Major depressive disorder in chronic heart failure patients: Does silent cerebral infarction cause major depressive disorder in this patient population?

Kronik kalp yetersizliği olan hastalarda majör depresyon: Sessiz serebral enfarktüs bu hasta popülasyonunda majör depresyona yol açar mı?

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ABSTRACT

Objective: Depression frequently occurs in patients with heart failure as similar pathophysiological mechanisms present in both these diseases. Patients with dilated cardiomyopathy (DCM) have a high incidence of clinically asymptomatic silent cerebral infarction (SCI). This study aimed to evaluate the relation between SCI and major depressive disorder (MDD), and between MDD and clinical and biochemical parameters in DCM patients.

Methods: Patients with ischemic and non-ischemic DCM who had chronic heart failure (CHF) (39 male, 10 female, age 60±10 years) were included in the study. Mean patient ejection fraction (EF) was 34±10%. Patients had no localized neurological symptoms or stroke history. The etiology of DCM was ischemic in 40 and non-ischemic in 9 patients. Twenty-five age-matched healthy volunteers served as a control group for comparison of SCI and MDD prevalence.

Results: Patients had mild to severe CHF symptoms. Prevalence of SCI and MDD was significantly higher in patients with DCM than in the control group; 63% vs 8%; p<0.001, and 52% vs 20%; p<0.001 respectively. Patients with SCI had a higher prevalence of MDD than patients without SCI in DCM (61% vs 27%, p=0.02).

Conclusion: CHF patients have an increased prevalence of SCI and MDD. Patients with SCI have a higher prevalence of MDD compared to patients without SCI in CHF.

ÖZET

Amaç: Depresyon kalp yeterizliği olan hastalarda sıklıkla ortaya çıkar. Benzer patofizyolojik mekanizmalar her iki hastalık için de geçerlidir. Dilate kardiyomiyopatili (DK) hastalarda klinik semptom vermeyen sessiz serebral enfarktüs (SSE) sık görülmektedir. Bu çalışmada majör depresyon ile SSE arasındaki ilişkiyi ve DK'li hastaların klinik ve biyokimyasal parametreleri arasındaki ilişkiyi araştırdık.

Yöntemler: Kronik kalp yetersizliği (KKY) olan iskemik ve iskemik olmayan DK'li hastalar çalışmaya dahil edildi (39 erkek, 10 kadın, ortalama yaş 60±10 yıl). Ortalama ejeksiyon fraksiyonu %34±10 idi. Hastaların lokalize nörolojik semptom veya inme öyküsü yoktu. Hastalarda DK etiyolojisi 40 hastada iskemik, dokuz hastada da iskemi dışıydı. Yaş olarak eşleştirilmiş 25 sağlıklı gönüllü SSE ve majör depresyon prevelansını karşılaştırmak için kontrol grubu olarak kullanıldı.

Bulgular: Sessiz serebral enfarktüs ve majör depresyon prevelansı DK'li hastalarda kontrol grubuna göre anlamlı olarak daha yüksekti (sırasıyla, %63 ve %8; p<0.001 ile %52 ve %20; p<0.001). SSE saptanan DK'li hastalarda majör depresyon prevelansı SSE olmayanlara göre daha yüksekti (%61 ve %27, p=0.02).

Sonuç: Kronik kalp yetersizliği olan hastalarda SSE ve majör depresyon prevelansı artmıştır. SSE mevcut olan KKY'li hastalarda olmayanlara göre majör depresyon prevelansı daha yüksektir.

