Objective: There have been few reports on the frequency of atherosclerotic diseases complicating carotid artery stenosis. This study was conducted to clarify the frequency of various atherosclerotic diseases concurrent with carotid artery stenosis that required revascularization.

Methods: Examinations concerning various atherosclerotic diseases were reviewed using clinical records of 152 consecutive patients who underwent carotid artery stenting from January 2012 to October 2016 at our hospital. The patients were also divided into those with systemic atherosclerosis (SA group) and those without SA (non-SA group), and their characteristics were analyzed.

Results: Of the 152 patients, carotid artery stenosis was complicated by other atherosclerotic diseases in 50 (32.9%), of whom 28 (18.4%) had coronary artery disease, 23 (15.1%) had peripheral artery disease, and 3 (2.0%) had renal artery stenosis. In the SA group, the frequencies of diabetes and dyslipidemia were significantly higher, hemoglobin A1c (HbA1c) level was higher, and high-density lipoprotein (HDL) cholesterol level and estimated glomerular filtration rate (eGFR) were lower.

Conclusion: Carotid artery stenosis that required revascularization was frequently complicated by other atherosclerotic diseases. It is considered necessary to treat carotid artery stenosis with the prevention of cardiovascular events.

Keywords: coronary artery disease, peripheral artery disease, renal artery stenosis

Introduction

Atherosclerosis is a primary cause of cardiovascular disorders, and carotid artery stenosis (CS), coronary artery disease (CAD), peripheral artery disease (PAD), and renal artery stenosis (RAS) are representative atherosclerotic diseases. A large-scale cohort study has shown that not only the mortality, but also the incidences of myocardial infarction and cerebral infarction are elevated in patients with such atherosclerotic diseases.

CS is known to be a cause of atherothrombotic brain infarction, and revascularization by carotid endarterectomy (CEA) as well as internal treatment is carried out as a standard treatment for severe internal CS. Also, with improvements in catheter technology, the therapeutic results of carotid artery stenting (CAS) have recently been improved, and CAS is being established as a therapeutic option for CS.

In actual clinical settings, we often encounter patients with CS complicated by other atherosclerotic diseases and those in whom CS is incidentally detected during the treatment for other atherosclerotic diseases such as CAD. In revascularization for CS, CAD has been reported to be a risk factor for early as well as late death, and PAD makes it difficult to perform CAS by the femoral approach and often limits devices and techniques that can be used. Thus, the concurrence of various atherosclerotic diseases affects the therapeutic strategy and outcomes of CS, but reports on the frequencies of CAD, PAD, and RAS as comorbidities of CS have been few. In the present study,
we investigated the frequencies of various atherosclerotic diseases complicating CS.

Materials and Methods

The subjects were 152 consecutive patients who underwent CAS for CS between January 2012 and October 2016. Those who underwent CAS for common CS, external CS, or iatrogenic internal carotid artery dissection associated with treatment were excluded. Clinical records were reviewed, and the results of transthoracic echocardiography (TTE), coronary angiography (CAG), and renal artery ultrasound and the ankle brachial pressure index (ABI) were retrospectively investigated.

Significant stenosis (≥75%) of the coronary artery demonstrated by CAG was defined as CAD, and, in patients who did not undergo CAG, left ventricular asynergy observed by TTE was defined as suspected CAD (sCAD). An ABI of <0.9 on either side was defined as PAD, and stenosis with a peak systolic velocity of ≥180 cm/sec on either side on renal artery ultrasound was defined as RAS.

The patients were divided into those with one or more atherosclerotic diseases (CAD, sCAD, PAD, and RAS) (systemic atherosclerosis [SA] group) and those with no atherosclerotic diseases (non-systemic atherosclerosis [non-SA] group), and the characteristics of each group and the frequencies of underlying diseases were compared.

Dual-antiplatelet therapy was performed before CAS in all patients who tolerated the therapy. CAS was performed using distal embolic protection devices in all patients, and the optimal device was selected for each patient by the operator.

