1 Epidemiology, Anatomy and Imaging

1 Epidemiology and pathophysiology of carotid artery disease

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Carotid artery disease can be the cause of cerebrovascular symptoms, namely transient ischemic attacks (TIAs), amaurosis fugax, and stroke. This chapter considers the epidemiology and pathophysiology of carotid artery disease.

Epidemiology

According to the most recent World Health Organization (WHO) report,[1] cerebrovascular disease (stroke) is the second leading cause of death worldwide after ischemic heart disease. In 2004, stroke was responsible for 9.7% (n = 5 700 000) of deaths worldwide. A further analysis by national income, showed that whereas stroke was the fifth leading cause of death in low-income countries, accounting for 1 500 000 deaths in 2004 (5.6% of total deaths), it was the second leading cause of death in high-income countries, accounting for 800 000 deaths (9.3% of total deaths) and the leading cause of death in middle-income countries, accounting for 3 500 000 deaths in 2004 (14.2% of total deaths).[1] Optimistic and pessimistic scenarios for the projected deaths due to stroke worldwide for the years 2008, 2015, and 2030 as calculated by the WHO are given in Table 1.1.

Approximately 9 000 000 episodes of first-ever stroke occurred worldwide in 2004.[2] A separate analysis by region showed 700 000 first-ever strokes in Africa, 900 000 in North and South America, 400 000 in the Eastern Mediterranean, 2 000 000 in Europe, 1 800 000 in South-East Asia, and 3 300 000 in the Western Pacific.[2]

Stroke is the third leading cause of death in the US after ischemic heart disease and cancer.[3] Among adults older than 20 years, the estimated prevalence of stroke in 2005 was 5 800 000 (approximately 2 400 000 males and 3 400 000 females). Each year about 780 000 people experience a new or recurrent stroke. About 600 000 of these are first attacks and 180 000 are recurrent episodes. On average, every 40 s someone in the US has a stroke.[3] Of all strokes in the US population, 87% are ischemic, 10% are intracerebral hemorrhage, and 3% are subarachnoid hemorrhage.[3]

Male stroke incidence rates are greater than female rates at younger ages but not at older ages. The male-to-female incidence ratio was 1.25 for 55–64 years; 1.50 for 65–74 years; 1.07 for 75–84 years; and 0.76 for over 85 years. Blacks have almost twice the risk of first-ever stroke compared with whites. The age-adjusted stroke incidence rates at 45–84 years are 6.6 and 4.9 per 1000 population in black males and females, and 3.6 and 2.3 in white males and females, respectively.[3]

Stroke accounted for 1 in every 16 deaths in the US in 2004.[3] Stroke mortality for that year was 150 074 (58 800 males; 91 274 females). Stroke total mention mortality (includes deaths where the given cause was listed anywhere on the death certificate or was selected as the underlying cause, whether primary or secondary) in 2004 was approximately 253 000.

Apart from being a leading cause of death, stroke is also a major cause of moderate/severe disability. According to the data provided by the WHO, in 2004 there were 30 700 000 stroke survivors worldwide: 1 600 000 in Africa, 4 800 000 in North and South America, 9 600 000 in Europe, 4 500 000 in South-East Asia, and 9 100 000 in the Western Pacific.[2] In terms of disease burden as measured using disability-adjusted life years (DALYs), where 1 DALY represents the loss of the equivalent of 1 year of full health, in 2004 and for all ages, stroke was the sixth leading cause of burden of disease, being responsible for 46 600 000 DALYs worldwide.[4] This ranking is deceiving because it is the average from both low- and high-income countries. If we consider low-income countries alone, stroke does not appear in the top 10 causes of disease; instead conditions such as malaria and tuberculosis dominate.[5] Thus, for medium- and high-income countries, stroke is in fact even higher in the ranking; it is the third leading cause of disease burden, being responsible for 27 500 000 and 4 800 000 DALYs, respectively.[4] Optimistic and Pessimistic scenarios for the

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Table 1.1 Optimistic and pessimistic scenarios for projected deaths due to stroke for the years 2008, 2015, and 2030.[2]

	2008 (Optimistic)	2008 (Pessimistic)	2015 (Optimistic)	2015 (Pessimistic)	2030 (Optimistic)	2030 (Pessimistic)
Projected deaths due to stroke worldwide (% of total deaths)	5 978 000 (10.2)	6 021 000 (10.1)	6 420 000 (11.2)	6 778 000 (10.6)	7 907 000 (12.5)	8 712 000 (11.8%)
Africa	457 000	458 000	517 000	535 000	731 000	786 000
The Americas	477 000	479 000	505 000	527 000	653 000	731 000
Eastern Mediterranean	275 000	276 000	313 000	326 000	458 000	492 000
Europe	1 432 000	1 437 000	1 419 000	1 497 000	1 350 000	1 498 000
South-East Asia	1 154 000	1 158 000	1 296 000	1 357 000	1 737 000	1 865 000
Western Pacific	2 201 000	2 213 000	2 371 000	2 536 000	2 979 000	3 340 000