Received: January 13, 2014 *Accepted:* January 28, 2015

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Depression and depressive symptoms are highly prevalent among patients with coronary artery disease. Prospective evidence suggests that depression confers risk for the development of cardiovascular disease (CVD) with an overall relative risk of 1.64.[1,2] A diagnosis of depression at index evaluation is associated with an increased odds ratio (OR) for adverse outcome: for myocardial infarction (MI), an OR of 4.5, and for stroke, an OR of 2.7.[3] Depression is also a risk factor for the development of heart failure (HF) and for adverse outcomes in patients with existing HF.[4,5] Major depressive disorder (MDD) prevalence can reach 33–45% in patients following MI. Although prevalence of MDD among New York Heart Association (NYHA) class I HF patients was as low as 8%, among class IV patients it reached 40%.[6] Reduced exercise capacity among HF patients has a negative impact on their psychological condition and can theoretically promote depressive symptoms. However, this explanation oversimplifies a complex situation. Studies show that the close relation between MDD and HF is caused by the common neuro-endocrine background of the two diseases. HF patients with MDD are at increased cardiovascular mortality risk compared to non-depressed patients.[6]

A silent cerebral infarction (SCI) is classified as a type III cerebrovascular disorder by the National Institute of Neurological Disorders and Stroke.[7] SCI was identified as a risk factor for clinical stroke.[8] In HF patients, prevalence of SCI varies between 27% and 78 %.[9,10] It may be related to depression.[11]

Patients with ischemic and non-ischemic dilated cardiomyopathy (DCM) have a high incidence of clinically asymptomatic SCI.[9]

The aim of this study was to evaluate the relation between SCI and MDD, and that between MDD and clinical and biochemical parameters in DCM patients with HF sypmtoms.

METHODS

Patient selection

Fifty-four patients (43 male, 11 female; aged 60±10 years) with DCM diagnosed according to World Health Organization criteria who were being followed in the heart failure clinic of the department of Cardiology due to chronic heart failure were included in the study. Mean ejection fraction (EF) was 34±10%, and the patients were NYHA classes II-IV (Table 1).[12] Exclusion criteria were: Poor acoustic window, intravenous inotropic drug treatment, heart valve disease with hemodynamic significance, atrial fibrillation, uncontrolled ventricular arrhythmias, atrioventricular block, previous transient ischemic attack or stroke, or neurological deficit secondary to cerebral pathology. All the patients had already had coronary angiography when included. Forty-five patients had ischemic DCM and 9 had non-ischemic DCM. In all patients, left ventricular enlargement (end-diastolic diameter >56 mm) and systolic dysfunction (EF <45%) were documented by 2-dimensional and M-mode echocardiography.

Abbreviations:

BDI	*Beck Depression Inventory*
CRP	*C-reactive protein*
DCM	*Dilated cardiomyopathy*
EF	*Ejection fraction*
HF	*Heart failure*
HF-ACTION	*Heart Failure And a Controlled Trial Investigating Outcomes of Exercise Training*
LR	*Logistic regression*
MDD	*Major depressive disorder*
MI	*Myocardial infarction*
MRI	*Magnetic resonance imaging*
NYHA	*New York Heart Association*
OR	*Odds ratio*
PND	*Paroxysmal nocturnal dyspnea*
SCI	*Silent cerebral infarction*
TTE	*Transthoracic echocardiography*

Twenty-five, age- and gender-matched healthy volunteers (17 male, 8 female; mean EF 70±8%; mean age 59±10 years) were accepted as a control group after routine clinical and laboratory evaluation.

Study approval

The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the local ethics committee and subjects gave informed consent prior to entry.

Echocardiography

All participants underwent transthoracic echocardiography (TTE) by an echocardiograph equipped with a broadband transducer (Vivid 7®, GE VingMed Ultrasound AS; Horten, Norway). Measurements of the left atrium, and left and right ventricles were obtained from the parasternal long- axis view, as recommended by the American Society of Echocardiography. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's rule in the apical-2 and 4-chamber views.

