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Cardiovascular and Cerebrovascular Problems in the Development of Cognitive Impairment: For Medical Professionals Involved in the Treatment of Atherosclerosis

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1. Introduction

When cognitive function declines at a rate greater than that expected based on the actual age, life circumstances and educational level, we define it as cognitive impairment (Blennow et al., 2006; Gauthier et al 2006). In the older generation, the neurodegenerative process is considered to occur several years before the development of clinically detectable cognitive impairment. Although aging is the most clear factor in the development of this disease process, several epidemiological studies have elucidated that cardiovascular risk factors, i.e., hyperlipidemia, hypertension, smoking and diabetes, are also associated with cerebrovascular disease processes that may deteriorate cognitive function and advance dementia (Casserly & Topol, 2004; Nash & Fillit, 2006; Whitmer et al., 2005). In this chapter, I would like to introduce the current positioning of cognitive impairment as a consequence of cardiovascular diseases as well as a form of cerebrovascular disease, to neurologists or psychiatrists as well as to general physicians or cardiologists.

2. Cognitive impairment

Currently, Alzheimer's disease is the most common form of dementia or cognitive impairment, but less than 20% of dementia patients exhibit the isolated form of Alzheimer's disease and around 50% of such patients exhibit a combination of Alzheimer's disease and intracerebral vascular disease. By contrast, the isolated vascular type only contributes 20% (Meguro et al., 2002). Therefore, various problems related to metabolic syndrome, i.e., hypertension, hyperlipidemia, diabetes, and smoking habit, contribute to the development or deterioration of cognitive impairment.

3. Cardiovascular problems in cognitive impairment

Furthermore, recent investigations have suggested that the incidence of cognitive impairment is higher in patients with congestive heart failure and that treatment for left ventricular (LV) systolic dysfunction may prevent or delay the development of dementia in

elderly patients (Zuccala et al., 2003, 2005). An Italian investigation indicated that the incidence of congestive heart failure was markedly higher in subjects with Mini-Mental State Examination (MMSE) scores <24 (20.2%), compared with those with scores ≥24 (4.6%) (Zuccala et al., 2003). Also, the presence of cognitive impairment has been associated with increased in-hospital mortality in older patients with heart failure (Zuccala et al., 2005). These data may indicate that low cardiac output due to heart failure is related to the deterioration of cognitive function, although there have been no reports regarding the pathophysiology or etiology of heart failure in relation to cognitive impairment. Another investigation indicated an independent relation between the levels of b-type natriuretic peptide (BNP) and the degree of cognitive impairment in older subjects (>55years of age) with cardiovascular disease; despite the fact that the mechanism was unclear (Gunstad et al., 2006).

In patients with heart failure, more than half of them, especially in females, showed normal or preserved LV ejection fraction (EF), i.e., exhibited heart failure resulting from LV diastolic dysfunction (Hogg et al. ,2004). Also, in heart failure patients with cardiovascular risk factors, i.e., hyperlipidemia, hypertension, smoking and diabetes, heart failure with preserved EF is also common. Therefore, we evaluated the relationship between LV diastolic dysfunction and cognitive impairment in Japanese patients with cardiovascular diseases (Suwa & Ito, 2009).

In our study, patients were divided into 2 groups; those patients with normal cognitive function or mild cognitive impairment (MMSE>=24; n=68: group N) and those with depressed cognitive function (MMSE<24, n=13). Diastolic function was evaluated based upon the ratio of the early diastolic mitral flow velocity (E) by pulse-wave Doppler echocardiography to the early diastolic mitral annular myocardial velocity (e') by tissue Doppler echocardiography (Diastolic Doppler index: E/e'). BNP was also evaluated as an index of heart failure. Consequently, in depressed cognitive function, diastolic Doppler index, E/e', was deteriorated (6.1±1.3 vs. N: 4.6±1.3, $p<0.0003$) and BNP was higher (137±142 pg/ml vs. N: 60±49 pg/ml, $p<0.007$), compared with those with normal cognitive function. Furthermore, the number of patients with diabetes was also higher in depressed cognitive function than in normal cognitive function (46% vs. N: 18%). From these studies evaluating the relation between cardiac and cognitive function, heart failure due to LV systolic and diastolic dysfunction can affect the development and the deterioration of cognitive impairment.

