Identification of Stroke Mechanism: Stroke Classification

11

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Abstract

In this chapter, the subtypes of stroke will be introduced to the readers. The classification of stroke into subtypes is not only for listing the causes of stroke through an academic approach but also helps in identifying the physiological behavior of stroke, which will help the physicians apply the optimal therapy to the patient, with a view to improving the prognosis of the patients. The most commonly used classification systems are the Oxfordshire Community Stroke Project (OCSP) classification system and the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification system. Here, the readers will be introduced to both these classification systems and will be allowed to have a glimpse into their strengths and weaknesses.

If a patient who is suspected of having a stroke arrives at the emergency room, the first thing that must be done is to check the history of the patient, followed by the conduct of neurological tests, and the provision of immediate emergency care. A brain computed tomography (CT) scan should be performed as soon as possible to determine whether the patient is having an ischemic stroke or a hemorrhagic stroke, and if the criteria are met, intravenous thrombolysis or intra-arterial thrombectomy should be performed. During this process, if the patient has an ischemic stroke, the subtype of the stroke has to be identified based on the information gathered so far from the diagnosis process. There are limited information available in the initial stage of the treatment, and as such, it may be difficult to identify the correct stroke subtype. This notwithstanding, it is important for the physician to do his or her best to diagnose the stroke subtype. It is an appropriate treatment approach to change the subtype diagnosis as more information becomes available because the disease behavior differs by stroke subtype, making it appropriate to consider the stroke subtypes as totally different diseases. This may significantly change the prognosis of the stroke in the future, and the medical and surgical

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treatment to prevent recurrence may also differ significantly. Incidence rates of early neurological deterioration may even differ according to their stroke subtypes. Therefore, it is more helpful for the patient to identify the stroke subtype as early as possible. The recent progress in the brain magnetic resonance imaging (MRI) technology allows the blood flow in the brain and the process of brain stroke to be observed almost in real time. In addition, various kinds of multidimensional tests including hematological or imaging methods can be performed to find out the embolic source. With this, it has now become possible to diagnose the stroke subtype earlier than before and to provide a more personalized secondary preventive treatment to stroke patients.

11.1 Classification Methods of Ischemic Stroke

The purpose of classifying strokes is to make a decision regarding the basic direction of treatments to be provided to the patient. Such classification is used to describe the characteristics of the patient's stroke. In spite of the recent progress in the diagnostic test technologies, it is still true that the causes of stroke are not identified in 25–40% of the patients and is dependent upon the quality, completeness, and timing of the tests performed. As such, a stroke with an unrevealed cause is called "cryptogenic stroke." When classifying stroke, certain overlapping risk factors need to be considered, making it difficult to determine which of the two or more subtypes is correct. For example, in the case of a patient who has severe carotid artery stenosis and atrial fibrillation (AF), it is difficult to determine which of the two conditions arouses the present stroke.

The classification of strokes is based on the unified and standardized systems of classification, both in the academic and clinical domains. This is a result of decades of endeavors. The classification of the disease is not standardized across the world, however, due to the differences in the healthcare system and environment of countries. The United Kingdom (UK) and some British Commonwealth countries use the Oxfordshire Community Stroke Project (OCSP) classification system [1], while others use the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification system [2], sometimes with minor modifications. These two subjects will be covered briefly herein.

11.1.1 Oxfordshire Community Stroke Project (OCSP) Classification System

OCSP classification was originally suggested to confirm the characteristics of the subjects in an epidemiological study in Oxfordshire, UK [1]. At that time, the researchers had to comply with their classification methods that were allowed under the UK's public healthcare system. All stroke patients were treated by primary care physicians in UK. Physical examination and CT were the diagnostic methods for stroke patients, but they had no other method to diagnose relevant problems in the cerebral vessels. For this reason, the researchers of OCSP chose to classify stroke patients only using physical examinations, based on the location and size of the ischemic stroke (Table 11.1). As the size and location of the stroke are not determined by the cause of the stroke, the analysis of the cause of stroke under this system is too difficult. A patient whose stroke is classified as lacunar stroke can still be having an embolic stroke. In contrast, this system is very easy to use in classifying stroke patients, and registration of the patient is rarely missed with a higher level of interobserver reliability. Because the prognosis of the patient is determined by the initial severity of the stroke, the estimation of the prognosis is relatively correct considering that the cause of the stroke is not known [3].

11.1.2 Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Classification System

The earliest stroke classification system was the Stroke Data Bank Subtype Classification system

Table 11.1 OSCP classification

Type of infarct	Diagnosis
Cerebral infarction	If a CT scan performed within 28 days of symptom onset shows an area of low attenuation, no relevant abnormality, or an area of irregular high attenuation within a larger area of low attenuation (i.e., an area of hemorrhagic infarction) or if a necropsy examination shows an area of cerebral infarction (pale or hemorrhagic) in a region compatible with the clinical signs and symptoms
Lacunar infarct (LACI)	One of the four classic clinical lacunar syndromes. Patients with faciobrachial or brachiocrural deficits are included, but more restricted deficits are not
Total anterior circulation infarct (TACI)	Combination of new higher cerebral dysfunction (e.g., dysphasia, dyscalculia, visuospatial disorders), homonymous visual field defect, and ipsilateral motor and/or sensory deficit of at least two areas of the face, arm, and leg. If the conscious level is impaired and formal testing of higher cerebral function or the visual fields is not possible, a deficit is assumed
Partial anterior circulation infarct (PACI)	Only two of the three components of the TACI syndrome, with higher dysfunction alone, or with a motor/sensory deficit more restricted than those classified as LACI (e.g., confined to one limb, or to the face and hand but not the whole arm)
Posterior circulation infarcts (POCIs)	Any of the following: ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit, bilateral motor and/or sensory deficit, disorder of conjugate eye movement, cerebellar dysfunction without ipsilateral long-tract deficit (i.e., ataxic hemiparesis), or isolated homonymous visual field defect