The signal intensity of the carotid artery plaques was evaluated using T1-weighted image (T1-WI) of MRI (GE SIGNA Scanner; GE Healthcare Life Sciences, Pittsburgh, PA, USA). The value of signal intensity ratio (SIR) of the plaque was calculated with reference to the signal intensity of adjacent sternomastoid muscle.

This study was approved by the institutional review board of our hospital.

Definitions of complications and underlying diseases

All deaths, symptomatic strokes, and myocardial infarctions that occurred within 1 month after the CAS were defined as the major adverse events (MAEs), and their cumulative incidence was calculated. Also, in patients who underwent diffusion-weighted MR imaging (DWI) before and within a few days after the procedure, hyperintensities newly observed after the procedure were defined as new DWI high lesions.

Conditions that met the following descriptions were defined as underlying diseases. Hypertension: The presence of a history of hypertension or current use of antihypertensive drugs. Diabetes: A hemoglobin A1c (HbA1c; National Glycohemoglobin Standardization Program [NGSP]) of ≥6.9% or current use of antidiabetic agents including insulin. Dyslipidemia: A total cholesterol level of ≥220 mg/dL, a low-density lipoprotein (LDL) cholesterol level of ≥140 mg/dL, or current use of antidyshlipidemic drugs.

Statistical analysis

Continuous variables were tested by the unpaired t-test or Mann–Whitney U-test, and nominal variables were tested by the chi-square test or Fischer’s exact test. The tests were performed using statistical software, EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), and a P value of <0.05 was judged to be significant.

Results

Table 1 shows the background of the 152 patients enrolled in this study. Their mean age was 75.2 ± 7.8 years, and they included 135 males (88.9%) and 111 patients with symptomatic internal CS (73.0%). The underlying diseases were hypertension in 121 (79.6%), diabetes in 60 (39.4%), and dyslipidemia in 90 (59.2%).

Dual protection (concomitant use of distal-filter protection and flow-reversal), which is the first-line distal embolic protection at our hospital, was used in 134 patients (88.2%), distal protection was employed in 13 (8.6%), and proximal protection was selected in 5 (3.3%). Of the 13 patients in whom distal protection was selected because the transfemoral approach was unable in 10 due to PAD and in 2 due to marked tortuosity of the aorta, distal protection, which can be used by the brachial approach, was employed. In the remaining one patient, dual protection was shifted to distal-filter protection alone during the procedure due to marked intolerance to common carotid artery occlusion.

Table 2 shows the results of examinations concerning various atherosclerotic diseases. Of the 152 patients, 141 (92.8%) underwent TTE, and 18 (11.8%) of them exhibited left ventricular asynergy. CAG was performed in 32 (21.1%), and 28 (18.4%) showed significant ≥75% stenosis of the coronary artery. As a result, CS was complicated by CAD or sCAD (CAD/sCAD) in 36 (23.7%).
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in 50 (32.9%) of the 152 patients. It was concurrent with CAD/sCAD and PAD in 10; CAD/sCAD and RAS in 2; PAD and RAS in 1; and CAD, PAD, and RAS in 1. No atherosclerotic disease other than CS was detected in the remaining 102 patients (67.1%).

The ABI was examined in 83 (54.6%), and it was <0.9 in 23 (15.1%). CS was complicated by PAD in 27.7% of those in whom the ABI was examined.

Renal artery ultrasound was performed in 31 (20.4%), and 3 (2.0%) showed stenosis with a peak systolic velocity (PSV) of ≥1.8 m/sec. CS was complicated by RAS in 9.7% of the patients who underwent renal artery ultrasound.

MAEs were observed within 1 month after the procedure in seven patients (4.6%), and they were cerebral infarction in five patients (symptoms were transient in two patients), cerebral hemorrhage in one patient, and death due to infection in one patient. New DWI high lesions were observed in 61 (40.1%) patients.

Figure 1 shows the frequency of various complications. CS was complicated by other atherosclerotic diseases in 50 (32.9%) of the 152 patients. It was concurrent with CAD/sCAD and PAD in 10; CAD/sCAD and RAS in 2; PAD and RAS in 1; and CAD, PAD, and RAS in 1. No atherosclerotic disease other than CS was detected in the remaining 102 patients (67.1%).

