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The Concealing effect of Major depression And other Chronic diseases on Metacognition of patients with Mild Alzheimer's disease, A cross-sectional study

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Abstract:

Background: Metacognition is a very important variable to improve the quality of life in patients with Alzheimer's disease (AD), also patients with Major depression are proved to have significant metacognitive awareness deficits and since depression is a common comorbidity in early AD we need to explore the effect of depression on metacognition of those patients. **Methods:** a sample of 64 patients with mild Alzheimer's disease were recruited and divided into a group of patients with comorbid depression and a control group having only mild Alzheimer's with no depression, they were subjected to detailed history taking, psychometric tests for cognitive functions as MMSE, MoCA, ACE III, for depression the Cornell depression in dementia scale (CSDD) and for metacognition the metacognitive awareness inventory (MAI). **Results:** A significant inverse correlation between prevalence and the severity of depression and the metacognitive awareness total and sub scores, also a significant correlation between the severity of cognitive impairment and the metacognitive awareness scores.

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chronic diseases were significantly associated with MAI scores, while diabetes showed direct correlation with total MAI scores, ischemic heart disease showed inverse correlation with total MAI scores, also hypertension, ischemic heart disease and regular intake of antiplatelet were associated with higher prevalence of depression in patients with mild Alzheimer disease. **Conclusions:** Metacognition is a very important variable in AD that needs to be assessed comprehensively given into account also assessing any depressive symptoms that might affect it using valid reliable scales as the MAI and the CSDD as our study showed that it's possible that depression might conceal the severity of metacognitive deficits in patients with mild Alzheimer's disease.

Keywords: Alzheimer's disease, metacognition, depression, CSDD, Metacognitive inventory

Introduction

Alzheimer's disease (AD) is one of the most important medical concerns all over the world nowadays, it is one of the top ten causes of death and disability in the elderly according to the world health organization (WHO) .(1, 2) AD is the most common cause of dementia, accounting for two thirds of patients with dementia worldwide.(3)

Given that the expected elderly population in Egypt in the year 2030 will be 7.7 million, therefore dementia and more specifically AD is becoming an escalating public health problem , but unfortunately the advances in the research of AD in Egypt is not coping with such escalating burden.(4)

What is Metacognition?

Metacognition is the ability of the person to monitor his own cognitive processes and to regulate it. It is very important for adaptation in order to adjust the person's behaviors and improve his social interactions, also to be able and willing to improve deficits in cognitive processes as it is responsible for this level of awareness.(5) So, it is a very vital variable to monitor in order to improve quality of life of patients with dementia. (6)

Metacognition can be assessed by measuring the difference between predicted level of performance by the patient and the actual level achieved on neuropsychological tests. (7)

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Metacognition in Alzheimer's disease (AD)

It has been known fact for many years that patients with AD mostly (25% to 81%) lack insight of their cognitive deficits i.e., have metacognitive deficits, this was first assessed using subjective methods but recently there is more focus on the objective one. The prevalence and frequency of such metacognitive deficits increases with the progression of the AD, and this affects treatment adherence and consequently the overall prognosis.(7)

Metacognitive disturbance signifies affection of brain regions including frontal, midline, and temporal regions that are crucial for self-assessment. Specifically, decreased insight of memory loss is associated with reduced connectivity between the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) and prefrontal hypoperfusion, also the ACC is responsible for error detection, and response to them, a Meta analysis recently proved that these cortical midline regions are the main neural basis of self-referential cognitive functions.(8)

Depression in patients with Alzheimer's disease

The prevalence of neuropsychiatric symptoms in AD are mostly 3 to 4 times higher than same age persons with no dementia, a meta-analysis showed that the prevalence of depression in mild AD was 38%.(9, 10)

The diagnosis of depression in those affected by AD, is challenging. Elderly patients may not meet full Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria for major depressive disorder.