OCSP Oxfordshire Community Stroke Project

[4]. It was composed of five classes developed when the National Institute of Neurological Disorders and Stroke (NINDS) established the Stroke Data Bank for the first time. These classes were brain hemorrhage, brain infarction (atherothrombotic and tandem arterial pathological abnormalities), cardioembolic stroke, lacunar stroke, and stroke from rare causes or with an undetermined etiology. Since 1993, almost all the clinical researchers in the world have been using the classification system suggested by the TOAST clinical researchers [2]. This classification method was originally intended to be used for comparing and analyzing the effect of danaparoid among the different subtypes of stroke. The basic principle of classification in this method was not significantly different from that of the Stroke Data Bank Subtype Classification system. The TOAST researchers originally divided stroke cases into eleven groups and then narrowed these down to five (Table 11.2). This classification method has the highest internal validity when the planned algorithms are followed strictly. Possible errors in classification are mostly corrected by discussion and agreement between specialized researchers. In the case of the lacunar stroke, however, which is defined by the clinical conditions and size of the stroke, there is still a risk of misclassification, where large-artery atherosclerosis (LAA) is mistaken as small-vessel occlusion (SVO) if there is an atherosclerotic artery that is too tiny to be spotted and clearly seen on MRI. As the definition of LAA includes 50% or more stenosis in the relevant arteries, it is still possible that a patient who is certain to have LAA can be classified with an undetermined etiology. It is also true that depending on the level of experience of the physician, the stroke cause may still be undetermined even if one of the candidate causes looks more promising. In this classification method, the ratio of undetermined causes is overestimated. Furthermore, while the cardioembolic stroke causes are classified into high- and medium-risk factors, patent foramen ovale (PFO), which has a high prevalence rate among normal individuals, is also a medium-risk factor. PFO may not be counted as cardioembolic causes and may be included in some cases. Accordingly, many researchers modify the TOAST classification system to suit their purposes. As there is no single modified version of this classification that is widely supported, however, it would suffice for the readers to understand the concept of the TOAST system clearly.

Table 11.2 TOAST classification

Type of infarct	Diagnosis
Large-artery atherosclerosis	Clinical evidence of cortical, subcortical, brain stem, or cerebellar dysfunction with more than 50% lesion or occlusion in an extracranial or intracranial vessel in the distribution of an infarct larger than 1.5 cm by CT or MRI. This diagnosis cannot be made if arterial studies show no evidence of pathology or if there is reasonable suggestion by history or studies that another mechanism is possible
Cardioembolism (high risk/medium risk)	Clinical evidence of cortical, subcortical, brain stem, or cerebellar dysfunction with a lesion size larger than 1.5 cm on CT or MRI and the presence of at least one high-risk (e.g., atrial fibrillation or mechanical heart valve) or medium-risk (e.g., lone atrial fibrillation or patent foramen ovale) cardiac pathology on diagnostic studies (electrocardiogram, rhythm strip, 24-h cardiac monitoring, transthoracic, or transesophageal echocardiography). Evidence of transient ischemic attacks or strokes in more than one vascular territory or of systemic emboli supports the diagnosis. Finally, other categories (large artery, small artery) must be excluded
Small-vessel occlusion (lacunar)	A lacunar syndrome (pure motor, sensorimotor, pure sensory, ataxia hemiparesis, dysarthria-clumsy hand) with normal CT or MRI or a lesion smaller than 1.5 cm on CT or MRI in the territories supplied by small-vessel penetrators. Large-artery and cardiac sources must be excluded
Stroke of other determined etiology	Stroke caused by nonatherosclerotic vasculopathies, hypercoaguable states, or hematologic disorders and other rare causes of stroke after diagnostic testing. Other categories must be excluded
Stroke of undetermined etiology (cryptogenic)	This diagnosis is made if two or more etiologies of stroke are possible, a complete evaluation reveals no possible source, or the patient had an incomplete evaluation

TOAST Trial of ORG 10,172 in Acute Stroke Treatment

11.2 Stroke Cases Classified Using the TOAST Classification System

To understand the classification and behavior of stroke, thrombosis, the main reason for the occlusion of the blood vessels, must first be understood. Thrombosis is the final product of the blood coagulation process and mainly consists of two parts: the platelet plugs and the fibrin meshwork. Normally, the conditions leading to the generation of thrombosis are collectively known as "Virchow's triad," which are (1) damages to the endothelial cells, trauma or arthrosclerosis; (2) abnormal blood flow, loss of laminar flow due to the delay of the flow in the veins or the turbulences in the arteries; and (3) hypercoagulability [5]. The thrombi can be classified into white thrombi, mostly composed of platelet plugs; red thrombi, mainly composed of red blood cells; and mixed thrombi, mixtures of the two. In stroke, all the three types of thrombi occur and are based on the type of thrombus that contributed most to the condition; the initial progress, the effectiveness of the treatment during the acute phase, and the treatment approaches for prognosis and secondary prevention are likely to be different. It is critical to identify the mechanism of thrombosis as well as relevant risk factors for the proper diagnosis and treatment of a stroke patient.

11.2.1 LAA

First, let me introduce the concept of the term large artery. This term is not basically used in the traditional anatomy, and it is not appropriate to understand it to be different from the small vessels based on the vascular histology. There are no clear definitions on the terms, but I suggest the following working definition: a blood vessel stemming from the vessels traveling toward the brain (aorta, brachiocephalic trunk, and common carotid artery) to those running the subarachnoid space in the brain. For more information, kindly refer to "Pathophysiology of Stroke," to be published as one of the *Stroke Revisited* series by the publisher, Springer Nature Inc.

