HEART FAILURE WITH LOW CARDIAC OUTPUT AND RISK OF DEVELOPMENT OF LESIONS IN THE CEREBRAL WHITE MATTER

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Aim: Diminished cardiac output can lead to the development of white matter lesions. White matter lesions are related to cognitive impairment, stroke risk and vascular death, yet the precise aetiology is uncertain.

Methods: In this study we recruited 130 patients attending our medicine and neurology outpatient department, and divided them into those with a history of heart failure (n:24), atrial fibrillation (n:26), and those with atherosclerotic risk factors (n:80). The patients without low output heart failure and atrial fibrillation were grouped as control. We studied the magnetic resonance imaging (MRI) findings associated with low cardiac output and adjusted for confounding factors. Heart failure with low cardiac output was diagnosed by a cardiologist.

Results: The presence of leukoaraiosis (LA) on MRI was assessed in 80 patients with modifiable atherosclerotic risk factors (control group) and 50 patients having heart failure or atrial fibrillation. Hyperintense lesions in T2 and proton weighted and non-hypotense lesions in T1 weighted sequences were considered as white matter abnormalities. MRIs of all cases were evaluated by means of a four grade scoring system -described previously in the literature- by the same neurologist. White matter lesions of patients with heart failure, atrial fibrillation or atherosclerotic risk factors were compared. Patients in the study group were divided into two groups according to the presence of heart failure due to etiologies other than atrial fibrillation (n:24) and atrial fibrillation (n:26). Leukoaraiosis was observed in 18 (75%) cases with heart failure, 18 (69.2%) cases with atrial fibrillation, and 61 (76.3%) patients in the control group. There was no difference between the three groups with respect to the presence of LA (x2:0.51, p: 0.77).

Conclusion: This study demonstrated that there was no significant association between heart failure and white matter abnormalities independent of other risk factors despite the fact that cardiac disorders apparently manifested themselves as cases with severe leukoaraiosis.

Key words: White matter, leukoaraiosis, risk factors, cardiac failure, atrial fibrilation

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INTRODUCTION

Although the etiology of white matter abnormalities has not been revealed completely, cerebral hypoperfusion is thought to be one of the factors (1-11). Heart failure and atrial fibrillation are among the frequently observed causative factors of reduced cardiac output. Reduced cardiac output may lead to cerebral hypoperfusion and development of white matter lesions (12-13). Although periventricular white matter structure was shown to be affected mostly from hypoperfusion in some studies, comparative studies performed with established cases with

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heart failure unrelated to atrial fibrillation are unsatisfactory to draw definite conclusions. The frequency and prognostic significance of neuroradiological white matter changes in cardiac insufficiency are unknown (14).

In this crosssectional study, we sought associations between white matter lesions on MRI and heart disease, defining groups with low cardiac output heart failure, atrial fibrillation, or neither.

MATERIAL AND METHODS

In this research, medical history of ninety-eight hundred and thirty patients followed by Internal Medicine and Neurology outpatient clinics in PTT Training and Research Hospital between July 2001 and July 2002 were included in present study and evaluated for the presence of leukoaraiosis (LA). Fifty patients with a history of heart failure or atrial fibrillation for at least five years were selected for the patient group and 80 patients with histories of most commonly accepted modifiable atherosclerotic risk factor (i.e. hypertension, diabetes mellitus, dyslipidemia, and smoking) and related diseases for at least five year duration comprised the control group. The various blood, cardiac, and brain imaging studies were done as part of routine care and follow-up.