Blood samples

Fasting blood samples were drawn from the large an-

Table 1. Clinical characteristics of patients with ischemic and non ischemic cardiomyopathy

Characteristics of study population	Patient (n=54)		
	n	%	Mean±SD
Age (years)			61.54±10.16
Gender (male/female)	43/11		
Blood pressure (mmHg)	147/82		
Hypertension	31	57	
Diabetes	25	46	
History of coronary bypass surgery	24	44	
History of acute myocardial infarction	32	59	
History of smoking	39	72	
History of alcohol consumption	7	13	
Left ventricular ejection fraction (%)			33.68±9.68
Left atrium (mm)			44.94±6.41
Brain Natriuretic peptid (pg/mL)		191.00_{median} (14.19 min–4000.00 max)	
Free-T_3 (pg/mL)			3.11±0.67
Symptoms and findings of patients			
Exercise-induced dyspnea	35	65	
Orthopnea	24	44	
Paroxysmal nocturnal dyspnea	15	28	
Jugular vein distension	13	24	
Angina	24	44	
Dyspnea at rest	11	20	
Ankle edema	11	20	
Medication			
Beta-blocker	47	87	
ACE-I/ARB	46	85	
Loop diuretics	25	46	
Digoxin	8	15	
Spironolactone	14	26	
Aspirin	46	85	
Clopidogrel	3	6	

Min: Minimum; Max: Maximum.

tecubital vein of each patient to detect biochemical and hemostatic parameters before TTE. The Elisa radioimmunoassay method (immunodiagnostic systems kit) was used to determine 25 (OH) D levels. Plasma fibrinogen levels were measured by the STA Compact auto analyzer using the STA® – Fibrinogen kit (Diagnostic Stago, Taverny, France). The samples were centrifuged for 10 min and serum FT_3, FT_4 (free-T_4), and TSH levels were measured by means of an Immulite® 2000 advanced immunoassay system (Siemens Medical Solutions USA, Inc.; Malvern, Pa). The reference intervals of our laboratory were as follows: TSH, 0.4 to 4 µIU/mL; FT3, 1.57 to 4.71 pg/mL; and FT_4, 0.8 to 1.9 ng/dL. BNP levels were analyzed by means of the Triage® BNP test (Biosite Incorporated; San Diego, Calif). Hematocrit, C-reactive protein (CRP) levels, parathormone levels and alkaline phosphatase levels were measured using standard methods.

Neurological and psychiatric examination

Neurological and psychiatric examinations of the study and control groups were performed by qualified neurologists and psychiatrists. A detailed history was obtained and a physical examination was performed on all patients. MDD was diagnosed based on clinical examination and screening interview (Structured Clinical Interview for DSM-IV Axis I Disorders [SCID-I]) for DSM-IV axis, Turkish version[13] conducted by trained interviewers. SCID-I is a diagnostic exam used to determine DSM-IV Axis I disorders (major mental disorders). The study participants were assessed with the SCID - Mood Disorders Module.

Brain magnetic resonance imaging

Patients and control group were examined with magnetic resonance imaging (MRI) to detect SCI. Cerebral MRI was performed on a 1.5-T MR scanner (Philips Intera Master, Eindhoven, Netherlands) using a standard quadrature head coil. After obtaining scout images, routine imaging was performed. Our routine MRI protocol for cerebral disease includes axial dual echo TSE, axial FLAIR, axial T1-weighted TSE, sagittal T2-weighted TSE, and coronal T2-weighted TSE images. All images were acquired with a field of view of 230x230 mm, and a section thickness of 5 mm with a 1-mm intersection gap. A neuroradiologist blinded to patient clinical status reviewed the images.

SCI in the subcortical white matter was defined as a focal lesion of at least 3 mm in diameter which was hypo-intense on T1-weighted image and hyperintense both on T2-weighted and FLAIR images (Figure 1).[14] MRI-defined brain infarcts were categorized as absent or present.

Carotid screening

A carotid duplex ultrasound for each patient was done by a radiologist independent of the study. It was accepted as a pathological result if there was ≥50% stenosis or calcified plaque in the carotid arteries.