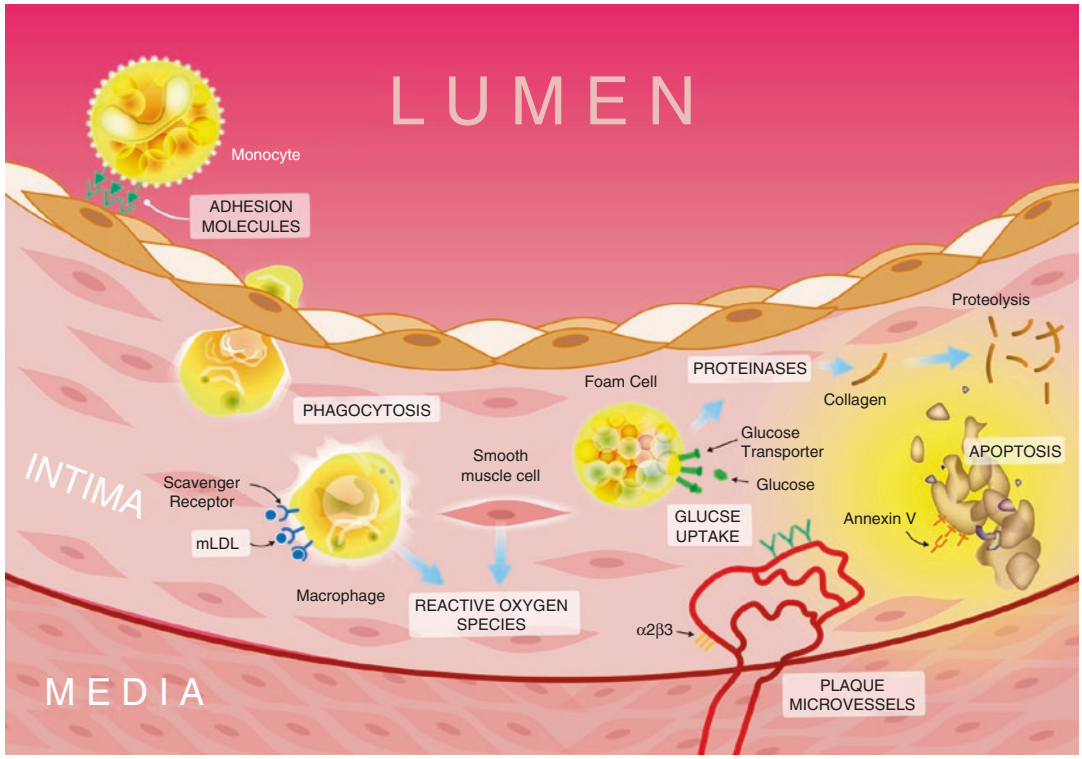

Fig. 11.1 Progression of atherosclerotic lesion (shown as time sequence from left to right)

The most important etiology of stroke among the vascular diseases in large arteries is atherosclerosis. Atherosclerosis is a chronic inflammatory disease mainly caused by the lipid on the walls of the artery due to innate and adaptive immunity. At first, it accompanies a functional disorder of the endothelial cells while the wall is exposed to an excessive amount of low-density lipoprotein (LDL), causing the LDL to pile up inside the intima (Fig. 11.1). With continued exposure to vascular risk factors (e.g., hypertension, diabetes, smoking, infection, stress, etc.), the damages to the endothelial cells are aggravated, and these damaged cells cause more LDL particles to be accumulated on the extracellular matrix. As a result, this area suffers the most from free radicals and cytokines. The modified LDL activates various inflammatory reactions. The main mechanism is the infiltration of the monocyte cells, which plays the most profound role in innate immunity. Monocytes come inside and reach the subendothelial areas to be differentiated into macrophages by the macrophage colony-stimulating factors. Macrophages accept the modified LDLs easily and develop pattern recognition receptors on the surface. Then it becomes lipid-containing macrophages and finally foam cells. The accumulation of foam cells leads to a disease in the arterial system through the movement of the vascular smooth muscle cells and the formation of a fibrous cap. Vascular status like this is called is "atherosclerotic plaques." The atherosclerotic plaques proceed to develop into thrombosis, which is the cause of LAA-related stroke.

Stable atherosclerotic plaques rarely result in stroke. Unstable or vulnerable plaques are the cause of LAA-related stroke. Most of these observations have originated from the coronary artery study reports. The World Health Organization (WHO) classified atherosclerotic plaques for the first time in 1958 [6]. Four classes were identified: fatty streak, atheroma, fibrous plaque, and complicated lesion. In the mid-1990s, the

Table 11.3 Classification of atherosclerotic lesion

Type of lesion	Subtype of lesion	Morphological description
Nonatherosclerotic intimal lesions	Intimal thickening	Natural accumulation of smooth muscle cells in the absence of lipid, macrophage foam cells, and thrombosis
	Intimal xanthoma	Superficial accumulation of foam cells without a necrotic core, fibrous cap, or thrombosis
Progressive atherosclerotic lesions	Pathological intimal thickening	Plaque rich in smooth muscle cells, with hyaluronan and proteoglycan matrix and focal accumulation of extracellular lipid. Absence of thrombosis
	Fibroatheroma	During early necrosis: focal macrophage infiltration into areas of lipid pools with an overlying fibrous cap. During late necrosis: loss of matrix and extensive cellular debris with an overlying fibrous cap. With or without calcification. Absence of thrombosis
	Intraplaque hemorrhage or plaque fissure	Large necrotic core (size >10% of plaque area) with hemorrhage and plaque area shows the presence of angiogenesis. Necrotic core communicates with the lumen through a fissure. Minimal tear without obvious thrombus
	Thin-cap fibroatheroma	A thin, fibrous cap (<65 μm) infiltrated by macrophages and lymphocytes, with rare or no smooth muscle cells and relatively large underlying necrotic core (>10% of plaque area). Intraplaque hemorrhage and/or fibrin might be present. Absence of thrombosis
Lesions with acute thrombi	Plaque rupture	Thin-cap fibroatheroma with cap disruption. Thrombosis is present and might or might not be occlusive. The luminal thrombus communicates with the underlying necrotic core
	Plaque erosion	Can occur on pathological intimal thickening or on a fibroatheroma. Thrombosis is present and might or might not be occlusive. No communication of the thrombus with the necrotic core
	Calcified nodule	Eruptive (shedding) of calcified nodule with an underlying fibrocalcific plaque with minimal or no necrosis. Thrombosis is usually not occlusive
Healed lesions	Healed plaque rupture, erosion, or calcified nodule	Healed lesion composed of smooth muscle cells, proteoglycans, and collagen type III with or without underlying disrupted fibrous cap, necrotic core, or nodular calcification. Lesions can contain large areas of calcification with few inflammatory cells and have a small or no necrotic core. The fibrotic or fibrocalcific collagen-rich plaque is associated with significant luminal stenosis. Absence of thrombosis