Poor cerebral circulation:	Left ventricular systolic dysfunction
	Left ventricular diastolic dysfunction
Stroke:	Atrial fibrillation, Atherosclerotic vascular diseases including of carotid artery stenosis
Deep white matter hyperintensity in brain MRI:	Atherosclerotic abnormalities, due to hypertension, diabetes, hyperlipidemia, and smoking
Hippocampal atrophy in brain:	Senile process

MRI: magnetic resonance imaging

Table 1. Relationship between cardiovascular abnormalities and cerebrovascular diseases affecting the decline of cognitive function

The occurrence of atrial fibrillation (AF) is a risk of stroke, and stroke increases the risk of cognitive decline and dementia. Therefore, AF has been reported to be associated with cognitive decline and dementia (Jozwiak et al., 2006). Recently, even in stroke-free patients it has been shown that AF is a risk for cognitive impairment and hippocampal atrophy (Knecht et al., 2008). For these reasons, it was considered that AF was associated with abnormalities of hemostasis, endothelial damage, platelet dysfunction, and low cardiac output.

As another measurable index in the vascular system, the ankle to brachial index is also related to incidence of total dementia, vascular dementia and Alzheimer's disease, especially in carriers of the apolipoprotein E gene abnormality (Laurin et al. 2007).

4. Common interest between cardiovascular and cerebrovascular diseases

Brain magnetic resonance imaging is conducted to screen for cerebrovascular disease as well as cerebral disease, and hyperintensities in the deep white matter on T2-weighted images can be incidentally detected in 10-20% in adults aged 64 to 94% at age 82 in the general population (Fig.1 and Fig.2). At present, these white matter lesions are related to chronic hypoperfusion and disruption of the blood brain barrier due to small vessel disease in the lesion area (Debette & Markus, 2010). Also, white matter hyperintensities are more common in patients with cerebrovascular disease as well as cardiovascular disease, with risk factors affecting atherosclerosis, inclusive of hypertension (Hajjar et al., 2011). Furthermore, meta-analysis reveals that the white matter lesions predict an increased risk of stroke, dementia, and death. Although data that treatment for these risk factors reduces the progression of white matter hyperintensities are limited, it is also reported that antihypertensive therapy reduced the progression in patients with stroke (Saxby et al., 2008). Therefore, white matter hyperintensities may be important markers to not only detect the risk of stroke and dementia but also diagnose the atherosclerosis in cerebro-cervical vascular system. The progression of white matter lesions is independently related to baseline cerebral lesion, higher age, hypertension, and current smoking. Also, atherosclerotic processes in the carotid artery, connecting to the cerebral artery, are associated with the cerebral small vessel disease (Romero et al., 2009).

Modified Mini-Mental State Examination scale falls more according to the worsening of white matter grade (prominently in grade Two +). (Fig.3. Longstreth et al. 2005) (with permission, License No.2776831264727)

To date, some angiotensin receptor blockers have been reported to significantly reduce the incidence and progression of Alzheimer's disease and dementia, compared with the use of angiotensin converting enzyme inhibitors or other cardiovascular drugs, in a predominant male population (Saxby et al., 2008). Therefore, when prescribing antihypertensive drugs we may have to consider the contribution of such medicines.

