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Chapter 2

Intracranial Carotid Artery Stenosis Diagnosed with CTA in a Western Population: Predictor for Poor Outcome

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Abstract

Background: The prevalence and impact of intracranial atherosclerosis in the white population is sparsely researched and optimal treatment remains to be defined. Previously, we found that 84% of the patients with extracranial internal carotid artery (ICA) stenosis also had an intracranial ICA stenosis diagnosed with CT angiography (CTA).

The purpose of this chapter is to investigate the relation between intracranial ICA stenosis and outcome.

Methods: We conducted a single center cohort study with long-term follow-up of 84 patients with TIA or infarct that underwent a CTA for the assessment of a carotid artery stenosis between April 1, 2006 and December 31, 2008. Intracranial ICA stenosis was categorised in four groups: without any stenosis (<30%), with any stenosis (≥ 30%), without severe stenosis (<70%), and with severe stenosis (≥ 70%), Primary outcome was recurrent TIA or infarct. Secondary outcomes were MI, vascular death and functional outcome. Poor functional outcome was defined as mRS ≥3.

Results: Mean follow-up in the 84 patients was 4.1 years (±1.2 years). Comparing patients without stenosis to patients with any stenosis (≥30%), no differences in primary and secondary outcomes were found. Severe stenosis (≥70%) was not associated with recurrent stroke, but was strongly associated with vascular death (OR 7.85 (1.9 - 32.5)) and poor functional outcome (OR 4.33 (1.15 - 16.37)).

Conclusion: Severe intracranial ICA stenosis on CTA in a white population is associated with a higher rate of vascular death and poor functional outcome.

Introduction

The presence of atherosclerotic disease in the extracranial part of the internal carotid artery (ICA) is a strong predictor for recurrent ischemic stroke in patients who have recently had symptoms (TIA or stroke). [1] It has been shown that the presence of intracranial atherosclerosis also is an independent risk factor for recurrent stroke, especially in blacks, Asians and Hispanics. [2] However, the prevalence and prognosis of intracranial atherosclerosis in the western (mainly white) population is still sparsely studied and optimal treatment remains to be defined. [3]

Kappelle et al. reported intracranial atherosclerosis in one third of the patients with symptomatic extracranial stenosis. [4]

Wityk et al. found a prevalence of intracranial stenosis of 24%. [5]

The diagnosis of an intracranial stenosis in these studies was based on evaluation with Digital Subtraction Angiography (DSA) and Transcranial Doppler (TCD). CT angiography (CTA) allows the assessment of the full 3D morphology of the intracranial vasculature. [6-8] Few studies determined the prevalence of intracranial stenosis using CTA. Recently, we reported a much higher prevalence of intracranial ICA stenosis on 64-section CTA compared with earlier publications: 84% for a degree of stenosis of ≥30% and 39% for a degree of stenosis of ≥50%. [4, 5, 9]

The clinical relevance of the presence of intracranial ICA stenosis on CTA images remains to be elucidated, the purpose of this chapter is to determine the relation between the presence of intracranial ICA stenosis on CTA images and the rate of recurrent stroke and other neurological, cardiovascular and functional outcomes.

Materials and Methods

Study Design

We conducted a single center cohort study with long-term follow-up of all consecutive patients with TIA or infarct that underwent a CT angiography on a 64-section CT scanner for the assessment of a carotid artery stenosis between April 1, 2006 and December 31, 2008.

Study Population

According to our current hospital guidelines, a duplex ultrasound examination was performed in all patients with a TIA or a cerebral infarct, suspected of having a carotid artery stenosis. If this duplex showed an extracranial stenosis of ≥30% in men and ≥50% in women, subsequent CTA was performed. [10] All consecutive patients that underwent a CTA on a 64-section CT scanner (Brilliance 64, Philips Healthcare, Best, the Netherlands) in the Academic Medical Center (AMC) under suspicion of a symptomatic carotid artery stenosis between April 2006 and December 2008 were included in our study. Patients were excluded if there was a history of previous carotid

endarterectomy or stenting, and if the images of the CTA studies were of insufficient quality. [9]

CTA Analysis

The degree of intracranial carotid artery stenosis was measured by an experienced neuroradiologist according to the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) criteria. [10] The most severe intracranial ICA narrowing of both carotid arteries was used as measurement for degree of intracranial ICA stenosis. For the comparative analyses four groups were defined: without any stenosis (< 30%), with any stenosis (≥ 30%), without severe stenosis (< 70%), and with severe stenosis (≥ 70%).

