I. PATHOPHYSIOLOGY AND CLASSIFICATION OF CEREBROVASCULAR DISORDERS

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1. Stroke

Stroke is a type of cerebrovascular disease that involves the vessels of the central nervous system. It usually occurs with sudden onset due to a burst of cerebral arteries, hemorrhage, or occlusion by a thrombus or other particles, leading to ischaemia and to focal brain dysfunction. Immediately, nerve cells depleted of oxygen in the involved vascular territory will be functionally disturbed and die if the circulation is not promptly restored. Two main mechanisms leading to ischaemic stroke are occlusion and haemodynamic impairment. These two situations decrease the cerebral perfusion pressure and eventually lead to cellular death. The brain blood flow can be maintained by autoregulation of cerebral arteries and collateral circulation within certain limits. When occlusion of an artery develops, blood flow in the periphery of the infarct core is usually reduced but there still remains sufficient to avoid structural damage, so that the functional modifications of cells may be reversible if circulation is restored. This ring-like area of reduced blood flow around the ischaemic center of infarct has been termed the penumbra as an analogy of the half-shaded part around the center of a solar eclipse. It may largely explain the functional improvement occurring after stroke. Indeed, the neurons surviving in this critical area of infarct at reduced blood flow may again function as soon as blood flow and oxygen delivery is restored.

1.2 Stroke types

Cerebral infarction is not a single disease and there are two main types of stroke: ischaemic or haemorrhagic. Ischemic stroke accounts for about 85% of strokes, and brain hemorrhage 15% of strokes.

Embolism is the most frequent cause of ischemic stroke. Embolism may originate from the heart, aortic arch or craniocephalic arteries. Artery-to-artery embolism is the main cause of ischemic stroke. Rupture of an atheromatous plaques is a potent cause of thrombosis. The progression of atheromatous plaques leads to arterial stenosis, formation of wall thrombus, and finally occlusion with high probability of thromb that may lead to embolisation. The size and composition of emboli, and the collateral system may determine the size of infarcts. Usually, small platelet emboli are rapidly desegregated and lead only to transient ischaemic attacks by temporary occlusion of distal cerebral arteries. On the other hand, large thrombotic embolism, rich in fibrin, is therefore less friable and may cause more persisting and severe ischaemia. The internal carotid artery at its origin, at the bifurcation, is the main site of atherosclerotic plaques, followed by the carotid siphon, the proximal and distal vertebral arteries and the mid-basilar artery. The onset of ischaemic stroke is thus related to the onset of embolism, which is linked to vascular territories, dynamic changes in atherosclerotic plaques and degree of stenosis.

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1.3 Stroke risk factors

For haemorrhagic strokes the main risk factors are hypertension and excessive alcohol consumption. Smoking is an important risk factor with an overall relative risk (RR) of 3.5 for stroke. In women smoking is a dominant risk factor for subarachnoid haemorrhage with a dose-response relationship. Heavy alcohol consumption is clearly associated with an increase of stroke risk but this association is less clear for moderate and light dose.

Risk factor for ischemic strokes are multiple and combined (age, hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, valvular disorders, coagulation disorders, smoking). Whereas hypertension (RR 4.0) and age (RR per decade 1.6) are other important risk factors for stroke, new data have shown that a family history of stroke might also increase the risk of stroke. Still, further studies have to confirm this. Other risk factors are recently related to stroke include high cholesterol, use of oral contraceptives, physical inactivity, obesity, hypercysteinemia, increased fibrinogen, coagulation disturbances (protein C or protein S deficiency, antiphospholipid antibodies). Chronic atrial fibrillation, transient ischaemic attacks, carotid bruits, patent foramen ovale, aortic arch atheroma are cardiovascular conditions associated with an increased risk of stroke. The risk of stroke is increased in patients with diabetes mellitus (RR 1.5-3.0), although there is still no evidence that treatment reduces the risk of stroke.

1.4 Pathophysiology of different stroke types

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Atrial fibrillation (AF) is the most common cardiac arrhythmia, and may occur without other detectable cardiac abnormality, but is more often associated with structural heart disease. During AF synchronous mechanical atrial activity is disturbed, resulting in haemodynamic impairment. This can give rise to thrombus
formation and embolism to the systemic circulation. Thrombus associated with AF arises most frequently in the left atrial appendage, as can be visualized by transoesophageal echocardiography.