Statistical methods

The SPSS 13.0 (SPSS Inc., an IBM company; Chicago, III) package was used for statistical analyses. Results are presented as mean±SD or as percentages and numbers for categorical data. In comparing patients with and without SCIs and MDDs, continuous variables that were normally distributed were analyzed with the 2-tailed t test, and non-parametric distributed variables were analyzed with the Mann-Whitney U test. The Kolmorov- Smirnov test was used to verify the normality of distribution of continuous variables. Continuous variables not normally distributed were shown as median (min-max). Categorical data and proportions were analyzed using the χ^2 or Fisher exact test where appropriate. Degrees of association between continuous variables were evaluated by Spearman's Rank correlation analyses. Multivariate logistic regression analysis including the variables showed p values <0.250. Univariate analysis was performed to identify the independent predictors of MDD. The backward logistic regression (LR) method was used in logistic regression analysis. Variables evaluated in the model were NYHA, left atrium, free-T3, usage of loop diuretics, SCI, carotid stenosis or calcified plaque, presence of angina and paroxysmal nocturnal dyspnea (PND). A p value <0.05 was considered significant.

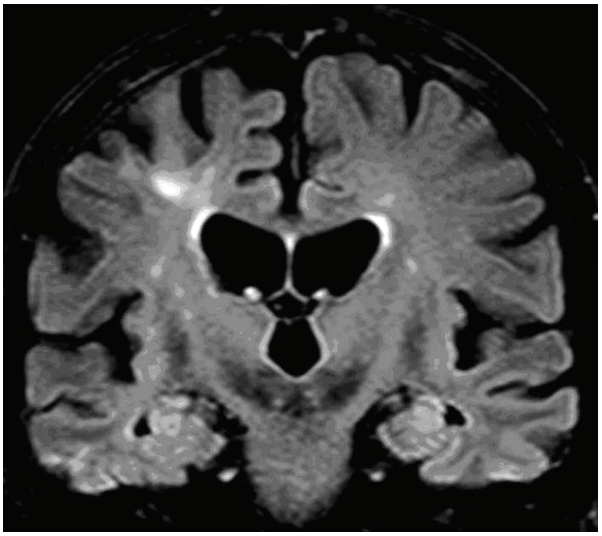

Figure 1. Coronal T2-FLAIR image shows hyperintense lesion at white matter.

RESULTS

Forty DCM patients had SCI, while only 2 in the control group had SCI, meaning prevalence of SCI was significantly higher in the patient group (74% vs. 8%; p<0.001). 40 patients (74%) had SCI, 14 patients (26%) had no SCI on MRI. There was no association between SCI and history of coronary artery disease, hypertension, diabetes, coronary bypass surgery and acute MI.

33 patients (61%) had ≥50% carotid stenosis or calcified plaque in carotid duplex ultrasonography. Twenty-eight (70%) patients with SCI and 5 (36%) without SCI had carotid stenosis or calcified plaque (p=0.024).

Association of silent cerebral infraction with major depressive disorder

In the present study, it was determined that 28 patients (52%) in the patient group and 5 (20%) in the control group (p=0.008) had MDD. However, on MRI, 24 of 40 SCI patients (60%) had MDD, while 4 of 14 non-SCI patients (29 %) had MDD. Patients with SCI had a higher prevalence of MDD than non-SCI patients (p=0.043). There was no association between MDD and history of coronary artery disease, hypertension, diabetes, coronary bypass surgery and acute MI.

Association of clinical and biochemical parameters with MDD in chronic HF patients

Patients with MDD were a higher NYHA class compared to patients without MDD (2.7±0.7 vs 1.8±0.7; p<0.001). Left atrium diameters were larger and free-T3 levels were lower in patients with MDD than in patients without MDD (p=0.035, p=0.037). Of 28 MDD patients, 24 (86%) had SCI compared to 16 (62%) of 26 non-MDD patients. Clinical symptoms such as PND and angina were more prevalent in patients with MDD compared to the non-MDD group (Table 2). Unfortunately, we could not find any association between MDD and hemoglobin, CRP, parathormone, fibrinogen and serum 25-OH Vitamin D2 levels.