Baseline Characteristics

Baseline characteristics included age, sex, ethnicity, index event (TIA, cerebral infarct or amaurosis fugax), cardiovascular risk profile (blood pressure, diabetes, smoking habit, and cholesterol), carotid interventions after the index event, and a history of cerebrovascular-, cardiovascular- and peripheral vascular disease. [11] Hypertension was defined as a clinical history of systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or the use of blood pressure lowering medication.

Diabetes was defined as a serum glucose level of ≥ 7.9 mmol/L or treatment with antidiabetic medication. Hypercholesterolemia was defined as a clinical history of hypercholesterolemia, the use of cholesterol lowering medication or a total cholesterol of ≥ 5.0 mmol/L if no further information could be found. Data was obtained retrospectively from medical records and discharge letters from our hospital.

Outcomes

The primary outcome was rate of recurrent TIA or infarct. If new focal neurological symptoms occurred and resolved within 24 hours without the presence of hemorrhage on radiological imaging of the brain, the event was classified as TIA. If the symptoms lasted longer than 24 hours and imaging showed no abnormalities or an infarct, it was defined as recurrent infarct.

Secondary outcomes were myocardial infarction, vascular death and a combined endpoint (TIA or cerebral infarct, myocardial infarction, and vascular death). Myocardial infarction was defined as symptoms of cardiac ischemia with the rise of cardiac biomarkers.

Vascular death was defined as sudden death or death within 30 days after any of these events: myocardial infarction, pulmonary embolism, rupture of an aortic aneurysm or terminal heart failure. In addition, we assessed the functional outcome, as defined on the modified Rankin Scale (mRS). A mRS-score ≥ 3 was considered a poor functional outcome.

Follow-Up

Outcomes were assessed by a structured telephone-interview by a single observer (W.E.S), blinded for all radiological test results. Patients were asked if any recurrent event had occurred. As part of the structured interview, the mRS was assessed. [12, 13] Medical records in our hospital were reviewed to verify if new events reported by the patient met our definitions. The general practitioner was contacted any case of uncertainty, if the patient had died, or if a recurrent event was evaluated in another hospital; the general practitioner was then asked for the discharge letter and additional information.

Statistical Analysis

Baseline differences between patients without any stenosis (<30%) and with any stenosis (≥ 30%) and between patients without severe stenosis (<70%) and with severe stenosis (≥ 70%) were compared using the χ^2 test. We compared the outcomes between the groups without any stenosis (<30%), with any stenosis (≥30%), without severe stenosis (<70%), and with severe stenosis (≥70%), using odds ratio's with 95% confidence interval. Kaplan-Meier survival analysis was used to assess the vascular mortality rate. Kaplan-Meier curves were compared using the Log-Rank test.

All analyses were performed using SPSS Statistics 19.0. A P-value of less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

Eighty-four consecutive patients were included. Baseline characteristics are shown in table 1. Mean age was 67.6 ± 12.6 years and 50 patients (60%) were male. Seventy-six patients (90.4%) were white. There were seven (8%) patients without any stenosis, 77 (92%) with any stenosis, 73 (87%) patients without severe stenosis and 11 (13%) patients with severe stenosis. Regarding the baseline characteristics no significant differences between patients without stenosis and patients with any stenosis were found. Patients with a severe stenosis (≥70%) were significantly more often male, non-white, had a history of coronary artery disease, diabetes and hypercholesteroleamia as compared with patients without a severe stenosis (<70%).