At present, the CHADS2 score is widely used to validate the risk for stroke in patients with AF. A newer clinical study has shown that the CHADS2 score is useful to predict ischemic stroke in patients with stable coronary artery disease, even in those without baseline atrial fibrillation (Welles et al., 2011)
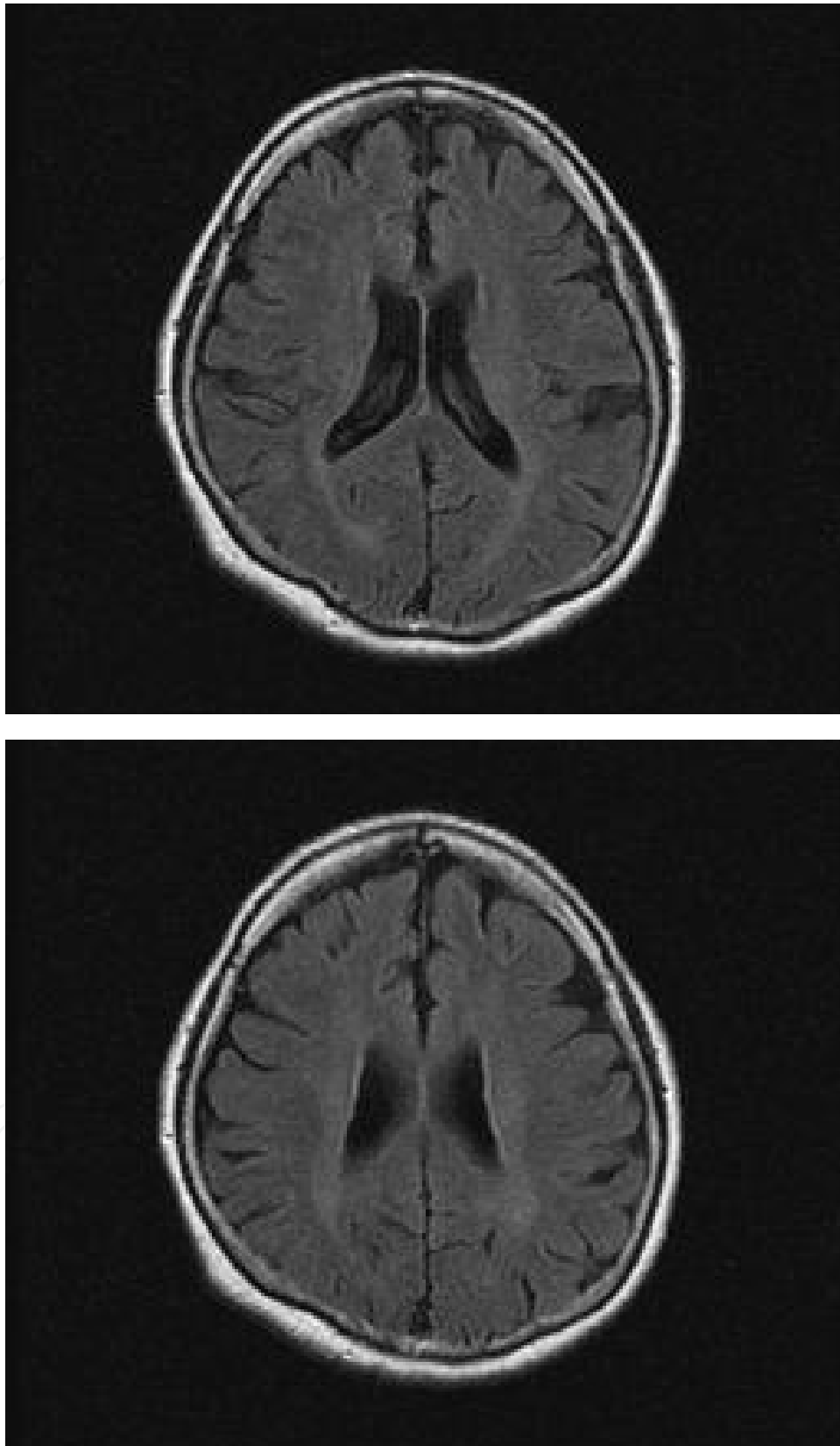
Fig. 1. Brain magnetic resonance imaging on T2 weighted images obtained from a 77 year old female without cognitive impairment and being under medication for hypertension. These images show somewhat brain atrophy but no white matter hyperintensities.
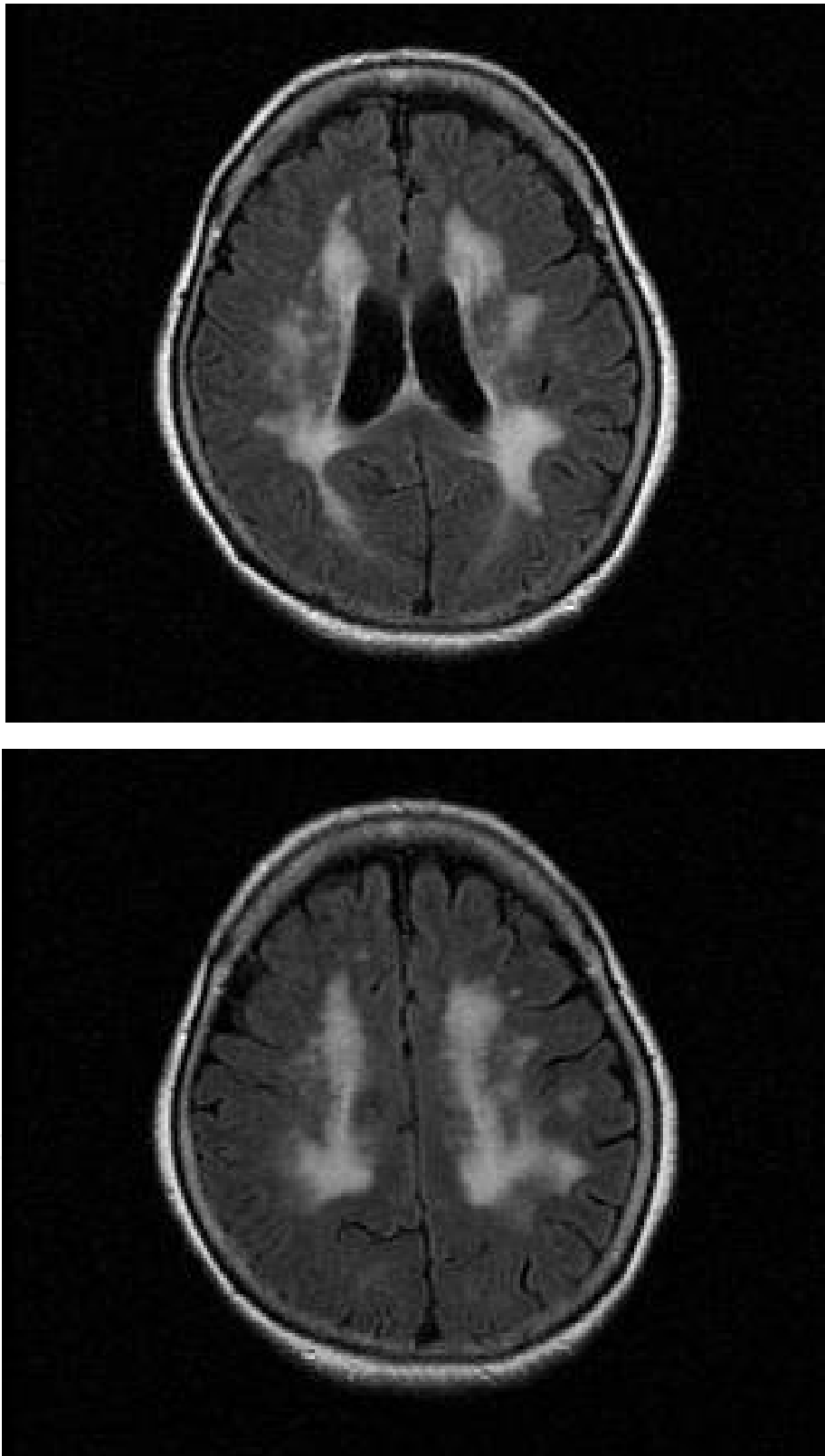