Table 1 Patient characteristics and devices

<table>
<thead>
<tr>
<th>All patients n = 152</th>
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<tr>
<td>Age, mean (SD)</td>
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<tr>
<td>Male gender, n (%)</td>
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<tr>
<td>Symptomatic lesion, n (%)</td>
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<tr>
<td>Left side, n (%)</td>
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<tr>
<td>Hypertension, n (%)</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
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<td>Dyslipidemia, n (%)</td>
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<td>HbA1c %, median (quartile)</td>
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<td>T-cho mg/dL, median (quartile)</td>
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<td>eGFR mL/min/1.73 m², median (quartile)</td>
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<tr>
<td>eGFR &lt;60 mL/min/1.73 m², n (%)</td>
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<tr>
<td>Dual protection, n (%)</td>
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<td>Distal protection, n (%)</td>
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<td>Proximal protection, n (%)</td>
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Table 2 The outcome of examination and complication

<table>
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<th>All patients n = 152</th>
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<tr>
<td>Transthoracic echocardiography, n (%)</td>
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<td>Asynergy, n (%)</td>
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<td>LVEF %, mean (SD)</td>
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<td>Coronary angiography, n (%)</td>
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<td>Coronary artery stenosis, n (%)</td>
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<td>CAD/sCAD, n (%)</td>
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<td>ABI examination, n (%)</td>
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<td>ABI &lt; 0.9, n (%)</td>
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<tr>
<td>Renal artery duplex scan, n (%)</td>
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<tr>
<td>Renal artery stenosis, n (%)</td>
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<td>Major adverse event at 1 month, n (%)</td>
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<td>Appearance of new DWI high lesion, n (%)</td>
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ABI: ankle brachial pressure index; CAD/sCAD: coronary artery disease/suspected coronary artery disease; DWI: diffusion-weighted MR imaging; LVEF: left ventricular ejection fraction

No comorbidity n=102 (67.1%)

Fig. 1 Incidence of comorbidities among the study patients. In 50 (32.9%) of the 152 patients, CS was complicated by other atherosclerotic diseases. It was complicated by CAD/sCAD and PAD in 10 patients; CAD/sCAD and RAS in two patients; PAD and RAS in one patient; and CAD, PAD, and RAS in one patient. CAD: coronary artery disease; CS: carotid artery stenosis; PAD: peripheral artery disease; RAS: renal artery stenosis; sCAD: suspected CAD.
Comparison between the SA and non-SA groups

Table 3 shows the characteristics of the SA and non-SA groups. No significant difference was observed in age, sex, or the percentage of symptomatic patients between the two groups. In the SA group, diabetes (56% vs. 31.4%, \(p < 0.01\)) and dyslipidemia (76% vs. 51%, \(p < 0.01\)) were observed significantly more frequently, the HbA1c level was higher (6.8% vs. 6%, \(p = 0.02\)), and the high-density lipoprotein (HDL) cholesterol level (44 vs. 48 mg/dL, \(p = 0.03\)) and eGFR (56 vs. 65 mg/dL, \(p < 0.01\)) were lower, than in the non-SA group (Fig. 2). The SIR of plaques showed no significant difference between the two groups (1.2 vs. 1.27, \(p = 0.24\)). Although MAEs were observed more frequently in the SA group than in the non-SA group, the difference was not significant (8.0% vs. 2.9%, \(p = 0.22\)).

Discussion

Of the 152 patients who underwent CAS for CS at our hospital, CS was complicated by CAD in 28 (18.4%), CAD/sCAD in 36 (23.7%), PAD in 23 (15.1%), and RAS in 3 (2%). In the SA group with these complications, the frequencies of diabetes and dyslipidemia were significantly higher, the HbA1c level was higher, and the HDL cholesterol level and eGFR were lower, compared with the non-SA group. Also, MAEs were observed within 1 month after the procedure more frequently in the SA group although the difference was not significant.