Primary Outcomes

Mean follow-up time was 4.1 (± 1.2) years. A total of 7 recurrent TIA's occurred during the follow-up period. One patient (14%) without any stenosis (<30%) had a recurrent TIA, compared with 6 patients (8%) with any stenosis (≥30%) (OR 0.51 (0.05 - 4.93)). Six recurrent TIA's (8%) occurred in patients without severe stenosis (<70%), compared with 1 (9%) in a patient with severe stenosis (≥70%) (OR 1.12 (0.12 - 10.27)). A total of 11 recurrent infarcts occurred during the follow-up period. All infarcts (14%) occurred in patients with any stenosis (≥30%) (OR 2.59 (0.14 - 48.6)). Ten infarcts (14%) occurred in patients without severe stenosis (<70%), as compared with 1 (9%) in a patient with a severe stenosis (≥70%) (OR 0.63 (0.07 - 5.5)). Table 2 and figure 1 and 2 show the outcomes for the different intracranial ICA stenosis groups.

Secondary Outcomes

Ten patients had a myocardial infarction during the follow-up period. No differences in the occurrence of myocardial infarctions were found comparing patients without any stenosis with patients with any stenosis, and patients with or without a severe stenosis. Fifteen patients deceased during follow-up (18%).

Table 1. Baseline characteristics for patients with and without intracranial ICA stenosis and for patients with and without severe intracranial ICA stenosis

Baseline characteristics		Intracranial internal carotid artery stenosis					
	Total	<30%	≥ 30%	p	<70%	≥ 70%	p
Patient Characteristic	n = 84	n = 7	n = 77		n = 73	n = 11	
Mean Age	67.6 (±12.6)	64.6 (±15.0)	67.9 (±12.5)		67,6 (±12.7)	67,8 (±12.9)	
Male sex	50 (59.5)	5 (71.4)	45 (58.4)	0.5	40 (54.8)	10 (90.9)	0.023
Ethnicity							
White	76 (90.4)	6 (85.8)	70 (90.9)	0.654	68 (93.2)	8 (72.7)	0.031
Non-White	8 (9.6)	1 (14.2)	7 (9.1)	0.654	5 (6.8)	3 (27.3)	0.031
Index event							
Amourosis Fugax	14 (16.7)	3 (42.9)	11 (14.3)	0.052	14 (19.2)	0 (0)	0.11
TIA	31 (36.9)	3 (42.9)	28 (36.4)	0.73	26 (35.6)	5 (45.5)	0.53
Ischemic infarction	39 (46.4)	1 (14.2)	38 (49.3)	0.075	33 (45.2)	6 (54.5)	0.56
Carotid intervention							
CEA	29 (34.5)	4 (57.1)	25 (32.5)	0.19	26 (35.6)	3 (27.3)	0.59
Stent	19 (22.6)	0 (0)	19 (24.7)	0.135	17 (23.3)	2 (18.2)	0.71
History							
Stroke	32 (38.1)	3 (42.9)	29 (37.7)	0.79	27 (37.0)	5 (45.5)	0.59
Coronary Artery Disease	20 (23.8)	0 (0)	20 (26.0)	0.12	13 (17.8)	7 (63.6)	0.001
Peripheral Artery Disease	13 (15.5)	0 (0)	13 (16.9)	0.24	10 (13.7)	3 (27.3)	0.25
Risk Factors							
Current Smoker	35 (41.7)	3 (42.9)	32 (41.6)	0.95	29 (39.7)	6 (54.5)	0.35
Ex-smoker	30 (35.7)	3 (42.9)	27 (35.1)	0.68	28 (38.4)	2 (18.2)	0.19
Hypertension	60 (71.4)	4 (57.1)	56 (72.7)	0.38	50 (68.5)	10 (90.9)	0.13
Diabetes mellitus	22 (26.2)	0 (0)	22 (28.6)	0.10	16 (21.9)	6 (54.5)	0.022
Hypercholesteroleamia	51 (60.7)	3 (42.9)	48 (62.3)	0.31	41 (56.2)	10 (90.9)	0.028
Symptomatic Extracranial Stenosis							
0 - 29%	10 (11.9)	2 (28.7)	8 (10.4)	0.16	10 (13.7)	0 (0)	0.19

Table 1. (Continued)

