DEPRESSION AS PRODROME IN ALZHEIMER'S DISEASE

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Abstract: *Depression symptoms may predict dementia. The objective of this study was to evaluate multiple measures of depressive symptoms and cognitive impairment in order to determine which model, based on multiple criteria will predict the evolution towards Alzheimer's disease (AD).*

INTRODUCTION

Alzheimer's disease is the most frequent cause of dementia. Neurodegeneration at microscopic level (amyloid plaques and neurofibrillary tangles) in Alzheimer disease is different from other diseases of the brain and also from the normal process of aging. As a frequent clinical entity in aged population, it is important to detect it at early stages where we can have best results with different therapies. We can also identify AD markers in healthy cognitive individuals so it posses the problem of incipient, asymptomatic subjects who are normal from the clinical point of view. In these cases, the first signs of dementia are attributed to other factors, such as anxiety and depression due to stress that came from the everyday life events.

We can identify markers of AD in undiagnosed individuals because they are in good cognitive condition and generally speaking are asymptomatic so the scores for dementia on rating scale are at low levels. Considering this, we can say that difficulties occur when we try differential diagnosis between normal aging and dementia and also when we self rate mood changes in the elderly.(1)

There are evidences that depression symptoms may mask but also may predict dementia. Alzheimer's disease and depression share symptoms and many people with Alzheimer's disease have nonspecific depressive symptoms alike: loss of interest, active social withdrawal, cognitive impairment and sleep disturbances. We can say that depression is defined as an affective-cognitive syndrome which can have somatic or physiological manifestations and almost the same we can say about dementia.(2)

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (American Psychiatric Association, 2000) lists the criteria for the diagnosis of depression.(3) These criteria are frequently used as the golden standard by which older patients' depressive symptoms are assessed in clinical settings (American Psychiatric Association, 2000.) According to these diagnosis system, five criteria from nine must be present nearly every day during a two-week period and symptoms and signs have a significant change from previous levels of functioning: (1) depressed, sad, or irritable mood, (2) anhedonia or diminished pleasure in activities that are usually pleasurable, (3) feelings of worthlessness or excessive guilt, (4) diminished concentration and difficulty with thinking, (5) suicidal ideas or suicide attempts, (6) fatigue and loss of energy, (7) modified appetite and consecutive modified weight, (8) insomnia or in some cases hypersomnia, and (9) psychomotor manifestation like agitation. The severity of depressive episodes range from mild to severe and, in some cases can have psychotic features (delusions of guilt or worthlessness). Also, depressive symptomatology can be in comorbidity with anxiety. We can identify some particularities related to age of patients like somatic concerns in older patients that are difficult to differentiate from somatic symptoms of normal aging.

The genesis of clinical manifestation in dementia and depression can have different etiologies, such as biological factors (neurotransmitter and brain metabolism anomalies) and psychological and social factors like cognitive distortions, stressful life events and chronic stress.

In dementia we can describe an early stage, with fewer symptoms, a middle stage with behavioural manifestations and a late stage that is rich in symptomatology and also requires surveillance of the subject. In early stages, patients live independently and cognitive decline goes undetected by the others. In the second stage, we can detect depressive and anxiety symptoms and a clinically significant level of apathy that is in contrast with episodes of wandering and agitation that can be with or without other behavioural symptoms. In the third stage, the patient requires close supervision to prevent incidents with others or self-harm. Progression through these three stages depends on several factors (age of onset, genetic vulnerability, chronic stressors). Each stage has an average time of 4-5 years for each. To evaluate in its broader sense the functioning in cognitive domain and other mental states I will use assessments made with the Mini Mental State Examination (MMSE) scale. On MMSE, the maximum score is 30 and low scores mean significant cognitive impairment as it can be seen in table no. 1.

Table no. 1. Dementia Stages

Mild Cognitive Impairment MMSE 26-30	**Preclinical stage of dementia**
Moderate Stage MMSE 10-21	Difficulties with complex activities
Middle stageMMSE 10-21	Difficulties with usual home activities
Severe - Late Stage MMSE 0-9	Requires considerable assistance

To detect depression in comorbidity with Alzheimer's disease one has to use evaluation scales, such as Geriatric Depression Scale, self-reports of patients and the clinical evaluation made by the medical staff.