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American Heart Association (AHA) recommendeds new classification criteria for atherosclerotic plaque (Table 11.3; Fig. 11.2) [7, 8]. This classification was followed by recommendations from several researchers who found out that plaque erosion could result in coronary thrombosis, which further refined the classification system. Currently, the pathological classification of coronary artery atherosclerosis is based on this system, and the classification of atherosclerotic plaque on the cerebral artery is yet to be suggested. With minor differences in vascular histology among the organs, cerebral atherosclerotic process is not likely to be different from coronary atherosclerosis. Therefore, it is appropriate to understand ischemic stroke due to LAA from the classification system of coronary atherosclerosis. As the classification states, atherosclerotic plaques, which result in thrombosis, consist in plaque rupture, plaque erosion, and calcified nodules. Such lesions stimulate and activate platelets, and this marks the beginning of thrombosis. Later, due to the activated platelets, the platelets adhere to the atherosclerotic lesion and aggregate to form primary plugs. Due to the activation of clotting factors, the primary plugs condensate by fibrin meshwork, which completes the process of generating thrombosis. In this way, the thrombi that originate from a stroke caused by LAA are mainly white thrombi, while the thrombi

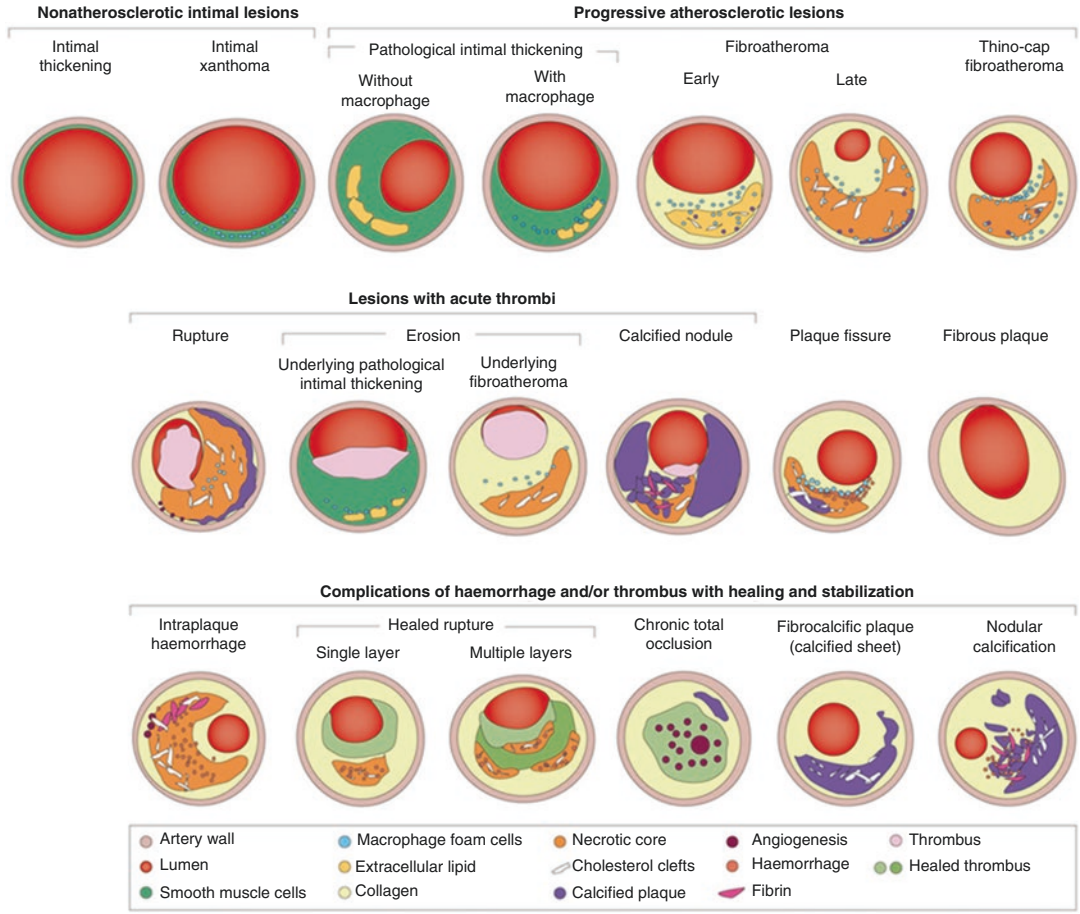

Fig. 11.2 Human coronary lesion morphologies categorized as nonatherosclerotic intimal lesions, progressive atherosclerotic lesions, lesions with acute thrombi, and complications of hemorrhage and/or thrombus with healing and stabilization. Reproduced by permission of Nature Reviews Cardiology [8]

generated from CE are basically red thrombi. Atherosclerotic plaque, which functions as the cause of thrombosis, is mostly attributable to plaque rupture, followed by plaque erosion and calcified nodule. These are the incidences in the coronary events, and it is yet to be confirmed if the incidences will be reproduce in the LAA-related stroke.

Briefly speaking, atherosclerosis, which may have been growing for years or even decades, develops into acute thrombosis due to a certain trigger, such as acute rupture. LAA-related stroke is divided into two kinds, depending on how the thrombi block the vessels. First one is in situ thrombosis, which blocks the cerebral vessel at the atherosclerotic lesion inducing thrombosis. In this case, ischemic infarction is likely to occur in the whole territory of the relevant blood vessel, but the size of the lesion may differ depending on the collateral circulation. The other one is artery-to-artery embolism: the thrombi, which are generated from the atherosclerotic lesion, crumble off and migrate to the distal vessels because of arterial pressure. In this case, stroke may involve a part of the vascular territory of the relevant artery, and the patient's symptoms are likely to be less severe. However, the atherosclerotic plaque from where the thrombi originated is still present, and a recurrent thromboembolism may cause a stroke recurrence or early neurological deterioration during the hospital