They frequently do not report a depressed mood, but actually they mostly present with somatic symptoms, insomnia, anorexia and fatigue.(11)

Being a challenging diagnosis as previously mentioned, A set of diagnostic criteria for depression in patients with dementia was developed in 2001 by the National Institute of Mental Health.

The number of symptoms required for a diagnosis of depression in DSM decreased from five to three, also cognitive symptoms were eliminated. Anhedonia criteria highlighted the decreased pleasure with social activities, other symptoms include, social isolation, and irritability, were the added new symptoms. (12)

Causes of depression in AD include both structural and functional causes as higher strychnine-sensitive glycine receptor (GlyRS) functioning and decrease of N-

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methyl-d-aspartate (NMDA) receptor, neurodegeneration and CSF tau levels, as well as other environmental causes one undeniable cause is the reaction to cognitive decline.(13)

Metacognition in depression

Studies showed a negative metacognitive bias in patients with depression. Particularly in tasks including executive functions as the Stroop task object recognition, general knowledge, verbal memory facial emotion recognition, judgment and adjective recognition. This can be explained by the selective attention to negative stimuli, or the increased salience of negative memories. (14)

Cognitive affection of patients with Alzheimer's with comorbid depression is a possibility. Depression already includes cognitive symptoms as impaired short-term memory and attention. (15)

Based on the three previously discussed findings in literature, The metacognitive disturbance in AD (patients predicting more than their actual performance), The metacognitive disturbance in Depression (patients predicting less than their actual performance) and the prevalence of depression as common comorbidity in Alzheimer's patients, We hypothesize that major depression might have a significant effect that can conceal or underestimate the metacognitive deficits in patients with Mild Alzheimer's disease.

Materials and Methods

Study design: A cross-sectional study.

Participants: A sample size of 64 patients With Mild Alzheimer's disease.

Patients were recruited from "Memory and neurocognitive disorders specialized clinic" at Nariman University Hospital, and also from private clinics, elderly nursery homes and community dwelling older adults in Alexandria and nearby governorates.

Categorized in to two groups :

Group 1: The patients with mild Alzheimer's and comorbid major depression (n =**19**).

Group 2 **(control group):** the patients with mild Alzheimer's only with no major depression (n =**45**)

The Ethics committee at Alexandria university faculty of medicine approved this study: Serial number of approvals: 0201782

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Recruited patients were subjected to:

I) Detailed history taking including information about personal and demographic data, age of onset of symptoms, course of illness, nature of cognitive, behavioral, and other psychiatric symptoms, past medical history of other comorbidities, family history of dementia, drug history, history of substance use and special habits.

II) Full neurological, mental state and physical examination.

III) Lab investigations and conventional radiological imaging studies, whenever needed to exclude other etiologies of neurocognitive impairment and confirm the diagnosis.

The diagnosis of AD is established based on the forementioned comprehensive clinical, laboratory and radiological assessment and in the view of the latest version of diagnostic and statistical manual of mental disorders (DSM-5-TR). The determination of the disease stage was made based on standardized assessment staging scales such as clinical dementia rating scale (CDR) and global deterioration scale (GDS).

The following was done for the recruited patients:

A. Baseline psychometric assessment scales for cognitive assessment including:

- Mini-Mental State Examination (MMSE), and Montreal Cognitive

Assessment (MoCA), (which are of the most commonly used tools to assess general cognitive performance in research, clinical and community settings. They are

generally convenient and can be easily administered. They entail evaluations for several cognitive domains and are of great value in detecting and monitoring AD patients.(16-18)

- Addenbrooke's Cognitive Examination – ACE-III which is a valuable psychometric tool for assessment of neurocognitive impairments and is considered sensitive for early stages of AD. It includes tests for memory, orientation, attention, language, visuospatial and visual perceptual skills. It has the advantage of overcoming some of the neuropsychological omissions evident in other tests as MMSE.(19)

- Metacognitive Awareness Inventory (MAI), (28) which is a valid and reliable tool to evaluate the patients' knowledge and awareness about their own cognition and thought process 52 items, 8 subscales of :

Declarative knowledge, Procedural knowledge, Conditional knowledge, Planning, Comprehension monitoring, Information management strategies, Debugging strategies and Evaluation.