Inclusion and exclusion criteria

Hypertension was considered to be present if the subjects had a history of systolic blood pressure ≥160 mmHg or a diastolic pressure ≥95 mmHg during follow-up periods, and if treatment for high blood pressure was administered previously. Hypercholesterolemia was considered present if subjects had a history of serum total cholesterol >200 mg/dL and if treatment for hyperlipidemia was started previously. Hyperglycemia was considered present if subjects had a history of serum glucose level >115 mg/dL and if treatment for diabetes was started previously. The subjects were accepted as smoker if he smoke 1 package daily for 5 years. Then the modifiable risk factors were noted. Subjects with large artery thrombosis were excluded because of difficulty in differentiation of LA. Anti-coagulation usage was an inclusion criteria in atrial fibrillation patients to make statistical analysis easy. All other patients with low cardiac output failure or risk factors were not used anti-coagulation any way. Subjects with brainstem stroke or large hemispheric infarcts were not included in the study.

Cases with hyperthyroidism, beriberi, cirrhosis, severe anemia, arterio-venous fistula and large vascular tumoral load and those with heart failure with normal or increased ejection fraction had been excluded from the study.

Routine blood tests

Routine biochemical tests were done while the presence of anemia (an indicator of cardiac decompensation), hyponatremia (an unfavorable prognostic factor) and increases in blood creatinine concentrations were especially monitored. Hyperproteinemia was also investigated.

Cardiac investigations

A cardiologist established the diagnosis of heart failure with low cardiac output and atrial fibrillation through clinical evaluation, ECG and echocardiographic examination. All of the patients were evaluated for arrhytmias. A 12- lead electrocardiogram was obtained and the absence of P waves and irregular atrial activity were accepted as diagnostic criteria for atrial fibrillation (12,13). The presence of ST-T changes, tachyarrhytmias, pathologic Q waves, low voltage or left ventricular hypertrophy on the ECG were noted. Enlarged cardiac silhouette, pleural effusion and pulmonary edema on chest X -rays were regarded as signs supporting a diagnosis of heart failure. Left ventricular enlargement and reduction in ejection fraction (≤40%) detected during echocardiography led to the diagnosis of heart failure with low cardiac output. All subjects completed those diagnostic procedures and then the participants were classified into three categories such as those with heart failure, atrial fibrillation and cases with atherosclerotic risk factors. The cardiologist collecting and abstracting information used in our analyses were blinded to results of the MRI.

Cranial MRI examinations

Axial cranial MRIs with T1, T2 weighted and proton intense images of all the cases were obtained with 1.5 tesla MRI equipment. Hyperintense lesions at T2 and proton weighted and non-hypointense lesions at T1 weighted images were regarded as white matter abnormalities. Hyperintense lesions were evaluated. Spin echo 1.5 tesla MRI images were graded from 0 to 4 according to the severity of white matter lesions (15). Grade 0 lesions did not manifest any focus of high signal intensity in the white matter. Grade 1 indicated punctuated foci of high signal

Table 1. Characteristics of the study population.

Characteristics	Cardiac Failure	Atrial Fibrilation	Atherosclerotic Risk factors
n-(%)	24-(18,5)	26-(20)	80-(61,5)
Mean age	70.8±9.3	71.0±10.7	68.5±7.8
Sex			
Male (%)	54.2	30.8	41.3
EF	36	54	66
Presence of LA (%)	75	69.2	76.3
LA grade (n)			
I	3	2	19
II	3	8	17
III	2	4	12
IV	10	4	13
Risk factors			
Hypertension	70.8	84.6	66.3
Diabetes	45.8	38,5	30
Dyslipidemia	20.8	7.7	25
Smoking	12.5	23.1	23.8

intensity in the white matter immediately at the top of the frontal horns of the lateral ventricules. Grade 2 indicated white matter lesions seen elsewhere but remained confined to the immediate subependymal region of the ventricles. Grade 3 indicated periventricular as well as separate, discrete, deep white matter foci with signal alterations. Grade 4 indicated discrete, large and coalescent foci in the white matter. All the MRI's were evaluated according to these criteria. MRIs of all the cases were evaluated by the same neurologist unaware of the risk factors according to the predefined categorization. The presence of thromboembolic infarcts outside the predefined categorization was also noted. Hypointense lesions in T1, hyperintense lesions in T2 and hyperintense or isointense lesions in proton weighted images more than 3 mm at its largest diameter were rated as infarcts.