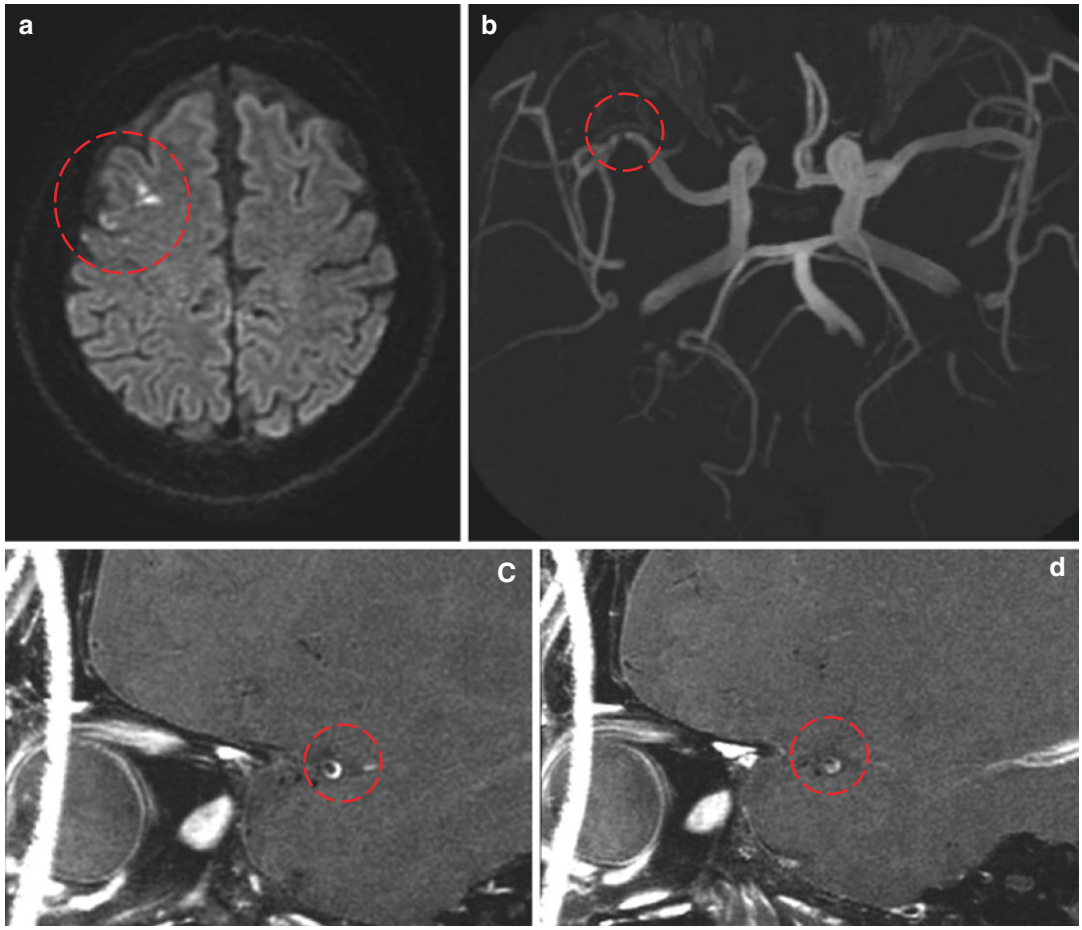

Fig. 11.3 A case of stroke caused by large-artery atherosclerosis. (**a**) New infarct lesions (*a dash-dot red circle*) were identified in diffusion-weighted imaging. (**b**) The patient had severe stenosis in the right middle cerebral artery lesions (*a dash-dot red circle*). (**c** and **d**) A vulnerable plaque with contrast enhancement was identified in the high-resolution magnetic resonance imaging (*dash-dot red circles*)

admission. In the TOAST classification, to decide that the stroke is caused by LAA, there must be a stenotic lesion on a vessel corresponding to LAA, and further, the stenosis degree should be at least 50% (Fig. 11.3). These criteria are under debate, but it does not change the fact that there is a need to find a stenotic lesion on the artery. Either magnetic resonance (MR) angiography or CT angiography may visualize the atherosclerotic lesion. The conventional angiography or digital-subtraction angiography (DSA) might be an option, but because of relatively frequent complications from the test, this test must be considered for patients with indications of carotid endarterectomy or carotid angioplasty with stenting. Carotid duplex ultrasonography and transcranial Doppler test are not usually counted as basic tests and are used as secondary confirmation methods. In the current status, it would be better that LAA is diagnosed via MR angiography or CT angiography.

11.2.2 SVO

In SVO, the mechanism of occlusion is quite different from that of LAA-related stroke. LAA-related stroke is basically caused by white thrombi related to activation of platelets, but the

contribution of platelets is not major in SVO-related stroke. The mechanism of SVO was fully understood and mainly attributed to Dr. Miller Fisher's studies. Dr. Fisher, who analyzed lacunar strokes with numerous studies using serial sections of rodent brains, reached the conclusion that most of the lacunar strokes were caused by the occlusion of penetrating arteries and that the diameter of these arteries was in most cases within 225 μm [9]. Lacunar infarctions occurring in the 300 μm or higher diameter vessels were very rare. He guessed that it might be because of the lower possibility of collateral circulation in the vessels with a diameter less than 300 μm. In these vessels, occlusion occurs due to a mechanical blockage on the blood vessels by the degenerated vascular cells that form the wall of the blood vessels mostly denatured into "lipohyalinosis" (Fig. 11.4) [10]. That is, it occurs when the denatured vessel wall itself suddenly blocks the blood flow, and infarction caused by a thrombus, as in large-artery atherosclerosis, very rarely occurs. The SVO in the TOAST classification, however, basically means small-artery occlusion. Venous infarction is not included in the TOAST classification system, and it is included in the "other determined" category. Small-artery occlusion would be better in this context, which is one of the minor shortfalls of the TOAST classification system.