Logistic regression analysis

In the present study, LR analysis showed NYHA (OR-5.37, 95% CI 1.86–15.50, p=0.002) presence of angina (OR-4.95, 95% CI 1.08–22.73, p=0.04) and SCI (OR-7.11, 95% CI, 1.23–41.14, p<0.001) to be independent predictors of MDD.

DISCUSSION

It was determined that 74% of the patient group had SCI. Carotid artery pathology rates were very high in SCI patients. These patients also had higher rates of MDD compared to non-SCI patients. Patients with MDD had a higher NYHA class, increased rates of SCI and carotid artery pathology, a larger left atrium, lower free-T3 levels, increased anginal symptoms and higher rates of PND in the study.

In the general population, prevalence of SCI varies between 10% and 28%, whereas in patients with stroke it is as high as 38%.[15–19] The prevalence of SCI has been reported as up to 78% in HF patients.[20] Our

Table 2. Clinical and echocardiographic characteristics of patients with and without MDD in ischemic and non-ischemic cardiomyopathy

	Patients with MDD (n=28)	Patients without MDD (n=26)	*p*
Age (years)	62.61±10.64	60.38±9.68	0.430
New York Heart Association class	3.00±0.75	2.00±0.69	<0.001
	(Min.: 1.00–Max.: 3.00)	(Min.: 1.00–Max.: 4.00)	
Left ventricular ejection fraction (%)	33.78±10.72	33.55±8.54	0.930
Left atrium (mm)	46.86±5.35	43.10±6.89	0.035
Free-T_3 (pg/mL)	2.92±0.53	3.30±0.75	0.037
BNP (pg/mL)	210.00_{Median}	186.50_{Median}	0.443
	($16.00_{Min.}$–$4000.00_{Max.}$)	($14.19_{Min.}$–$379.00_{Max.}$)	
hs-CRP	1.41±1.94	1.02±1.31	0.451
Loop -diuretic use, n (%)	17 (61)	8 (31)	0.027
Silent cerebral infarction, n (%)	24 (86)	16 (62)	0.043
Paroxysmal nocturnal dispnea, n (%)	12 (43)	3 (12)	0.010
Carotid stenosis or calcified plaque, n (%)	21 (75)	12 (46)	0.030
Presence of angina, n (%)	15 (54)	7 (27)	0.017

BNP: Brain natriuretic peptid; hs-CRP: High sensitive C-reactive protein; Max.: Maximum; Min.: Minimum.

patients had 70% SCI, which was among the highest rate in other studies. Patients with SCI are at increased risk of stroke.[8] It is known that disabling stroke is the fourth leading cause of disease burden and the second leading cause of death among adults worldwide.[21] Stroke history has been a predictor for worse prognosis in chronic HF patients.[22]

Depression has a significant prevalence in patients following a stroke. Studies have found rates to be between 25–54%.[23] Most studies have examined the prevalence rates of depression and the clinical correlates of depression. The overall prevalence of major depression has been reported as 21.7%, and minor depression 19.5%. The strongest single correlate of depression is severity of impairment in activities of daily living. Depression following acute stroke has also been associated with greater cognitive impairment and increased mortality.[24] Terroni et al. reported that 31% of stroke patients had experienced a major depressive episode following stroke.[25] It is known that prevalence of major depression can vary between 8–40% in HF patients.6 In this population, depression has been independently associated with a poor quality of life, limited functional status, and an increased risk of morbidity and mortality.[26–31] In the present study, prevalence of MDD was 52% in the patient group. While 60% of patients with SCI had MDD, 29% of patients without SCI had MDD. 60% prevalence of MDD in SCI patients is significantly higher than in depressive patients with stroke. Our high MDD ratio could result from our patient group comprising chronic HF patients with increased SCI rates. We speculated that both HF and SCI could be associated with increased depressive symptom rates. When two co-morbid conditions coexist, MDD rates may be expected to be higher than in patients with either chronic HF or SCI.