Baseline characteristics		Intracranial internal carotid artery stenosis					
	Total	<30%	≥ 30%	p	<70%	≥ 70%	p
Symptomatic Extracranial Stenosis							
30 – 49%	9 (10.7)	1 (14.2)	8 (10.4)	0.75	9 (12.3)	0 (0)	0.22
50 – 69%	27 (32.1)	3 (42.9)	24 (31.2)	0.53	22 (30.1)	5 (45.5)	0.31
70 – 99%	30 (35.7)	1 (14.2)	29 (37.7)	0.23	25 (34.2)	5 (45.5)	0.47
Occlusion	8 (9.6)	0 (0)	8 (10.4)	0.37	7 (9.7)	1 (9.0)	0.96

Data are in mean ± standard deviation (SD) or number (n) of patients (%).
TIA = Transient Ischaemic Attack. CEA = Carotid Endarterectomy.

Table 2. the distribution of events in the follow-up period in patients with and without intracranial ICA stenosis (left part) and in patients with and without severe intracranial ICA stenosis (right part)

Follow-up	Intracranial internal carotid artery stenosis (n=84)					
	<30%	≥ 30%	OR (95% CI)	<70%	≥ 70%	OR (95% CI)
Event	n=7	n=77		n=73	n=11	
TIA	1 (14)	6 (8)	0.51 (0.05 - 4.93)	6 (8)	1 (9)	1.12 (0.12 - 10.27)
Cerebral Infarct	0 (0)	11 (14)	2.59 (0.14 - 48.6)	10 (14)	1 (9)	0.63 (0.07 - 5.5)
Myocardial Infarction	0 (0)	10 (13)	2.33 (0.12 - 43.9)	9 (12)	1 (9)	0.71 (0.08 - 6.23)
Vascular Death	0 (0)	12 (16)	2.86 (0.15 - 53.4)	7 (10)	5 (46)	7.85 (1.9 - 32.5)
Combined Endpoint	1 (14)	28 (36)	3.4 (0.39 - 30)	23 (32)	6 (55)	2.6 (0.72 - 9.43)
mRS ≥ 3	0 (0)	28 (36)	8.64 (0.48 - 157)	21 (29)	7 (64)	4.33 (1.15 - 16.37)

Data are in number (n) of events (%) or OR (95% CI).
OR = Odds Ratio.
TIA= Transient Ischaemic Attack.
mRS = modified Rankin Scale.

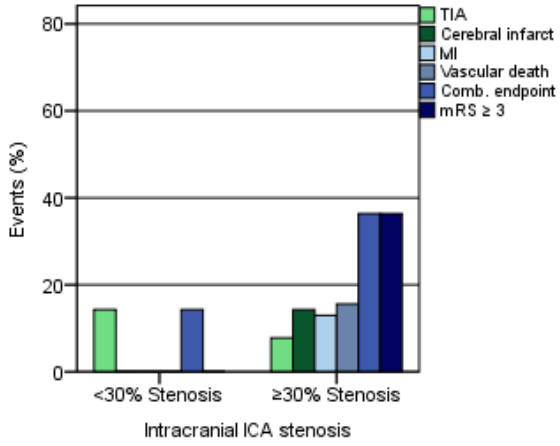

Figure 1. Bar chart of number of events (%) comparing patients without stenosis (<30%) to patients with stenosis (≥30%).

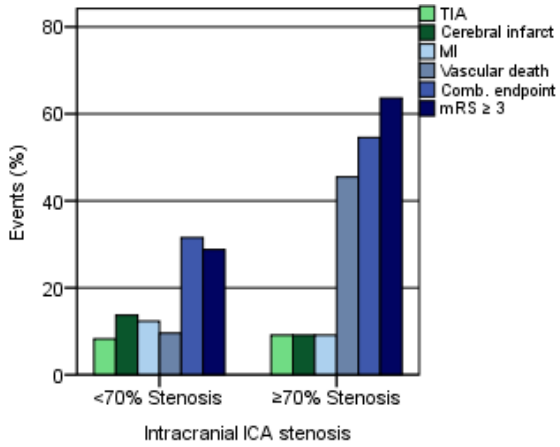

Figure 2. Bar chart of number of events (%) comparing patients without severe stenosis (<70%) to patients with severe stenosis (≥70%).