Among the lacunar strokes, around 50% are caused by occlusions originating from the thrombi in the blood vessels with a 300 μm or higher diameter, and the rest are caused by the atherosclerotic plaque itself, micro-stripping, plugging, etc., according to the reports. Arteriolosclerosis that is a cause of thrombus is located in the proximal penetrating artery in many cases, and this pathological finding is called "microatheroma." In particular, microatheroma occurring in the site branching from the great vessel is also called junctional atheroma, and in this case, the penetrating artery from which the thrombus that occurred here branches out is often completely closed. The definition of lacunar stroke is ambiguous in clinical setting. Traditionally, it is the occlusion of the penetrating artery that is called lacunar infarction, but it is difficult to tell them apart in the clinical settings without a pathologic information. Then, at the clinical settings in recent years, a less than 1.5 or 2 cm cerebral infarction that occurred deep inside as shown on the diffusion-weighted MRI is defined

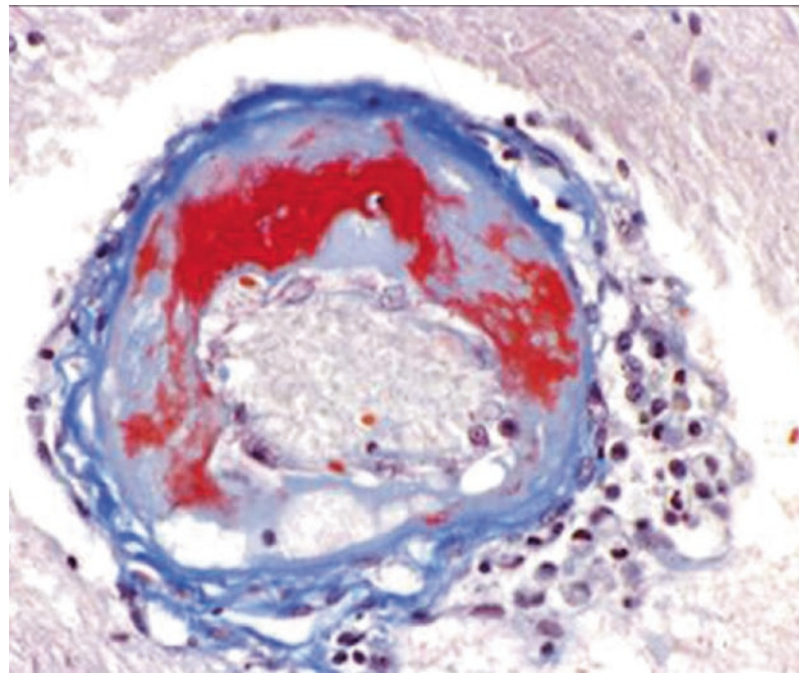

Fig. 11.4 Pathological features of lipohyalinosis. Reproduced by permission of Lancet Neurology [10]

Table 11.4 Lacunar syndromes

Syndrome	Lesion localization	Vessels involved
Pure motor stroke	Posterior limb of internal capsule Corona radiata Ventral pons Cerebral peduncle	Lenticulostriate perforators, anterior choroidal artery, perforators from basilar artery, or perforators from posterior cerebral artery
Pure sensory stroke	Ventroposterolateral (VPL) nucleus of thalamus	Perforators from thalamogeniculate artery
Sensorimotor stroke	Thalamocapsular area: posterior limb of internal capsule and VPL nucleus of thalamus	Lenticulostriate perforators, anterior choroidal artery, or perforators from thalamogeniculate artery
Dysarthria-clumsy hand syndrome	Same as pure motor stroke	Same as pure motor stroke
Ataxic hemiparesis	Same as pure motor stroke	Same as pure motor stroke

as lacunar infarction for classification. In this case, however, as even cerebral infarction with a hemodynamic cause or cerebral infarction caused by embolism meets this definition, misclassification is common. In most cases, it would be most reasonable if lacunar infarction would be considered to be caused by mechanical occlusion due to the blood vessels denatured into lipohyalinosis.

The stroke due to SVO is caused by the occlusion of a single perforating artery. Therefore, in many cases, they are found in the deeper areas, such as the internal border zone. As stated above, junctional atheroma or branch atheromatous diseases (which in fact belong to the LAA category) are not easy to be differentiated. Instead of the old name "lacunar infarction," some argued that they deserved a new name such as small deep infarction. Even if it is a misnomer, however, the name has been widely used for such a long time, and changing the status quo does not matter for now. It is more important to understand the difference between the meaning of lacunar infarction and its actual pathological characteristics.

The strokes caused by SVO cause a very small ischemic lesion, and the number of symptoms is not more than one or two. No matter how numerous they may be, they rarely go over three at a time. Acute cognitive decline is very rare as well. Lacunar syndromes are classified by citing its characteristics determined through clinicopathologic studies (Table 11.4). It is useful for communication between physicians and paramedical persons, but with the advances in stroke lesion pattern analysis through MRI, it would not be of much clinical importance. Moreover, lacunar syndromes are not always caused by SVO. Many patients with lacunar syndromes show LAA, cardioembolism (CE), or other determined causes of strokes, even small intracerebral hemorrhages. The OCSP classification system, which classifies patients based on physical symptoms and signs, may be exposed to critical errors, especially in lacunar stroke.

Symptoms are mild and the prognosis is very favorable in patients with SVO stroke. A lot of cases is likely to be fully recovered even without medical treatments. If the initial treatment is not properly done, however, the case might be worsened during the early phase. It would require a specific strategy to prevent a recurrence in different but graver forms of vascular events.

11.2.3 Cardioembolism (CE)

CE accounts for about 25% of all strokes. In most cases, LAA, SVO, and CE happen in similar proportions, each accounting for around 25% of the overall cases. The remaining 25% consist of strokes with undetermined or other determined