In previous studies, patients of a higher NYHA class had increased depression compared to those of a lower NYHA class.[6] Significant correlations predicting MDD included disability due to the illness and more severe illness (NYHA class).[32]

The Heart Failure And a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) evaluated the relation between objective and subjective parameters and made comparisons with scores on the Beck Depression Inventory (BDI) in HF. At baseline, the 2331 subjects enrolled in HF-ACTION completed questionnaires to assess depression (BDI). Objective markers of HF severity included EF, B-type natriuretic peptide, and peak oxygen consumption. Measures more likely to be affected by perceived functional status included NYHA classification and the 6-minute walk test. Objective assessments of disease severity were slightly related (peak oxygen consumption) or not related (B-type natriuretic peptide and EF) to BDI scores. Using multivariate analysis only age, gender, cardiopulmonary exercise testing duration, NYHA class, 6-minute walk distance, and peak respiratory exchange ratio independently correlated with BDI scores. Authors concluded that depression was minimally related to objective assessments of severity of disease in patients with HF, but was associated with patient (and clinician) perceptions of disease severity.[31] Although there was no association between some parameters such as EF, B-type natriuretic peptide level, hs-CRP level and fibrinogen level and MDD, there was a relation between larger left atrium and lower free-T3 level, and MDD in the patient group in our study. Patients with MDD had a higher NYHA class, a larger left atrium and lower free-T3 levels. We found a positive correlation between subjective parameters such as NYHA, PND and angina. Larger chamber dimensions and lower free-T3 were markers of advanced disease and poor prognosis in chronic HF.[33,34] Premachandra et al. reported that patients with major depression had 6.4% low T3 syndrome. Since these patients had normal metabolic parameters, the low T3 levels could not have depended on malnutrition or any other illness. Depression might constitute an illness having the same relation to low T3 as found in the low T3 syndrome previously described in euthyroid sick subjects.[35]

Although Brott et al. found that degree of carotid artery stenosis was not associated with SCI in a group of patients with high-grade asymptomatic carotid artery stenosis,[36] in the present study 70% of patients with SCI had carotid artery stenosis or calcified plaque in carotid duplex ultrasonography. There was no association between depressive symptoms and carotid intima media thickness in the Baltimore Longitudinal Study of Aging, which included healthy community-dwelling volunteers.[37] We found a clear association between carotid artery stenosis or calcified plaque and MDD in our study group. We speculated that results for our patients may have been different because they were more morbid, with very advanced disease com-

pared to those in the above-mentioned studies.

We may conclude that MDD is associated with both objective symptoms of HF such as higher larger left atrium diameter and decreased free-T3 level, and subjective symptoms of HF such as NYHA and PND. It was shown in this patient group that depressive symptoms in HF patients are closely associated with SCI and carotid artery pathology.

Patients with SCI had a higher prevalence of MDD compared to patients without SCI in this study. We showed that prevalence of MDD in SCI patients may be higher than in patients with stroke, as reported in previous studies (60% vs 25–54%).[23] We may speculate that depression could be attributed to perception among stroke patients. While patients with stroke may have many difficulties and restrictions in their daily life activities,[38,39] patients with HF might have restrictions in daily life[40] due to fatigue and shortness of breath. Daily life difficulties may be one reason for depression in patients with stroke and HF. It is known that in SCI, the accumulation of infarct lesions induces obstruction in the neuron network related to mood and once this exceeds a certain threshold, the patient becomes predisposed to vascular depression.[41] When both silent infarcts and overt infarcts cause enough obstruction in the neuron network related to mood, depressive symptoms may be seen in stroke and SCI in chronic HF patients.

Limitations

Patient and control group size was the most important limitation of this study. Our numbers were not high because some candidate patients and healthy controls did not agree to participate in the study because of MRI-related claustrophobia or because evaluation of depression would take up too much of their time in daily routine.

Conflict-of-interest issues regarding the authorship or article: None declared

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Keywords: Cardiomyopathy; chronic heart failure; major depressive disorder; silent cerebral infarction.

Anahtar sözcükler: Kardiyomiyopati; kronik kalp yetersizliği; majör depresif bozukluk; sessiz serebral iskemi.