Fig. 2. White matter hyperintensities on brain magnetic resonance imaging from a 73 year old female with advanced cognitive impairment (score 18 on MMSE). Extensive hyperintensities can be seen in deep white matter, especially in periventricular region. She is under medication for hypertension and hyperlipidemia
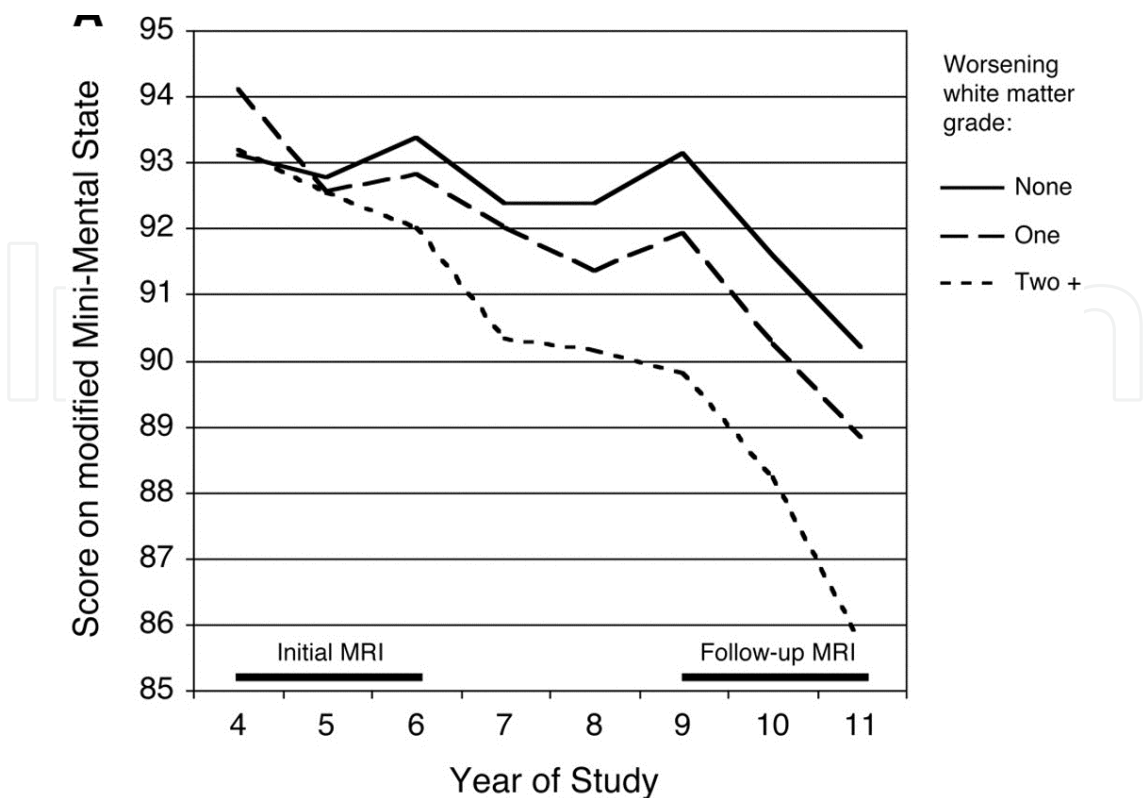
Fig. 3. Scores on modified Mini-Mental State Examination (vertical axis) for each year of study from initial to follow-up brain MRI scans (horizontal axis) by groups of participants (people aged 65 years and older) defined by worsening grade of white matter hyperintensity (three grade: None, grade One, and grade Two+).