- **The Cornell Scale for Depression in Dementia (CSDD)** was specifically developed to assess signs and symptoms of major depression in demented patients, Scores above 18 indicate a definite major depression.

The CSDD is reliable for those with a Mini-Mental State Examination. (MMSE) score of 17 or more; it has not been validated in any group of people with MMSE less than 17.

Results

Statistical analysis of the data

Data was fed to the computer and analyzed using IBM SPSS software package version 20.0. **(**Armonk, NY: IBM Corp**)**. Categorical data were represented as numbers and percentages. For continuous data, they were tested for normality by the **Kolmogorov-Smirnov test**. Quantitative data were expressed as range (minimum and maximum), mean, standard deviation and median for not normally distributed quantitative variables **Mann Whitney test** was used to compare between No depression and depression **Spearman coefficient** was used to correlate between not

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normally distributed quantitative variables. The significance of the obtained results was judged at the 5% level.

Table (1): Correlation between Cornell Depression in Dementia (CSDD) with MAI MMSE, MoCA and ACE III (n = 19)

Cornell Depression in Dementia vs.	r_s	p
MAI total score	-0.993*	<0.001*
Declarative knowledge subscale score	-0.878*	<0.001*
Procedural knowledge subscale score	-0.564*	0.012*
Conditional knowledge subscale score	-0.771*	<0.001*
Planning subscale score	-0.554*	0.014*
Comprehension monitoring subscale score	-0.611*	0.005*
Information management subscale score	-0.729*	<0.001*
Debugging strategies subscale	-0.753*	<0.001*
Evaluation score	-0.932*	<0.001*
MMSE	-0.118	0.630
MoCA	-0.029	0.908
ACE III	0.034	0.891

r_s: Spearman coefficient *: Statistically significant at $p \leq 0.05$

We found a significant inverse correlation between the severity of depression on Cornell scale and the total scores on the metacognitive awareness inventory (MAI)

Also, a significant inverse correlation between depression severity and all the eight MAI subscales

There was no significant correlation between depression severity on Cornell depression in dementia scale and the severity of cognitive impairment on MMSE, MoCA or the ACE III scales (Table 1)

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Table (2): Relation between Cornell Depression in Dementia with MAI score, MMSE, MoCA and ACE III (n = 64)

	Cornell depression in dementia		U	P
	No depression (n = 45)	Depression (n = 19)		
MAI total score				
Median (Min. – Max.)	38.0 (14.0 – 52.0)	20.0 (12.0 – 34.0)	156.50*	<0.001*
Declarative knowledge				
Median (Min. – Max.)	7 (4 – 8)	3 (1 – 5)	24.00*	<0.001*
Procedural knowledge				
Median (Min. – Max.)	3 (1 – 4)	2 (1 – 4)	284.50*	0.030*
Conditional knowledge				
Median (Min. – Max.)	4 (1 – 5)	2 (1 – 4)	200.50*	0.001*
Planning subscale score				
Median (Min. – Max.)	4 (1 – 7)	3 (1 – 4)	227.00*	0.003*
Comprehension monitoring				
Median (Min. – Max.)	4 (1 – 7)	3 (2 – 5)	242.50*	0.006*
Information management				
Median (Min. – Max.)	7 (2 – 10)	3 (2 – 8)	131.50*	<0.001*
Debugging strategies				
Median (Min. – Max.)	4 (1 – 5)	2 (1 – 3)	172.50*	<0.001*
Evaluation score				
Median (Min. – Max.)	4 (1 – 6)	2 (1 – 5)	217.00*	0.002*
MMSE				
Median (Min. – Max.)	21 (20 – 23)	21 (20 – 23)	359.50	0.292