Twelve were regarded vascular deaths (16%) and all occurred in patients with any (≥30%) stenosis (OR 2.86 (0.15 - 53.4)).

Five of these deaths (46%) occurred in the group of patients with a severe stenosis (≥70%) (OR 7.85 (1.9 - 32.5)). Twenty-nine patients reached the combined endpoint of TIA, cerebral infarct, myocardial infarction, or vascular death.

One patient (14%) without any stenosis reached the combined endpoint, as compared with 28 patients (36%) with any stenosis (OR 3.4 (0.39 - 30)). Twenty-three patients (32%) without a severe stenosis reached the combined endpoint, as compared with 6 patients (55%) with a severe stenosis (OR 2.6 (0.72 - 9.43)). A total of 28 patients had a poor functional outcome (mRS ≥3). All of these patients had any intracranial stenosis. Twenty-one patients (29%) without a severe stenosis had a poor functional outcome, as compared with 7 patients (64%) with a severe stenosis (OR 4.33 (1.15 - 16.37)) (Table 2) (Figure 1 and 2). A Kaplan–Meier survival curve is shown in figure 3. This figure shows that the mortality rate is higher in patients with any intracranial ICA stenosis as compared with patients without any intracranial ICA stenosis, but this was not statistically significant (p=0.28)

Discussion

In this chapter we have shown that patients with any intracranial ICA stenosis (≥30%) on CTA images did not have a significantly higher rate of recurrent TIA, infarct or secondary outcomes compared to patients without stenosis (<30%). When comparing patients without severe stenosis (<70%) with patients with a severe stenosis (≥70%), also no increase in rate of recurrent TIA of infarct was found, but severe intracranial ICA stenosis was associated with vascular death and a poor functional outcome. In our previous study, we found that as much as 84% of the patients with extracranial internal carotid artery (ICA) stenosis and acute ischemic symptoms did also have an intracranial ICA stenosis in CT angiography data sets. We believe this prevalence is high as a result of the use of 64-section CTA for imaging.

In this previous study, we have also shown that the degree of extracranial ICA stenosis is not correlated with the degree of intracranial stenosis in this patient group. [9]

Present study shows that severe intracranial ICA stenosis (≥70%) is associated with male sex, non-white race, a history of ischemic heart disease, diabetes and hypercholesteroleamia. A previous analysis of the WASID cohort shows that diabetes and lipid disorder are associated with severity of intracranial stenosis, our study supports these findings. [11] This chapter also shows that diabetes was specifically associated with intracranial carotid artery stenosis, compared with other locations of intracranial stenosis, however, the pathological mechanism of this difference remains unclear.

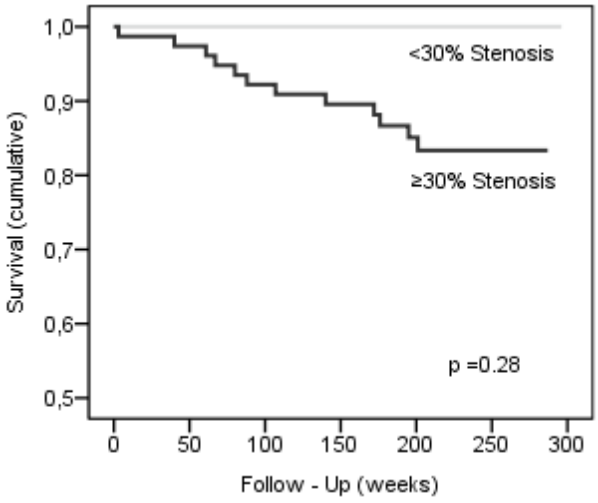

Figure 3. Kaplan-Meier analysis showing vascular death in patients with and without intracranial carotid artery stenosis.

Other studies show an association between male sex [5] and black race [14] and symptomatic intracranial stenosis, but an association between these risk factors and severity of intracranial ICA stenosis has not been reported before.