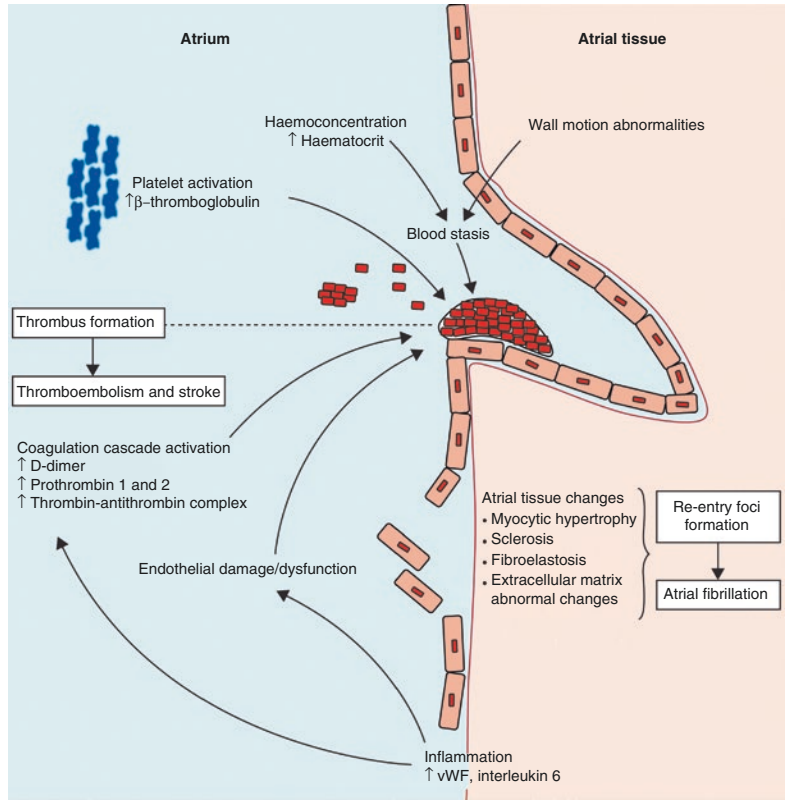

Fig. 11.5 Mechanism of thrombogenesis in atrial fibrillation. Reproduced by permission of Lancet Neurology [11]

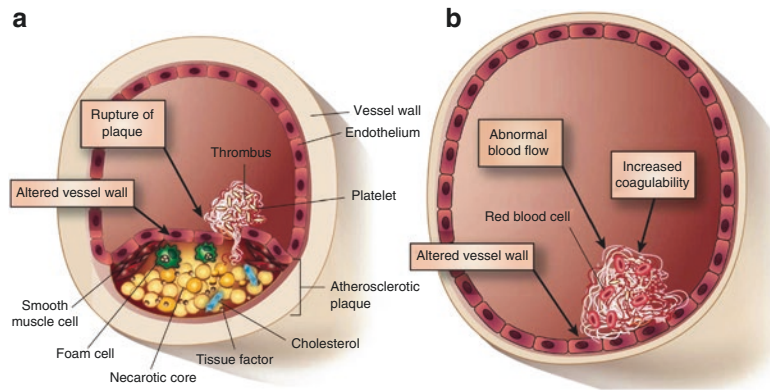

Fig. 11.6 White thrombus versus red thrombus. (**a**) White thrombus produced by platelet activation after plaque rupture. (**b**) Red thrombus formation by clotting factor activation. Reproduced by permission of Nature [12]

causes. CE is the type of stroke that occurs in patients with cardiac diseases with an obscured blood flow (i.e., acute myocardial infarction, left ventricular [LV] aneurysms, cardiomyopathies and myocarditis, valve disease and/or prosthesis, and AF) (Fig. 11.5) [11]. The activation of platelets and the resultant white thrombi are the main causes of LAA-related strokes. In strokes caused by CE, however, the clotting factor rather than the activation of platelets plays a more critical role. Stagnation of blood flow makes red blood cells form a passive, temporary core. Then, various physical and chemical stimuli activate the clotting factor cascade. The final product of this process, the fibrin meshwork, forms red thrombi (Fig. 11.6) [12]. The red thrombi mainly consist of red blood cells held together with fibrin, in which platelets are rarely discovered. They are

more fragile, because there are no platelets therein to play the role of the primary plug and a structural core, as is the case with the white thrombi. Immediately after the occurrence of CE, it is more likely that high arterial pressure to the occluded vessel will recanalyze it. If the recanalization happens before any tissue damage is not severe, it is possible that the patient's neurological status will abruptly improve. If this happens too late, on the other hand, the recanalized blood flow may travel into the ischemic tissues, resulting in hemorrhage (hemorrhagic transformation). If a stroke patient shows an abrupt improvement of his or her neurological status or if a hemorrhagic transformation is observed on CT or MRI, the physician should consider CE as the cause of the stroke. CE stroke has a characteristic to show a greater tendency of the highest level of neurological damages happening in the beginning stage (maximal onset), which will be easily understood if we guess how abruptly cardiogenic emboli occlude the cerebral vessel.

The blood flow directly into the brain comes from the left side of the heart. Therefore, except for the diseases leading to a right-to-left (R–L) shunt, the heart diseases that create thrombi in the LV and left atrium (LA) are the main causes of CE. The heart diseases that generate thrombi in the LV mainly occur at the LV apex, but if the patient has an LV aneurysm or acute myocardial infarction, the chance that the thrombi may be generated from the LV is also high. This is because with myocardial infarction, dyskinesia (akinesia or hypokinesia) on the wall of the heart in the LV may result in a serious obstruction of the blood flow. In acute myocardial infarction, the chance of thrombus formation is highest after the occurrence of the disease, and then the possibility sharply decreases over time. However, the proportion of the strokes caused by acute myocardial infarction is by far surpassed by those caused by old myocardial infarction. This is because of the higher morbidity rate of old myocardial infarction, which contributes to the higher frequency of occurrence while the chance of forming thrombi is still lower. Likewise, with AF, the chance of thrombus formation is not as high as with the others, but due to the higher morbidity rate of the elderly population, it is known as the most frequent cause of CE.

Appendages are the pocket-like attachments to each atrium. The left atrial appendage has a structure extending to the narrow entrance, and it is a probable site of blood stasis. If the history of AF is longer, there are bound to be changes with the structures and tissues on the left atrium. Such changes are sometimes linked with the frequency of thrombosis occurrence. The change, called "rough endocardium," refers to a finding of wrinkled appearance caused by edema and is characterized by peeled endothelial cells, so that fibrin or thrombi may be easily generated. Besides, findings of myocytic hypertrophy or necrosis and a mononuclear cell infiltrate, etc. are observed. The phenomenon where it is difficult to come back to the normal atrial rhythm even after successful cardioversion in atrial fibrillation patients can be explained by pathological findings like this. Additionally, due to these findings, atrial fibrillation patients are highly likely to require an anticoagulant despite the return to the normal rhythm. The failure of contraction of the atrium in AF may not only delay or obstruct the blood flow but may also aggravate the situation as the left atrium may be enlarged progressively. Such condition is further aggravated by mitral stenosis. The expansion of the left atrium increases the chance of the occurrence of thrombosis and stroke. This has been confirmed by other studies, where the sizes of the left atrium were standardized in accordance with the physical dimensions. The blood flow stasis in the left atrium or left atrium appendage is confirmed via transesophageal echocardiography (TEE) through spontaneous echo contrast (SEC). This SEC may be related to stroke occurrence. It is known that about 1/3 of the SEC persists after an AF returns to a normal rhythm, which necessitates continued anticoagulation treatment.