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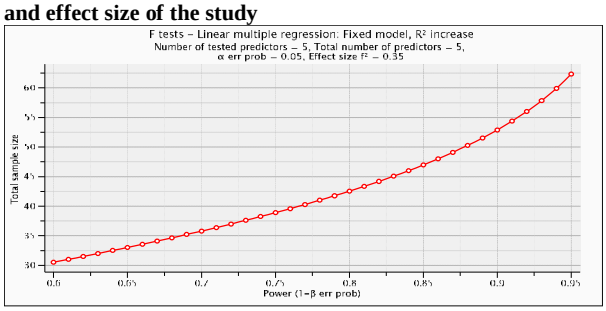
MATERIALS AND METHODS

The population of the study consist of 40 subjects. The number was computed based on effect size and power analysis from previous studies. This is a nonexperiemental, observational design according to ethical regulations, based on the following inclusion criteria:

- Age between 50 and 90 years old;
- Diagnosis of dementia, Alzheimer type;
- Depressive symptomatology or diagnosis in the psychiatric history;
- Cognitive impairment level that allow to perform the study;
- No medical conditions that are unstable and can interfere with evaluations;
- No comorbidity with substance abuse, dependence syndrome or withdrawal syndrome.

Group population consists of 42 subjects with a mean age of 72.4 years who receive a diagnosis of dementia and have also symptoms and signs of depressive episodes in their medical history. The number of the patients has been chosen in order to have a medium effect size and medium power of the study that uses multiple regression analysis as the main method.

Figure no. 1. Sample size required to obtain specific power and effect size of the study



Several depression screening tools have been developed and several studies show that Geriatric Depression Scale (GDS) (4) is a very good detector for subsyndromal depressive symptoms and for major depressive episodes.

The GDS is a 15-item self-report depression screening tool and it is validated for older subjects who have mild to moderate cognitive impairment. Responses on item scales are dichotomous (yes/no), a score of at least 11 shows the first evidence for depression and a score of 6 to 9 shows possible depression. The scale has questions about somatic complains that rise the problem of confusion with the same complains from a medical disorder.

For cognitive evaluation, the following tools assessment were used: MMSE - Mini Mental State Examination (5) for cognitive evaluation (5,6) and CDT - clock drawing test (7) in order to improve sensibility and specificity of cognitive decline detection (8), Instrumental Activity of Daily Living (IADL) to evaluate global functioning in major areas, Global Assessment of Functioning (GAF) and Global Assessment of Relational Functioning (GARF). For analysis, the following variables were taken into account: years at dementia onset, years at the onset of depressive episode, somatic complains, anxiety and depressive mood.(9)

RESULTS AND DISCUSSIONS

A. Correlation study between different evaluations of dementia

The study identifies the links between different variables that describe cognitive functioning, executive functioning and functioning in all major areas (table no. 1).

Table no. 1. Correlations IADL-MMSE

		IADL	MMSE
IADL	Pearson Correlation	1	**.696****
	Sig. (2-tailed)		.000
	N	42	42

**Correlation is significant at the 0.01 level (2-tailed).

I identified significant correlations between the results at MMSE and the activity of daily living that gives the residual functional capacity of the patients regarding their usual activities. The results show that cognitive impairment is a reflection of reduced capacity of functioning on usual activities.

Table no. 2. Correlations MMSE-CDT

		MMSE	CDT_SHULMAN
MMSE	Pearson Correlation	1	**.590****
	**Correlation is significant at the 0.01 level (2-tailed).		

I found a significant correlation (r=0.59 la p<0.01 two tailed) between the results at MMSE and the results at CDT (table no. 2). If using these three instruments to evaluate dementia we improve specificity and sensibility of diagnosis and also we decrease the level of type I and type II errors.

There is also a consistent comorbidity at the onset of depressive and dementia symptomatology. This is supported by the significant correlation (r=0.9, p<0.05) between the age at the onset of dementia and the age at the onset of depressive syndrome. These results are at high levels due to specified criteria for depression in patients who will further develop dementia.

Table no. 3. Correlation between the age at onset of dementia and of depressive symptomatology

		ONSET YEAR OF DEMENTIA	ONSET YEAR OF DEPRESSION
Pearson Correlation	DEMENTIA ONSET	1.000	.918
	DEPRESSION ONSET	.918	1.000

If we rely on relative common onset of clinical syndromes we can say that the depressive episode can be a predictor for dementia, at least in some well documented cases (table no. 3). For prediction of dementia based on depressive syndrome, I used different prediction models in order to improve the accuracy of results (table no. 4).