The rate of recurrent stroke in our current study (22%), 8% recurrent TIA and 14% cerebral infarct in patients with intracranial ICA stenosis, is comparable to previously reported 18% and 19% recurrent stroke in comparable cohorts. [4, 15] These studies, however, had shorter follow-up periods compared with present study. When comparing cardiovascular events during follow-up between the four subgroups, we found some remarkable results. Firstly, we found a difference in the number of events between patients with any stenosis, as compared with patients without any stenosis: only 1 event (TIA) occurred in 7 patients without any stenosis, whereas 39 events (TIA, infarct, myocardial infarction or vascular death) occurred in the 77 patients with any stenosis. Though this was not statistically significant, there is a clear trend that the presence of any intracranial ICA stenosis is associated with an increase of cardiovascular events during follow-up. Secondly, we found a clear association between the severity of intracranial ICA stenosis and functional outcome. The odds ratio for vascular death and poor functional outcome was significantly higher for patients with presence of severe intracranial ICA stenosis. The high number of vascular deaths may be due to

the high number of patients with vascular risk factors in the group of patients with severe intracranial ICA stenosis. 91% of these patients had diabetes and hypercholesteroleamia and 64% had a history of coronary artery disease, all of these factors contribute to the risk of vascular death. An increase of vascular deaths in patients with intracranial ICA stenosis has been reported previously and our results support these findings. [16] The functional outcome, as measured on the modified Rankin Scale (mRS), in patients with severe stenosis, has to our knowledge not been reported before.

However, six of the seven patients with severe stenosis and a poor functional outcome were deaths. There was no increase in patients with severe disability (mRS = 4 or 5) in patients with severe intracranial stenosis (figure 4).

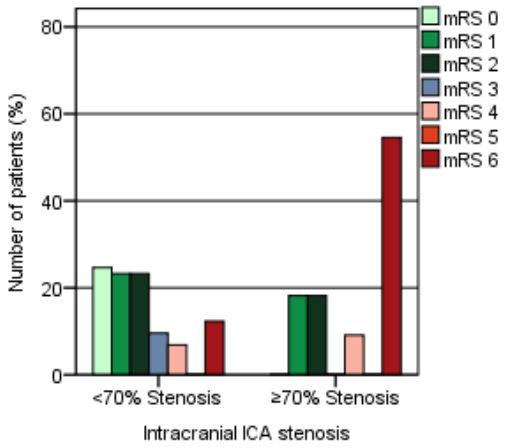

Figure 4. Modified Rankin Scale in patients without and with severe intracranial ICA stenosis.

We found a clear association between severe intracranial ICA stenosis and vascular death, however, we could not find such an association for the occurrence of recurrent TIA or stroke. This result was unexpected, as previous studies show a clear increase in risk of recurrent stroke in patients with intracranial stenosis, especially in patients with severe stenosis (≥70%). [15, 17] Our results support a large study in a German population that concludes that there is no clear association between recurrent stroke and intracranial stenosis. [18] However, this study had a considerably lower prevalence of intracranial stenosis (6.5%) as compared with present study. An explanation for the difference may be the composition of the study population. Studies by

Kasner et al. and Wong et al. used a 42% non-white and Asian population, whereas the study by Weimar et al. and present study used a largely white population. The association between intracranial stenosis and recurrent stroke in a largely white population is less clear as compared with other populations. Considering the current risks of intracranial stenting, this association needs to be further evaluated. [19]

There are several limitations to our study. Patients were asked to recall events in a time span of 3 to 5 years.

As a result, events could have been missed, which results in an underestimation of the incidence of events. We limited this risk by collecting medical records of all patients, and by contacting the general practitioner in case of doubt. A second limitation to our study is the relatively small group size. The findings now need to be confirmed in a larger cohort with longer follow-up; in particular to investigate whether the risk of ipsilateral stroke is higher in patients with intracranial ICA stenosis.

Conclusion

Patients with any intracranial ICA stenosis did not have a significantly higher rate of recurrent TIA or infarct. Severe intracranial ICA stenosis on CTA in a white population is associated with a higher rate of vascular death and poor functional outcome. A larger prospective trial using CTA is needed to gain more insight on recurrent stroke rate and prevalence of intracranial ICA stenosis.

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