11.2.4 Other Determined (OD) Causes

This category does not refer to the category of strokes that occur in accordance with certain definitions. Literally, it means that the stroke has not been classified as it is rare, while the direct cause of a particular stroke case has been identified. It is

important not to confuse this category with the "undetermined" category as OD includes only those with clearly known causes. Therefore, if the cause of a particular stroke is known but it is not included in the LAA, SVO, or CE categories, it is classified as an OD. This particular category is a collection of a variety of causes of strokes. Their prevalence and distribution, while being scarce, differ among countries and races. As such, the distribution within countries and races is expected to be significantly different. For example, moyamoya disease is a very important cause of stroke in Asia but is extremely rare in Western countries, while the opposite is true for carotid artery dissection. Due to population aging, the frequency of cancer-related stroke is increasing sharply. In addition, a number of genetic factors have been confirmed. For the strokes that correspond to this definition, please refer to Sect. 8.3, where they are discussed in detail.

11.2.5 Undetermined (UD) Causes

The strokes belonging to this category have not been clearly explained in terms of their causes. This category is divided into two types: that with a cryptogenic source and that with two or more sources. In strokes with a cryptogenic source, the cause of the stroke is not definitely identified. While the patient has a territorial infarction, there is no LAA in the vessel, and the patient does not have a CE source, and this case belongs to UD category. The case where multiple embolic infarction occurs but CE or a systemic embolic source is not found is a common example of UD stroke. If a patient has stenosis that is not high enough to satisfy the definitions of LAA, how do you classify this case? In the TOAST classification system, the criterion for LAA is 50% or more vessel stenosis. If the relevant vascular stenosis is found below such threshold on MR or CT angiography (e.g., 30% M1 stenosis), we have to classify the case into the UD category. While the grade of stenosis itself is important, however, it is understood that the unstable or vulnerable plaque, which causes thrombosis, is more common in 50% or lower stenosis. Would it not be reasonable to classify this case as an LAA patient? This weakness in the TOAST system explains why many of the studies do not use the definition of 50% stenosis as it is. The 50% threshold was only an arbitrary consensus among the TOAST researchers, and moreover, there were no conditions specifying the type of imaging. Thus, the current consensus is that it would be reasonable to classify the patient as an LAA patient if there is a stenosis, even if it is as low as 10%, which could lead to LAA-related stroke. This strategy is not without problems, however, because the level of the diagnostic tests given to identify the cause of the stroke differs across countries. In addition, the MRI technology is advancing at a fast pace, and as such, it is not possible to set a high-resolution MRI with 3.0 T or higher as the norm. It would be appropriate to have an experienced stroke team and to share and communicate their own classification system.

If a patient has multiple embolic infarctions with no cardioembolic source, the patient is classified as having stroke with a cryptogenic source. During the hospitalization period, the patient goes through 24-h Holter monitoring, but if the patient shows AF in ECG 6 months after discharge, what category should the initial stroke be classified into? In principle, it may be classified as a stroke with a cryptogenic source, but we are likely to guess that the original stroke was caused by CE. The cause of the stroke might have been paroxysmal AF, which was not discovered during the hospitalization period. When paroxysmal AF is to be discovered long after discharge, it would be reasonable to consider anticoagulation.

Here is another example. A patient visits the hospital with multiple embolic infarctions, but no one is sure about the cause. One year after discharge, however, the patient receives a lupus anticoagulant test from another department. The result is positive, and in the follow-up test after 12 weeks, the result is again positive. This patient has antiphospholipid syndrome, but during the hospitalization period, the patient was not tested for it. Perhaps the patient had a stroke caused by antiphospholipid syndrome and should have been classified as an OD patient. If so, what level of diagnostic tests should be considered to be

performed while the patient is admitted to a hospital? This is a question without a clear answer and that is significantly affected by the healthcare insurance issues of each country. The chance of finding the real cause will be higher, however, if the physician finds some clues and pursuits undiscovered causes enthusiastically.

As for strokes with two or more sources, if a patient have 60% stenosis in a carotid artery and AF at the same time, the typical classification will be stroke with two or more sources. What should be done, however, if the patient has 60% stenosis in the carotid artery and also has PFO? PFO, according to the TOAST classification, is a medium-risk cardioembolic source, but after many studies, the PFO morbidity rate among normal elderly adults was found to be as high as 20–30%. If all PFOs will be taken as cardioembolic sources, too many patients will be classified as having had a stroke with two or more sources. It is not that PFO should be removed from the list of CE sources, however, as it is still true that there are patients who suffer strokes caused by it. In the end, it is clear that not a single classification regime should be accepted as it is. The intuition and experience of the stroke neurologists who observe the patients in person remain important.

Conclusion

In this chapter, the history of the existing major stroke classification systems was examined, and a closer look was made into several classification regimes commonly used today. Currently, most of the studies use the OCSP or TOAST classification system, but the OCSP system has the critical weakness of not being able to identify the cause of stroke. The TOAST classification system, on the other hand, was developed in 1993 and has been used ever since, for more than two decades. Even today, this system is widely used. As was discussed earlier, however, the use of this system may pose problems as it may involve critical flaws and as there are too many loopholes in the system. What is most important is to understand why there is a need to classify the stroke of the patient to begin with. If the purpose of the classification is to find out the severity distribution of the patient, even the OCSP system will provide a good deal of information, but if the purpose of the classification is to find the optimal therapy and to provide the highest level of preventive effect after hospital discharge, the TOAST classification system may well serve such purpose, but there is a need to customize it based on the accumulated experience of the center.

Suggestions from Current Clinical Practice Guidelines Not applicable to this chapter.

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