In an International Stroke Trial, the typical stroke patient in AF was more likely to be female than male (56% versus 45%), to be older (mean age 78 versus 71 years), and to have more severe strokes, with impaired consciousness (37% versus 20%) than stroke patients without AF. The initial stroke in AF patients was more often a large infarct with the clinical deficit suggesting involvement of the entire territory of the middle cerebral artery (36% versus 21%), while lacunar stroke was less common (36% versus 21%). After 6 months AF stroke patients are more likely to be dead or dependent than stroke patients in sinus rhythm (78% versus 60%).

Other studies suggest that for AF patients the age-adjusted mortality rate is approximately double that in patients in sinus rhythm. Because both the prevalence of AF and the risk of embolism due to AF increase with advancing age, the age-adjusted stroke rate of AF patients can vary more than 20-fold, from 0.5% per year in young (<65 years old) AF patients without detectable heart disease ("lone AF") to 12% per year for patients with prior stroke or TIA. In the Framingham Study the annual overall AF stroke rate increased from 1.5% in participants aged 50 to 59 years to 23% in octogenarians. Fortunately, not all new cases of AF are diagnosed because of stroke. In the Cardiovascular Health Study, 12% of new cases of AF were asymptomatic and diagnosed only with yearly ECG screening.

Atherosclerosis may involve small cerebral arteries in the deep perforative network, especially in patients with hypertension or diabetes, leading to small deep "lacunar" infarcts, due to the fact that these arteries are terminal branches and have no collaterals. Microatheromatous or lipohyalinotic occlusion is the main cause of lacunar infarction. Compared to other stroke types, patients with lacunar infarction subtypes have better prognosis. The risk of death from the primary brain lesion is likely to be minimal.

Due to the small infarct size, the rate of recovery is generally more rapid, decreasing the risk of death due to secondary complications, and the proportion of patients with cardiac co-morbidities is less than in most other stroke subtypes. The risk of death remains low for the first few years after stroke onset, although the rate of death significantly exceeds that of the general population. Compared to other stroke types, these patients tend to have a better functional outcome. Marked cognitive deterioration during the first years after stroke onset is rare, and sometimes develops in conjunction with a recurrent stroke. Asymptomatic progression of small vessel disease seems to outweigh new symptomatic ischemic stroke several fold.

Intraparenchymal and subarachnoid haemorrhages are due to the rupture of the brain vessel wall. The main mechanisms underlying haemorrhage include hypertensive arteriopathy, arteriovenous malformations, amyloid angiopathy, drugs (anticoagulants, thrombolytics) and inflammatory vasculitides. The 30-day case fatality is about 42% in unselected cohorts. Overall prognosis with respect to survival and residual disability is similar to that for ischaemic stroke of equivalent clinical severity. Greater age and stroke severity, whether graded by neurological score or extent of haemorrhage on imaging, are both associated with increased case fatality and poorer functional outcome.

### 1.5 Clinical presentation of stroke

The heterogeneity of stroke pathogenesis and difference between stroke subtypes may hamper diagnosis and management. Usually, the neurological findings help to identify the location of lesions and to predict the stroke mechanism, which is fundamental for determining the initial investigations and treatment. Different patterns of weakness may be found in lesions of the middle cerebral artery (MCA) territory. Hemiplegia is related to large or deep MCA infarcts. Lesions in the upper branch of MCA produce hemiparesis with faciobrachial predominance.

On the other hand, weakness predominates in the contralateral lower limb with lesions in the anterior cerebral artery territory. Sensory deficit is common in MCA stroke, resulting from lesions affecting the territory of the posterior parietal artery. Usually, complete contralateral sensory loss is produced by lesions in the ventroposterolateral part of the thalamus. However, a pseudohemiparesis paresis may be found in infarcts involving the anterior parietal artery territory. Visual symptoms predominate in the posterior cerebral artery territory. Homonymous hemianopia or quadrantopia may occur and paretic walking or driving.

They are sometimes associated with alexia or apraxia. Ocular disturbances, such as diplopia, are produced by lesions in the brainstem. They are often associated with hemiparesis or ataxia. Many patients can develop speech disorders, called aphasia, related to infarcts in the dominant hemisphere, as a cortical sign. It affects the capacity of speaking, listening, reading or writing. Neurobehavioral manifestations are also prominent in stroke and can involve the capacity of thinking and planning activities. Hemineglect is usually found in cortical lesions of the nondominant hemisphere. After stroke, many patients develop depression, which can affect motor improvement. Oculomotor or swallowing can be affected, usually with medullary infarctions or bilateral lesions. As a complication, bronchoaspiration can also occur. From those matters previously mentioned, it is clear that the clinical picture depends on the brain territory affected, and can point out the stroke subtype, as well as mechanism.