Table no. 4. Prediction model

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics					Durbin-Watson
					R Square Change	F Change	df1	df2	Sig. F Change	
1	,918[a]	,842	,839	3,255	,842	234,992	1	44	,000	2,071

a. Predictors: (Constant), Year onset of depression
b. Dependent Variable: Year onset of dementia
the level of R squared showed a good value for prediction of dementia onset in cases where patients showed consistent signs of depressive disorder at the beginning of the continuous cognitive decline.

B. Depression as prodrome of Alzheimer's disease

I elaborate the regression model based on the following assumptions of general linear model: linearity, normality of residuals and equal variance. Accuracy of the model depends on the evaluation of dependent and independent variables that are made with the aid of evaluation scale I have already described. I elaborated several models with increased complexity. I achieved this by adding variables. The dependent

variable was the cognitive evaluation with mental state examination scale, widely accepted in clinical settings for patients with dementia. The independent variables for regression models are those represented in table no. 5.

Table no. 5. Models for regression analysis based on different predictors

Model	Variables Entered	Method
1	NO._EPISODES	Enter
2	GAF_SCALE	Enter
3	GARF_SCALE	Enter
4	GER_DEP_SCALE	Enter
5	MOOD	Enter
6	SUBJ_AGE	Enter
7	ANERGIA	Enter
8	ANXIETY	Enter
9	SOMATIC CONCERNS	Enter

After regression analysis with the specified variables, the following results were obtained (table no. 6).

Table no. 6. Regression analysis results

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.451[a]	.203	.166	3.151
2	.500[b]	.250	.196	3.093
3	.511[c]	.261	.189	3.107
4	.518[d]	.268	.177	3.131
5	.518[e]	.268	.155	3.171
6	.677[f]	.459	.359	2.763
7	.691[g]	.478	.365	2.749
8	.698[h]	.487	.359	2.762
9	.701[i]	.491	.346	2.791

a. Predictors: (Constant), No. of episodes_ depression onset year
b. Predictors: (Constant), No. of episodes_ depression onset year, GAF_scale
c. Predictors: (Constant), No. of episodes_ depression onset year, GAF_Scale, GARF_Scale
d. Predictors: (Constant), No. of episodes_ depression onset year, GAF_Scale, GARF_Scale, GER_DEP_Scale
e. Predictors: (Constant), No. of episodes_ depression onset year, GAF_Scale, GARF_Scale, GER_DEP_Scale, Mood
f. Predictors: (Constant), No. of episodes_ depression onset year, GAF_Scale, GARF_Scale, GER_DEP_Scale, Mood, Age,
g. Predictors: (Constant), No. of episodes_ depression onset year, GAF_Scale, GARF_Scale, GER_DEP_Scale, Mood, Age, Anergia
h. Predictors: (Constant), No. of episodes_ depression onset year, GAF_Scale, GARF_Scale, GER_DEP_Scale, Mood, Age, Anergia, Anxiety
i. Predictors: (Constant), No. of episodes_ depression onset year, GAF_Scale, GARF_Scale, GER_DEP_Scale, Mood, Age, Anergia, Anxiety, Somatisation
j. Dependent Variable: MMSE

Data analysis shows that the accuracy of the models - estimated by R coefficients improves with the addition of information form variables and reaches a significant level.

Variance of values calculated through binding of variables in models, described by R^2 coefficient adjusted for number of the patients.

There has been assessed the utility of predictors by performing regression with or without specified variable – for example depression or somatic concerns.

Durbin-Watson test has been use to compute the errors in order to see whether the regression model is accurate.

CONCLUSIONS

Depressive disorder is frequently associated with memory impairment related to older age. While depression at middle age could be a risk factor for development of dementia, at older ages, depression can took the place of an early sign or it can be a predictor for Alzheimer dementia. Also, untreated depressive episodes that span more than six months could be a risk factor for the development of dementia. The elaborated complex models show good consistency and accuracy in the detection for progression of cognitive, deficit masked by depression, to Alzheimer dementia. We have to pay attention that depressive episodes has cognitive deficit but also we can have initial cognitive impairment followed by depression, as a distinct entity, results that confirm previous research.(10)

The limit of this study consists of sample size, the need for additional imagistic testing in order to improve the diagnosis of dementia.

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