 13 patients no comparisons of the prevalence between baseline and follow-up would be appropriate.

4. Discussion

The general goal of this study was to assess the neuropsychological and neuropsychiatric status of patients below 75 years seeking help for subjective memory complaints at an out-patient memory clinic. Furthermore, the purpose was to determine the prevalence of certain psychiatric conditions that might influence the memory performance or the experience of memory deficits, as well as to conduct follow-up examinations after three years.

The mean age at baseline was 59.6 years thus representing a fairly young population compared to several other studies (Petersen et al., 1999; Arnaiz et al., 2004; Maruff et al., 2004; Geslani et al., 2005). At baseline as many as 41% showed normal cognitive performance (SMI), while 37% fulfilled criteria for MCI and 22% were diagnosed with a dementia disorder. The number of clinical studies reporting data on patients with subjective memory complaint but with normal cognitive performance are rather limited (Vraamark Elberling et al., 2002; Elfgren et al., 2003; Alladi et al., 2006; Glodzik-Sobanska et al., 2007; Vestberg et al., 2007). Alladi and co-authors studied 166 consecutive referrals to a memory clinic and found that 18% of these patients performed normally on all memory and non-memory tests and were categorized as “worried well” (mean age 64.1 years). Vraamark Elberling et al. (2002)

studied all referred consecutive younger patients (mean age 47.6 years) to a memory clinic over a period of 54 months. Fifteen percent fulfilled the criteria for dementia, 17% had selective cognitive deficits, 13% with mild subjective cognitive symptoms could not be classified further, while as many as 55% had no cognitive deficits at all. These results confirm our findings that among rather young attendees at an out-patient memory clinic there is a fairly large number who do not fulfil the criteria for either MCI or dementia.

To our knowledge studies of the conversion rate of patients seeking help in a memory clinic because of memory problems, but showing no objective cognitive impairment are very rare (Lehrner et al., 2005; Glodzik-Sobanska et al., 2007; Vestberg et al., 2009). In our study we investigated the outcome of patients complaining of memory problems but with normal cognitive performance (SMI) as determined by neuropsychological examination. Of the SMI patients, studied for three years, 88% remained stable while two had converted to MCI, which corresponds to an annual conversion rate of 2.9%. None of the SMI patients developed dementia. In the study by Lehrner et al. (2005) the annual conversion rate to dementia for patients reporting memory problems but showing no memory deficit at testing was approximately 3%. In the Lehrner et al. (2005) study there was no report of conversion rates from the state of no memory deficit at baseline to MCI. Our data are important because they indicate that the risk of developing dementia among fairly young patients seeking help for subjective memory complaints but with no objective memory decline is small.

Among the MCI patients, 60% remained stable; one had improved (SMI), while 27% were diagnosed with a dementia disorder; corresponding to an annual conversion rate of 10%. This number is well within reported figures of earlier studies (Palmer et al., 2003, Bruscoli and Lovestone, 2004). In the review of 19 conversion studies by Bruscoli and Lovestone (2004) there was a mean annual conversion rate of 10% from MCI to dementia. However, there was a considerable heterogeneity within the reported studies, ranging from 2% to over 30% per year. These differences in the mean annual conversion rate were mostly due to the selection of the subjects, with the clinic attendees having a conversion rate twice that of the community living volunteers (15 vs. 7.5%) (Bruscoli et al., 2004).

At baseline there were significant associations between the three patient groups and certain psychiatric variables. The prevalence of psychosocial stress was highest

among the SMI patients (71%), whereas it was seen in only 18% of the MCI and in none of the dementia cases. The presence of psychosocial stress at work and/or at home was recorded when the patient reported experiences of daily stress during the last three months. The background of memory complaints when not related to dementia or MCI has been discussed and reported to be associated with a variety of psychiatric variables (Derouesne et al., 1999; Comijs et al., 2002). Derouesné et al. (1999) found that memory complaints were strongly related to affective status, mainly to severity of anxious symptomatology. In accordance with those results, our study showed that the symptom of anxiety was most frequent in the patients with SMI (63%), however, this was seen in only 27% of the MCI patients. Depressed mood was seen in about a third of all patients, but with no difference between the groups.

The 3-year follow-up assessment revealed diminished prevalence of psychiatric symptoms among the SMI patients; a significant decrease of the presence of psychosocial stress, only 14% compared to 71% at baseline. Furthermore, there was also a reduction of anxiety symptoms. Since the number of patients belonging to the MCI group was relatively changed, it was not possible to make a reliable comparison regarding psychiatric symptoms for this group. The high prevalence of psychosocial stress and feelings of anxiety among the SMI patients might be the reason why individuals suffer and seek help for memory problems although they do not show any significant decline on memory testing. Factors, such as depression and anxiety and/or stressful life events, may disturb the memory processes and interfere with the patients' evaluation of their memory function. The reduction of psychosocial stress and anxiety at the follow-up might be explained by the patients' benefit from earlier investigations and feeling relief of not having a dementia disorder. Thus, a thorough clinical examination is crucial in order to recognize these patients and to separate them from MCI patients with a higher risk of future dementia.

There are limitations in the present study. The size of the sample is fairly small. However, the groups have been carefully assessed at all visits by the same neuropsychologists and the same specialists in geriatric psychiatry. Another limitation is that while psychosocial stress, feelings of anxiety and depressed mood have been looked at as a possible cause of memory problems there might also be additional psychological factors that we were not aware of.

In conclusion, complaints of memory loss in middle-aged and young old patients should not be neglected. A thorough clinical and neuropsychological examination,

which considers individual differences in the premorbid cognitive level, is required. Our study indicates that the risk of developing dementia in patients with normal test results (SMI) is small within a three year span. It also confirms the risk that MCI patients will develop future dementia. Psychosocial stress and feelings of anxiety might be one explanation as to why these patients with normal cognitive performance experience memory problems. Thus, identifying the SMI patients may facilitate the planning of treatment.

Conflict of interest statement: None.

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Table 1. Characteristics at baseline of the 59 patients, n(%), mean±S.D.

	SMI	MCI	Dem	p <
Number	24 (41)	22 (37)	13 (22)	
Sex, male/female	9/15	10/12	6/7	0.821
Age, years	56.6±8.3	61.3±6.3	62.4±9.5	0.055
Range	35-69	50-71	37-73	
Education, years	12.0±2.4	11.9±2.7	10.7±2.8	0.307
Range	7-16	7-16	8-18	
Duration of memory problems, months				
	41.5±24.0	35.5±17.2	29.5±6.2	0.181
Range	12-84	12-60	24-36	
Family history of dem	12 (50)	14 (64)	7 (54)	0.639
MMSE scores	29.1±1.1	27.9±1.4	22.2±2.8	0.001
Range	26-30	24-30	19-30	
		SMI vs. Dem		0.001
		MCI vs. Dem		0.001
Medications use (n)				
Antidepressants	3	3	1	
Antidepr./Sedatives	0	0	2	
Sedatives/Hypnotics	1	2	0	

Note: dem = dementia

Table 2. Psychiatric symptoms and signs at baseline, n; n(%)

	SMI	MCI	Dem	All X^2, p <	SMI/MCI p <	SMI/Dem p <	MCI/Dem p <
Number	24	22	13				
Depressed mood							
	8 (33)	6 (27)	3 (23)	0.813			
Psychosocial stress							
	17 (71)	4 (18)	0 (0)	0.001	0.001	0.001	0.274
Feelings of anxiety							
	15 (63)	6 (27)	7 (58)	0.0410	0.021	0.544	0.139