Left ventricular systolic dysfunction:	Low left ventricular ejection fraction
Left ventricular diastolic dysfunction:	Reduced e', Increased E/e' ratio
B-type natriuretic peptide (BNP):	Increased BNP or N-terminal pro-BNP
Rhythm disturbance:	Development of atrial fibrillation
Ankle-brachial index (ABI):	Low ABI
Carotid ultrasonography	Internal carotid artery stenosis

e': early diastolic mitral annular myocardial velocity by tissue Doppler echocardiography

E: early diastolic mitral flow velocity by pulse-wave Doppler echocardiography

Table 2. Cardiovascular indexes possibly to detect cognitive impairment

5. Relationship between echocardiographic parameters and age

Currently, LV diastolic function is evaluated based upon the following indices. Using pulse-wave Doppler echocardiography, the ratio of E velocity and the late diastolic transmitral flow velocity (A): (E/A ratio), and early diastolic flow deceleration time are measured. By tissue Doppler echocardiography of mitral annular motion, e' myocardial velocity can be evaluated. Also, diastolic function was evaluated by the diastolic Doppler index (E/e'), and this index is also useful to evaluate LV end-diastolic pressure or left atrial pressure in patients with heart failure with depressed or normal LV EF (Ommen et.al., 2000).

Among the healthy subjects, the previous reports have evaluated the changes with age in various parameters. LV systolic function, obtained from LV EF by standard echocardiography or LV myocardial performance index using Doppler echocardiography, have shown minimum increments with age. However, LV diastolic function declined with age on echocardiographic parameters, i.e., E/A ratio and e' velocity decreased, and E/e' ratio increased (Munagala et al., 2003). Furthermore, LV wall thickness and LV mass increased gradually with age, and suggested depression of LV myocardial compliance (Daimon et al., 2008).

In some reports discussing the relationship between cognitive impairment and cardiovascular dysfunction, LV diastolic function was depressed with the deterioration of cognitive function, which may be more progressive than that with aging alone (Hogg et al. ,2004). Furthermore, in patients with heart failure, cognitive function is depressed, but there is no clear data as to whether LV systolic function is depressed with the decline of cognitive function and its decline is improved with the correction of systolic dysfunction.

6. Conclusion

While age is the most significant contributing factor to the development of cognitive impairment, several epidemiological studies have elucidated that cardiovascular risk factors, i.e., hyperlipidemia, hypertension, smoking and diabetes contribute to the deterioration of cognitive function. Furthermore, LV systolic and diastolic dysfunction, have been reported to cause cognitive impairment, likely as a result of the development of poor cerebral perfusion. Brain white matter hyperintensitiy and thromboembolic stroke due to atherosclerotic factors and atrial fibrillation are also related to producing cognitive impairment. Therefore, doctors and medical professionals, who are involved with medical treatment for cerebrovascular and cardiovascular diseases must keep in mind that atherosclerotic disease processes are also related to the development of cognitive impairment and progression of dementia.

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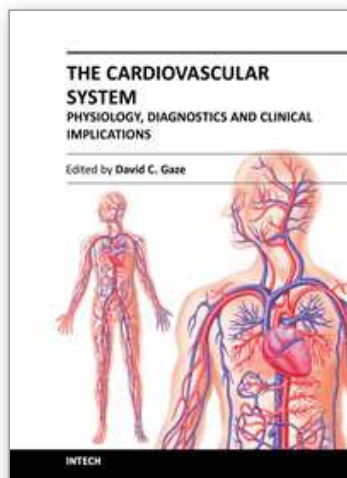
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