Table 1.2 Optimistic and pessimistic scenarios for projected disability-adjusted life years (DALYs) due to stroke for the years 2008, 2015, and 2030.[2]

	2008 (Optimistic)	2008 (Pessimistic)	2015 (Optimistic)	2015 (Pessimistic)	2030 (Optimistic)	2030 (Pessimistic)
Projected DALYs due to stroke worldwide (% of total deaths)	47 328 000 (3.3)	47 807 000 (3.2)	48 544 000 (3.6)	52 181 000 (3.5)	54 617 000 (4.3)	63 858 000 (4.2%)
Africa	5 279 000	5 322 000	5 868 000	6 140 000	7 912 000	8 957 000
The Americas	4 032 000	4 055 000	4 109 000	4 346 000	4 485 000	5 280 000
Eastern Mediterranean	2 846 000	2 870 000	3 121 000	3 299 000	4 081 000	4 637 000
Europe	9 263 000	9 358 000	8 421 000	9 076 000	7 164 000	8 486 000
South-East Asia	10 103 000	10 217 000	10 851 000	11 576 000	13 067 000	15 045 000
Western Pacific	15 805 000	15 985 000	16 173 000	17 743 000	17 908 000	21 453 000

projected DALYs due to stroke worldwide for the years 2008, 2015, and 2030 as calculated by the WHO are shown in Table 1.2.

Pathophysiology

Atherosclerosis is the primary pathologic entity responsible for the development of carotid artery disease, accounting for approximately 90% of lesions in the Western world. The remaining 10% are caused by a variety of diseases (Table 1.3).[6]

Atheromatous lesions characteristically occur at branches or arterial bifurcations. The most common site is at the bifurcation of the common carotid artery, particularly the carotid bulb. The predilection of the carotid bifurcation for atheromatous plaques relates to arterial geometry, flow velocity profiles, flow streamline patterns, and wall shear stress.[7]

The initial lesion of atherosclerosis is the "fatty streak".[8,9] The formation of fatty streaks arises from a focal increase in the content of lipoproteins within the intima. These lipoproteins undergo chemical modifications, namely lipoprotein oxidation and non-enzymatic glycation.[8,9] After the accumulation of extracellular lipid, recruitment of leukocytes (monocytes and lymphocytes) occurs.[10] Low-density lipoprotein (LDL) particles augment the expression of leukocyte adhesion molecules and also promote the chemotaxis of leukocytes through induction of cytokine release from vascular wall cells, such as interleukin-1 (IL-1) and tumor necrosis factor- (TNF-).[9] The monocytes differentiate into macrophages and begin to ingest the lipoprotein particles by receptor-mediated endocytosis, thus transforming into lipid-laden foam cells.[11] Some lipid-laden foam cells may die as a result of programmed cell death (apoptosis). This death of mononuclear phagocytes results in formation of the lipid-rich center, often called "the necrotic core," of more complicated atherosclerotic plaques.[9] Cytokines and growth factors [such as transforming growth factor- (TGF-)] elicited by modified lipoproteins, vascular wall cells, and infiltrating leukocytes can modulate func-

Table 1.3 Other causes of carotid artery disease.

- Fibromuscular dysplasia
- Arterial kinking
- Traumatic occlusion
- Intimal dissection
- Radiation-induced carotid stenosis
- Fibrinoid necrosis
- Amyloidosis
- Polyarteritis nodosa
- Wegener's granulomatosis
- Granulomatous angiitis
- Giant cell arteritis
- Amphetamine-associated arteritis
- Infectious arteritis
- Moya-moya disease
- Allergic angiitis

tion of arterial smooth muscle cells. These molecules stimulate the migration of smooth muscle cells from the tunica media into the intima.[9] The smooth muscle cells synthesize the bulk of the extracellular matrix of the complex atherosclerotic lesion. In addition to locally produced mediators, atherogenic signals, related to blood coagulation and thrombosis, contribute to the evolution of atheroma.[9,12] Fatty streak formation begins under a morphologically intact endothelium.[12] In advanced fatty streaks, however, microscopic breaches in endothelial integrity occur.[12] Microthrombi rich in platelets form at such sites due to exposure of the highly thrombogenic extracellular matrix of basement membrane.[12] Platelet adhesion to the exposed matrix is the initial step in thrombus formation.[12]