Statistical analysis

For the evaluation of associations between white matter abnormalities and heart failure, atrial fibrillation and other atherosclerotic risk factors and relevant alterations as for age and gender ; frequency, percentage ratio, chi-square, Fisher's exact test, and student-t were used.

RESULTS

The study group consisted of 54 (41.5%) male and 76 (58.5%) female patients with similar distribution of age in each other. Descriptive features of patients are shown in Table 1. Mean ages of all subjects were 69.4 (SD:8.76 years, R:48-89). The heart failure with low cardiac output due to other factors (n:24), the presence of atrial fibrillation (n: 26) and atherosclerotic risk factors (n:80) were detected. Grade I LA was present in 24 (18.5%) cases, II in 28 (21.5%), III in 18 (13.8%) and IV in 27 (20.8%) cases.

There was no LA on MRI in 33 (25.4%) patients. As it was seen on Table 1, LA was observed in 18 (75%) patients with heart failure, 18 (69.2%) cases with atrial fibrillation, and 61 (76.3%) cases with atherosclerotic risk factors (p:0.77).

LA of grade ≥3 was observed in 45 cases (31%). The percentages of LA of grade ≥3 in groups with heart failure, AF and atherosclerotic risk factors were 66.7% (n: 12), 44.4% (n:8) and 45% (n:25) respectively (p:0.16). Though no statistically significant correlation was found, the frequency of leukoareosis of grade ≥3 in the group with heart failure was more than that in the group with atherosclerotic risk factors. When heart failure, AF and every other risk factors were evaluated separately, the distribution of leukoaraiosis in patients with previous ischemic lesions varied greatly and 25% (n: 6) of patients with heart failure had previous ischemic lesions (p:0.001).

The presence of leukoareosis was not related to the presence of having two or more risk factors and there were two or more risk factors in 46 (47.4%) patients out of 97 patients (p:0.85). The LA and gender association was shown Table 1. Male gender was associated with higher incidence of LA. Forty-five male patients (83.3%) had LA and 52 female patients (68.4%) had LA(p:0.05). When you think about group differences ;

only patients with AF showed a relationship between LA and gender. All male patients (n: 8) had LA on cranial MRI examination, as only ten female (55.6%) had LA (p:0.03). The p values for cardiac failure and risk factor groups were 0.24 and 0.66 respectively. The relationship between the presence of leukoareosis and age was determined. Mean age was higher in the patients having LA. The mean ages of patients having LA or not were 71.15 (SD:7.43) and 64.36 (SD:10.39) respectively. Age increased the incidence of LA significantly
(p:0.0001). All subjects with history of diabetes or smoking had LA in cardiac failure group. The percantege of hypertensive patients with LA in cardiac failure group was 76.5. Only 54.5% of diabetes patients had LA in the cardiac failure group.