MoCA				
Median (Min. – Max.)	18 (17 – 20)	18 (17 – 20)	407.50	0.758
ACE III				
Median (Min. – Max.)	76 (73 – 80)	75 (73 – 80)	391.50	0.594
Age (years)				
Median (Min. – Max.)	70.0 (63.0 – 84.0)	67.0 (64.0 – 78.0)	U= 367.00	
Duration of illness				
Median (Min. – Max.)	1.0 (0.50 – 4.0)	2.0 (1.0 – 4.0)	U= 304.00	0.372
Marital status				
Single	1 (2.2%)	0 (0.0%)		0.050
Married	35 (77.8%)	13 (68.4%)	FET=	0.478
Divorced	2 (4.4%)	0 (0.0%)	2.758	0.789
Widow	7 (15.6%)	6 (31.6%)		^{FE}p=1.000
Smoking index				
Non-smoker	34 (75.6%)	13 (68.4%)		
Smoker	8 (17.8%)	5 (26.3%)	FET=	
Ex-Smoker	3 (6.7%)	1 (5.3%)	0.792	
Family history of AD	9 (20.0%)	3 (15.8%)	χ^2=0.155	

U: Mann Whitney test; p: p value for Relation between Cornell Depression in Dementia with MMSE, MoCA and ACE III
*: Statistically significant at $p \leq 0.05$

We found a significant inverse correlation between depression prevalence and all the eight MAI subscales

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This study also showed no significant correlation between the presence or absence of depression with the severity of cognitive impairment on MMSE, MoCA or the ACE III

There was no significant effect of the Age, duration of illness, marital status, smoking index or family history of Alzheimer's disease on the prevalence of depression in patients with Mild Alzheimer's disease. (Table 2)

Table (3): Correlation between MAI with MMSE, MoCA and ACE III (n = 64)

	MMSE		MoCA		ACE III	
	r_s	p	r_s	p	r_s	P
MAI total score	-0.566*	<0.001*	-0.526*	<0.001*	-0.519*	<0.001*
Declarative knowledge subscale score	-0.383*	0.002*	-0.391*	0.001*	-0.401*	0.001*
Procedural knowledge subscale score	-0.612*	<0.001*	-0.525*	<0.001*	-0.501*	<0.001*
Conditional knowledge subscale score	-0.616*	<0.001*	-0.541*	<0.001*	-0.519*	<0.001*
Planning subscale score	-0.672*	<0.001*	-0.600*	<0.001*	-0.601*	<0.001*
Comprehension monitoring subscale score	-0.689*	<0.001*	-0.663*	<0.001*	-0.645*	<0.001*
Information management subscale score	-0.496*	<0.001*	-0.504*	<0.001*	-0.466*	<0.001*
Debugging strategies subscale	-0.553*	<0.001*	-0.472*	<0.001*	-0.474*	<0.001*
Evaluation score	-0.565*	<0.001*	-0.503*	<0.001*	-0.502*	<0.001*

There was a significant inverse correlation between total metacognitive awareness inventory score MAI and all its eight subscales with the severity of cognitive impairment on the MMSE, MoCA and the ACE III scales (Table 3)

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Table (4): Relation between MAI total score with medications and comorbidities (n = 64)