### 1.6 Diagnostics in differentiation of stroke aetiology

An early and correct diagnosis of stroke is made by evaluating symptoms, reviewing the patient's medical history and risk factors, and performing routine tests to assess patient's status and underlying pathology leading to stroke. Clinical examination is crucial for the choice and timing of the investigation.

Electrocardiography (ECG) and blood tests are the first to be done in acute stroke. They include sedimentation rate, red and white cell count, platelet count, haematorcit, blood ionogram, glucose, serum enzymes, cholesterol and lipids levels, and routine coagulation profile, including serum fibrinogen, prothrombin time and partial thromboplastin time. In suspected cardioembolism, the investigation must include at least a 24-hour one- to three lead electrocardiogram monitoring.

Brain CT scan is the most useful radiological investigation in the acute phase. It allows to distinguish between ischemic and hemorrhagic lesions and also to rule out nonstroke brain conditions. In the first hours after an ischemic stroke, a CT scan can be normal. Indirect signs of stroke can be visualized: focal brain edema, obliteration of cortical sulcus, spontaneous hyperdense artery. Then present in the early phase, are the predictor of the worse functional outcome.
The main limitations of CT are the detection of brainstem and cerebellar infarcts. Magnetic resonance imaging (MRI) is a technique which offers different possibilities to detect ischemic lesions in the acute phase of stroke. It is especially useful for brainstem infarcts. Compared with CT scan, MRI is more sensitive in the detection of recent and old strokes. MRI can improve stroke localization and detect small infarcts. It may also better define the age of an ischemic lesion. MRI has not replaced CT in the emergency phase of stroke, because of its availability and difficulty in differentiating recent hemorrhage from ischemia. With MRI, angiographic pictures can also be noninvasively obtained. MRI has certain limitations, the major one are longer time of investigation and good collaboration of patients needed to obtain good images.

Parallel with the patient management, other tests to determine the stroke aetiology are done. Doppler ultrasound investigation easily allows noninvasive bedside evaluation of the cerebral haemodynamic. It provides information on a potential arterial source of emboli and on arterial occlusion at the precerebral levels in the carotid and vertebral artery systems. Inflammatory diseases can be detected, as well as dissections, vasculopathies and other causes of stroke at this level. By means of transcranial Doppler sonography, the site of arterial occlusion can be assessed, and the recanalisation can be monitored. In haemorrhagic stroke, the hyperperfusion in the presence of arterovenous malformations can be assessed, as well as the feeding artery. The development of vasospasm can be monitored, enabling evaluation of the therapy. Noninvasive Doppler ultrasound evaluation of the patients can avoid conventional angiography in many instances. Therefore, conventional angiography is reserved for special situations with suspicion of multiple or intracranial stenosis, arteritis or uncommon angiopathies. In haemorrhagic stroke, it has to be performed in cases of subarachnoid bleed or in the cases of atypical intraparenchymal haemorrhage.

The electroencephalogram is usually not performed in stroke patients, although it can sometimes be useful. It can provide information on stroke localization, whether deep or superficial, especially when CT is inconclusive. It may make it possible to differentiate stroke from migraine or epileptic seizure, although not always. In a comatose patients, it gives information on the depth of coma, functional asymmetry and may exclude associated epileptic seizures.

Besides routine ECG, 24 hours electrocardiogram monitoring is done in selected patients. Non-invasive studies also include echocardiography to look at the heart in selected patients. Transthoracic two-dimensional echocardiography gives reliable information on the ventricular wall and the aortic and mitral valves. It can exclude a left ventricular thrombus and demonstrate intracardiac shunts when used with a contrast microbubble test. Trans-oesophageal echocardiography represents an advantage for the assessment of the posterior part of the heart, particularly the left atrium and appendage. It provides information on atheromatosis and ulcerated plaques in the aortic arch. Its disadvantage is the endoscopic procedure, which necessitates a good cooperation of the patients.

Cerebrospinal fluid examination is rarely required in acute stroke, but it can provide information on specific conditions, including subarachnoid hemorrhage, cerebral venous thrombosis, vasculitis, menigitis and demyelinating diseases.

Stroke is a complex syndrome, requiring, parallel with the patient management, assessment of the underlying mechanism to avoid the risk of recurrence.

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