DISCUSSION

In this study we investigated the association between cardiac disease and white matter lesions on magnetic resonance brain imaging. We looked for this association in patients with a reduced ejection fraction with a previous stroke and compared to patients having atherosclerotic risk factors. We wanted to confirm earlier reported findings and we investigate our research question in patients with a previous stroke, usually also people with also many other risk factors for LA. Leukoaraiosis, a term that defines an abnormal appearance of the subcortical white matter of the brain on neuroimaging (bilateral patchy or diffuse areas of low attenuation on CT or hyperintense T2 MR areas), has gained evidence in retrospective studies to demonstrate its association with stroke and in prospective studies to demonstrate its prognostic value related to the occurrence of stroke, both ischemic and hemorrhagic, or the occurrence of vascular death (16-17). Since LA began before cognitive decline and LA in elderly people might cause cognitive and/ or gait disorders and urinary dysfunction, diagnosis and prevention of white matter lesions are important issues (13,19). LA is sometimes accepted normal but mostly shows ischemic pathology or predicts stroke (18-20). The onset of LA progress is insidious and gradual. Transient ischemic attacks, hypertension, hyperlipidemia, smoking, and male gender accelerate LA which was correlated with cognitive decline, and dementia (18,19). Age is the most important factor that significantly increased the risk of leukoaraiosis (18,21,22). Underlying pathologies including atherosclerosis, hypertension, hyperlipidemia, hyperglycemia are other factors in the development of white matter abnormalities with weak associations. The association between these factors and leukoaraiosis mostly manifest themselves in individuals with cerebrovascular diseases (18,22-24). De Leeuw et al (13) mentioned about the interaction between AF and leukoaraiosis and emphasized the importance of a compulsory 5 year follow-up period. They found that thromboembolism and infarct formation are not important factors in the development of white matter lesions. In our study, patients already reported that they had heart disease and other disorders relevant to atherosclerotic risk factors for the past 5 years. The presence of ischemic lesions was important in relation to LA in this study. There was a statistically significant relationship between the presence of LA and ischemic lesions (p:0.001). In this present study, we found that ischemic infarction most likely played a key role in the development of LA and ischemic lesions affected formation of LA. Although gender was not an independent risk for LA, LA in this present study was more prominent in males similar to data reported by Meyer et al (19).

Heart failure with low cardiac output in other words, systolic heart failure is characterized by a loss of contractile strength of myocardium accompanied by the compensations of ventricular hypertrophy and/or dilatation. Mechanical or myocardial abnormalities or arrhythmias may cause cardiac pump failure. The reduction in ejection fraction is in linear correlation with dysfunctional myocardial tissue. AF or cardiac insufficiency reduces cardiac output and hypoxic episodes develop in vulnerable area such as periventricular white matter which is an arterial border zone (10,25). We did not evaluate periventricular and other white matter areas separately, this could be a critism for our study. Heart disease accelerates cerebral atrophy, ventricular enlargement, leukoaraiosis, and the decline in cortical perfusion (23,26). Tarvonen-Schroder et al studied the clinical features of leukoaraiosis and found that the frequency of heart failure and systolic hypotension -but not hypertension- was higher in the leukoaraiosis positive group than in the controls (27). Another study showed that LA is more likely to be associated with a cardiovascular cause of death suggesting a relationship between LA and cardiac disorders (28). In our study, an

association between cardiac insufficiency and leukoaraiosis was not found although subjects with cardiac insufficiency were at a risk of having white matter lesions. It could be thought that the association between cardiac failure and LA might be confounded by the underlying cause of other risk factors. To solve that problem, we made our control group from patients with other most commonly accepted modifiable risk factors. We did not find a significant association between heart failure and high grade LA (Grade>3) in this present study either.

The higher grades of LA were more frequent in older patients and the greatest number of the patients had grade III LA or higher. In addition, subjects who had cardiac failure with dyslipidemia, smoking or hypertension, showed a higher prevalence of LA. Evaluation of heart failure, AF and other risk factors separately revealed that subjects with ischemic lesions were at risk of having LA ($p<0.05$). This suggests that different pathophysiologic factors like hypertension or age induced atherosclerosis may underlie LA. Although we did not perform actual cerebral blood flow measurements during our studies, the availability of five year-records of disease in cardiac failure or AF patients was the strength of this study.

In summary, this study demonstrated that there was no significant association between heart failure and white matter abnormalities, the presence of atherosclerotic risk factors seems the most important determinant and the prevention of LA requires the control of these risk factors. In critizm, there are two main problems with this study. Firstly, the absence of a relationship between cardiac disease and white matter lesions is probably due to small number of patients. Secondly, this is hospital based study and not a community based study, so it is likely that patients with milder cardiac failure or undiagnosed AF are not included. Again, this might have biased the results. Anyway this study is timely and relevant, because white matter lesions are related to vascular death and the precise aetiology is still uncertain.

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