		No.	Median (Min. – Max.)	U	p
Medications	**Anti-hypertensive**				
	No	**29**	30.0 (14.0 – 52.0)	502.50	0.946
	Yes	**35**	28.0 (12.0 – 51.0)		
	Oral hypoglycemic				
	No	**43**	28.0 (14.0 – 52.0)	309.50*	0.042*
	Yes	**21**	38.0 (12.0 – 51.0)		
	Anti-platelets				
	No	**39**	35.0 (14.0 – 52.0)	326.50*	0.027*
	Yes	**25**	25.0 (12.0 – 49.0)		
	Statins				
	No	**57**	34.0 (12.0 – 51.0)	169.50	0.527
	Yes	**7**	28.0 (14.0 – 52.0)		
	Thyroxin sodium				
	No	**60**	29.50 (12.0 – 52.0)	99.00	0.583
	Yes	**4**	26.0 (15.0 – 49.0)		
	Analgesics				
	No	**58**	29.50 (12.0 – 51.0)	167.00	0.884
	Yes	**6**	35.50 (14.0 – 52.0)		
	Anticoagulants				
	No	**62**	29.50 (12.0 – 52.0)	61.500	0.984
	Yes	**2**	31.0 (28.0 – 34.0)		
Comorbidities	**Hypertension**				
	No	**28**	32.0 (14.0 – 52.0)	469.50	0.640
	Yes	**36**	28.0 (12.0 – 51.0)		
	Diabetes				
	No	**43**	28.0 (14.0 – 52.0)	309.50*	0.042*
	Yes	**21**	38.0 (12.0 – 51.0)		
	Ischemic Heart disease				
	No	**46**	37.50 (14.0 – 52.0)	183.00*	0.001*
	Yes	**18**	20.50 (12.0 – 38.0)		
	Thyroid disease				
	No	**60**	29.50 (12.0 – 52.0)	99.00	0.583
	Yes	**4**	26.0 (15.0 – 49.0)		

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History of Cancer				
No	**61**	29.0 (12.0 – 52.0)	83.00	0.811
Yes	**3**	36.0 (16.0 – 38.0)		
Osteoarthritis				
No	**53**	29.0 (12.0 – 51.0)	280.00	0.838
Yes	**11**	34.0 (14.0 – 52.0)		

U: Mann Whitney test
p: p value for Relation between MAI total score with medications and comorbidities
*: Statistically significant at $p \leq 0.05$

The metacognitive awareness (MAI) total score showed significant direct correlation with the comorbidity of diabetes (with median MAI total score in patients without diabetes was 28 and in patients with diabetes was 38) while it showed significant inverse correlation with ischemic heart disease (with median MAI total score in patient without ischemic heart disease was 37.5 and in patients with ischemic heart disease was 20.5) (Table 4)

Table (5): Relation between Cornell Depression in Dementia with medications and comorbidities (n = 64)

	Cornell depression in dementia			
	No depression (n = 45)	**Depression (n = 19)**	**χ^2**	**p**
Medications				
Anti-hypertensive	21 (46.7%)	14 (73.7%)	3.935*	0.047*
Oral hypoglycemic	17 (37.8%)	4 (21.1%)	1.695	0.193
Anti-platelets	8 (17.8%)	17 (89.5%)	28.849*	<0.001*
Statins	3 (6.7%)	4 (21.1%)	2.838	FEp=0.182
Thyroxin sodium	4 (8.9%)	0 (0.0%)	1.801	FEp=0.309
Analgesics	5 (11.1%)	1 (5.3%)	0.538	FEp=0.660
Anticoagulants	1 (2.2%)	1 (5.3%)	0.408	FEp=0.509
Comorbidities				

Hypertension	21 (46.7%)	15 (78.9%)	5.657*	0.017*
Diabetes	17 (37.8%)	4 (21.1%)	1.695	0.193
Ischemic heart disease	1 (2.2%)	17 (89.5%)	50.311*	<0.001*
Thyroid disease	4 (8.9%)	0 (0.0%)	1.801	FEp=0.309
History of cancer	3 (6.7%)	0 (0.0%)	1.329	FEp=0.549
Osteoarthritis	9 (20.0%)	2 (10.5%)	0.842	FEp=0.483

χ^2: **Chi square test** **FET: Fisher Exact test**
p: p value for Relation between Cornell Depression in Dementia with MMSE, MoCA and ACE III
*: Statistically significant at $p \leq 0.05$

This study showed a significant correlation between the prevalence of depression and having certain comorbidities as Hypertension (present in 79% of depressed patients and only in 47% of non-depressed patients) and Ischemic heart disease (present in 89.5% of depressed patients and only 2.2% of non-depressed patients)and only in while it showed no significant correlation with diabetes Also being compliant on certain drugs mainly the anti-hypertensives (in 74% of depressed patients and only 47% of non-depressed patients), The antiplatelets (in 89.5% of depressed patients while only in 18 % of the non-depressed patients) was significantly Associated with depression in patients with mild Alzheimer's disease On the other hand there was no significant correlation between compliance on oral hypoglycemic and the prevalence of depression in patients with mild Alzheimer's disease (Table 5).