Atherosclerosis is a systemic disorder, and CS, CAD, PAD, and RAS have been reported to often concur with one another.\(^{13,21,22}\) Since such diseases that cause thrombosis based on atherosclerosis show a common pathogenic pattern, a pathological concept called atherothrombosis (ATIS) has been proposed recently.\(^{23,24}\) In addition, the presence of carotid artery plaque and intima-media thickness (IMT) of the carotid artery is recognized as surrogate markers of atherosclerosis, and CS has been reported to be often complicated by other atherosclerotic diseases.\(^{25–27}\) Hertzer et al.\(^{12}\) performed CAG in 506 patients with extra-cranial CS and reported that the coronary artery was normal in only 7% and markedly stenosed in 35%. Gates et al.\(^{28}\) reported that 1124 (39.9%) of 2815 patients with symptomatic CS had a history of symptomatic CAD and that 371 (13.5%) had already received coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). There is also a report that CS was complicated by RAS in 27% of the patients.\(^{17}\)

Conversely, the frequencies of concurrence of CS in CAD and PAD patients have also been reported.\(^{11,29}\) Kawarada et al.\(^{16}\) observed that CAD was complicated by CS in 13.7% and by PAD in 15.3% of the 380 patients who underwent elective CABG and reported the necessity of screening patients with cardiovascular risk factors for atherosclerotic diseases.\(^{11}\) Marek et al.\(^{29}\) performed carotid artery ultrasound in 188 patients showing claudication with no history of cerebrovascular disorder and reported that ≥50% internal CS was noted in 24.5% and that it was occluded in 2.7%.

In this study, of the 152 patients who underwent CAS, CS was complicated by CAD/sCAD in 36 (23.7%), PAD in 23 (15.1%), and RAS in 3 (2%), but the frequencies of these complications were lower than those observed in the
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In large-scale clinical studies, perioperative myocardial infarction occurred in 1%–4% of the patients who underwent CAS, and this incidence was reported to be lower than in CEA. However, if findings suggestive of ischemic heart disease such as left ventricular asynergy can be detected before the procedure, preventive measures such as the preoperative consultation with the cardiologist and use of cardioprotective drugs can be taken, with possible decreases in perioperative complications of CAS. Moreover, in patients judged to be at a high risk of perioperative complications of CAS by preoperative screening, intervention in complications before carotid artery intervention and, in some cases, change of the therapeutic strategy to medical treatment should be evaluated as options. For these reasons, preprocedural cardiodynamic screening should be performed as much as possible for safe execution of CAS except special cases such as emergency CAS. Particularly, as TTE is a noninvasive and inexpensive test, and as it can detect left ventricular asynergy and severe valvular disease, it is recommended to be performed aggressively.

Since, in this study, the complication rates of diabetes and dyslipidemia were significantly higher, and the eGFR was lower, in the SA group, we consider that noninvasive screening should be performed aggressively, particularly, in CS patients with diabetes, dyslipidemia, or renal dysfunction.

In the management of patients with CS in the chronic period after revascularization, also, it is considered necessary to attend to the prevention of systemic cardiovascular events as well as cerebral infarction and to conduct systemic management and aggressive control of underlying conditions.
diseases in association with other departments including the cardiology department.

Limitations of this study were as follows: 1) the number of subjects was small, 2) the study was retrospective, 3) it was a single-center study, and 4) there was selection bias because the study did not include patients who underwent revascularization by CEA or did not undergo revascularization. In addition, as mentioned above, many patients did not have some examinations, and there is a possibility that the frequency of the concurrence of complications is underestimated due to differences in the definition of diseases.

**Conclusion**

CS that required revascularization was frequently complicated by CAD, PAD, and RAS. In treating CS, it is considered necessary to conduct a search for complications and aggressive management of underlying diseases with the prevention of not only cerebral infarction but also systemic cardiovascular events.

**Disclosure Statement**

Neither the first author nor any of the coauthors have any conflicts of interest to disclose.

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