The atherosclerotic plaque evolves with time. A complex balance between entry and removal of lipoproteins, accumulating leukocytes, cell proliferation and cell death, extracellular matrix production, and accumulation of calcium (calcification of the plaque) contribute to plaque evolution and lesion formation.[9] With time, the atherosclerotic plaque increases in size, causing stenosis of the vascular lumen. The increasing stenosis of the vessel lumen has an adverse effect on blood flow and may give rise to an auscultated bruit. Whether detection of a carotid bruit during the general physical examination should be considered an alarming sign or an accidental finding has been extensively debated.[13,14] Carotid bruits predict cardiovascular events and probably deserve further investigation.[13,14] In addition, carotid bruits are associated with vascular risk factors (e.g., smoking, hypercholesterolemia, hypertension, diabetes mellitus).[13,14]

As the atherosclerotic plaque increases in size, a number of additional events take place that explain many of the clinical manifestations of atherosclerosis. With time, the microthrombi on the endothelium give rise to larger thrombi.[12] These further occlude the lumen, restricting blood supply to the tissues. Additionally, large plaques have a propensity to rupture.[9,12,15] Plaques that have proved vulnerable to rupture tend to have thin fibrous caps, relatively large lipid cores, and a high content of macrophages. As a result of plaque instability and plaque rupture, the thrombi formed on the surface of the plaque are released into the circulation (emboli), giving rise to acute ischemic events (i.e., stroke).[9,12,15] Following such an atheromatous discharge, an open cavity remains within the central portion of the lesion, a so-called carotid ulcer. Carotid ulcers are the nidus for platelet aggregation and further thrombus formation and, thus, the source of further atherosclerotic emboli (secondary arterial emboli).[9,12,15]

Carotid plaque echolucency, as assessed by ultrasonography, also defines which plaque is high risk for atheroembolic events.[16–18] Plaque echolucency is associated with increased lipid content and macrophage density (and sometimes hemorrhage).[16–18] On the other hand, fibrous tissue and calcification dominate echodense plaques.[16–18] Echolucent carotid plaques are associated with a higher risk for future ischemic stroke episodes,[16–18] as well as coronary events.[19] These plaques are also associated with elevated levels of triglyceride-rich lipoproteins and reduced levels of high-density lipoprotein (HDL) cholesterol.[17] Risk factor intervention may be more beneficial in patients with echolucent than in those with echodense plaques.[16–18]

Several risk factors have been associated with an increased risk for the development of carotid atherosclerosis and carotid artery disease. These include smoking,[18,20–23] hypertension,[18,20–23] hyperlipidemia,[18,23,24] and diabetes mellitus.[18,24,25] Modification of these risk factors (i.e. smoking cessation, tight blood pressure, blood glucose, and lipid control) is associated with a considerable vascular risk reduction.[18,20–25]

Is reversal of carotid atherosclerosis possible?

Since carotid atherosclerosis is a progressive disease, measures to delay (or even reverse) its progression are of crucial importance. Early studies reported an association between LDL and carotid intima–media thickness (IMT).[26,27] As a result several studies have evaluated the effect of lowering LDL (e.g. with statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) on carotid IMT progression rates [i.e. the Asymptomatic Carotid Artery Progression Study (ACAPS),[28] the Kuopio Atherosclerosis Prevention Study (KAPS),[29] the Monitored Atherosclerosis Regression Study (MARS),[30] the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study,[31] the Regression Growth Evaluation Statin Study (REGRESS),[32] etc.). The vast majority of these trials demonstrated a significant regression of carotid IMT after statin therapy.

Two meta-analyses[33,34] have reported an overall decrease in IMT following statin treatment. The first, which included over 90 000 participants in statin trials, showed that there was a strong correlation between LDL lowering and carotid IMT reduction ($r = 0.65$; $P = .004$).[33] Each 10% reduction in LDL cholesterol concentration was estimated to reduce carotid IMT by 0.73% per year (95% CI = 0.27–1.19).[33] The other meta-analysis, which included 10 trials and a total of 3443 individuals, showed that statin therapy significantly reduced the rate of carotid atherosclerosis progression.[34] The total weighted mean difference of carotid IMT progression between patients receiving statins *versus* placebo was −22.35% (95% CI = –18.14–26.56%; $P < .00001$).[34]

In a review of the literature, our group showed that routine statin treatment in patients with carotid artery disease not only favorably modulates carotid IMT progression, but also reduces the risk of stroke and combined cardiovascular events.[35] Routine statin use, however, is not cost-effective in asymptomatic patients with a 10-year Framingham risk score of less than 10% and evidence of subclinical carotid atherosclerosis.[36]

Conclusions

Carotid artery disease is a leading cause of death and moderate/severe disability worldwide. Its manifestations (TIAs and stroke)

are not only associated with increased hospital costs, but are also an important psychosocial and economic burden (as expressed in DALYs) for all countries, irrespective of whether they are low, moderate or high income. It is therefore crucial to decrease its prevalence and prevent the occurrence of the projected scenarios shown in Tables 1.1 and 1.2.

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