Discussion

According to our results there was a significant inverse correlation between metacognitive awareness and depression severity ; While this point was not clearly settled in the literature as the findings were conflicting between some studies showing that patients with better insight and metacognition might present with more depressive symptoms as a psychological reaction to their condition while other studies showing no significant Association at all between them.(7, 20-27) On the other hand, fewer studies showed that impaired metacognition was related to more depression.(28)

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Since that the etiology of depression in Alzheimer's is heterogenous, therefore explaining the correlation between metacognition and depression in AD by only the fact that the effect of awareness and insight of the cognitive impairment in patients with AD is mainly responsible for the depressive symptoms is not a satisfying explanation and completely missing all the other environmental and biological causes for depression in those patients.

As it remains unclear whether intact metacognition in early AD is linked with depression or if, depression actually occurs independently of the level of awareness and insight, as a result of the neurodegenerative process or other personal and environmental factors.(7)

So, we suggest a new interpretation viewing the correlation from a different angle, instead of only observing the effects of metacognition in Alzheimer on the depressive symptoms as in the previously mentioned studies, we suggest observing the opposite direction which is the possible effect of depression with different and heterogenous etiologies on the metacognition of the same patients with Alzheimer's disease.

Also, our study showed that metacognitive awareness was significantly affected by the level of cognitive impairment which might be explained by a recent study that showed that Aβ predicted longitudinal changes in memory awareness, such that awareness decreased faster in participants with increased Aβ burden.

This study showed a significant correlation between the prevalence of depression and Ischemic heart disease and this was in agreement with a study published recently in October 2023 that included 49,735 participants that confirmed that patients with both cardiac disease and depression are three times more likely to have AD .(29)

Also, a very recent case report published on February 2024 confirmed that ischemic heart disease is an important risk factor for depression.(30) Given that hypertension is a known risk factor for dementia, it was also proved in a recent systemic review published in November 2023 that high hypertension is a significant risk factor for developing depression in elderly.(31, 32)

Regarding the finding that there is higher levels of depression in patients on antiplatelets (mostly prophylactic) yet not having cardiac disease, this finding in our study can be explained by the conclusion of a recent meta-analysis that confirmed Aspirin use is risk factor for depression especially if used for duration more than 5 years.(33)

Metacognitive awareness (MAI) total score showed significant direct correlation with the comorbidity of diabetes while it showed significant inverse correlation with ischemic heart disease.

The inverse correlation with ischemic heart disease can be explained by the fact that ischemic heart disease was more associated with depression and that depression was inversely correlated with MAI total scores because of the negative bias with depressed patients, patients with depression report more severe cognitive impairment than what's actually detected by objective tests as they underestimate their cognitive performance. (34)

Regarding the significant direct correlation between MAI total scores with diabetes which was not matching the actual performance of the patients, this can be explained by the documented cognitive impairment associated with diabetes including metacognition even in diabetic patients with only family history of diabetes. (35)

Limitations

The sample size of 64 patients with mild Alzheimer's disease, only 19 of them having comorbid depression as one of the main limitations in our study so we recommend observing this correlation on a larger scale study with a larger sample size.

Conclusions

Metacognition is a very vital variable in cases of Alzheimer's disease that needs to be assessed comprehensively given into account also assessing any depressive symptoms that might affect it using valid reliable scales as the MAI and the CSDD as our study showed that it's possible that depression might conceal the severity of metacognitive deficits in patients with mild Alzheimer's disease.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Conflict of interest: The authors declare that there is no conflict of interest.

The Ethics committee at Alexandria university faculty of medicine approved this study.

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