Seung-Hoon Lee *Editor*

Stroke Revisited: Pathophysiology of Stroke

From Bench to Bedside

Springer

Stroke Revisited

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Editor

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Preface

It has been 2 years since the publication of *Diagnosis and Treatment of Ischemic Stroke*, the first volume in the "Stroke Revisited" series. As promised, a new volume has now been published, entitled *Pathophysiology of Stroke: From Bench to Bedside*. This is the fourth publication in the series, preceded by *Hemorrhagic Stroke* and *Vascular Cognitive Impairment*. Originally predicted to be published at the end of 2018, this volume was delayed longer than expected due to editing issues. That said, I would like to apologize to readers who showed great interest in the previous volumes and eagerly awaited this volume. I will make every effort to publish the remaining two volumes at the beginning of 2021.

As its title suggests, the fourth volume is a textbook that covers the pathophysiology of stroke. In volume one, *Diagnosis and Treatment of Ischemic Stroke*, the focus was on the practical diagnosis and treatment of ischemic stroke, with minimal discussion of pathophysiology. With this new addition, along with the second volume, *Hemorrhagic Stroke*, I now cover nearly every aspect of stroke medicine. Improving our understanding of stroke pathophysiology, great strides were made in the 2000s, in which we saw significant progress in radiologic imaging technology. In terms of MRI advancements, we are now able to recognize stroke pathophysiology in near real-time and at high resolution via diffusion- and perfusion-weighted sequences, arterial spin labeling techniques, and 3 tesla high-resolution imaging. In addition, the introduction of 64-channel multi-detector CT technology made it easier to obtain perfusion imaging and cerebral angiography. These developments, discussed in this fourth volume, have helped us better understand the pathophysiology of stroke more than ever before. Furthermore, we discuss new disease concepts in depth, such as cerebral amyloid angiopathy or cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy (CADASIL). Finally, in an effort to help readers understand stroke pathophysiology from a cellular level, we address basic aspects of stroke pathophysiology, including cell death and repair mechanisms. As the editor of this volume, I recommend it be read cover to cover rather than as certain chapters only. This will enable the reader to comprehensively understand every aspect of stroke pathophysiology and learn the most cutting-edge research on stroke diagnosis and treatment.

Not many textbooks explore stroke in depth. I used two to three books during my residency and fellowship, and no book sufficiently discussed the significant improvements in stroke care that occurred between 1990 and 2000.

Owing to advancements in brain MRI and CT imaging, it has become possible to gain an immediate understanding of a patient's pathophysiology as it changes moment by moment. Despite these developments, most textbooks published previously still focused on outdated neurological examinations that are unable to support the advances made in the practice field. Moreover, most textbooks simply lacked explanation of core concepts and listed insignificant details about research findings that often conflicted. Before the development of smartphones and tablets, studying stroke required great perseverance. Nowadays, people around the globe are communicating via social media and are exposed to a previously unexperienced wealth of information. In tandem with recent technological advances, textbooks must change the way they deliver medical knowledge in order to provide information in a concise yet precise way. I decided to write a textbook reflecting such changes and contacted *Springer Nature*, who ultimately agreed to publish the "Stroke Revisited" series. Despite facing communication and language obstacles, I would like to thank the many staff members of *Springer Nature* who have nevertheless helped publish this book.

This latest volume targets residents and fellows, physicians and scholars in their early careers who specialize in stroke, and physicians and researchers in other fields who aim to study stroke. Most textbooks are organized according to the traditional academic format, in which it can be difficult to obtain information required in clinical settings. Instead, I strived to organize concise one-subject chapters in order for readers to be able to finish them quickly and efficiently. I have taken great care to compile the best academic expertise and latest findings, and I hope that that effort communicates to readers.

In order to publish this volume with the most extensive and up-to-date information, each chapter was written by the best medical scientists from around the world. I wholeheartedly thank all authors who have participated in this process. I hope that this textbook will be reviewed well and act as a strong example for future textbooks.

Seoul, Korea Seung-Hoon Lee
2019 . 12

Acknowledgment

Although I had an ideal model for a textbook in my brain, I rarely had an active conversation with publishers about my idea. This textbook was conceived in an e-mail proposal of the textbook after an unplanned meeting with Ms. Lauren Kim, the editor of Springer Nature. The editorial team and I have obtained manuscripts from renowned medical experts in the world and have edited the manuscripts according to the principles we have set for this textbook. Therefore, the contents of this book were completed only after tremendous efforts from the editorial team. I would like to especially thank Dr. Min Kyoung Kang as associate editor and other colleagues for their enormous effort for the completion of this book. In addition, I would like to thank the executive members of edition of the publisher, Springer Nature Inc. who agreed with the philosophy behind this textbook and provided the title for this textbook series "Stroke Revisited." Finally, I greatly appreciate the financial and technical support of the Korean Cerebrovascular Research Institute.

Throughout my research career, I focused on publishing papers as an author and becoming a famous, prosperous scientist. I rarely thought of writing a textbook. I would like to express my love toward my wife and my kids for changing my selfish thoughts and helping me understand my responsibilities, that is, to help others and provide education to future medical doctors.

Seung-Hoon Lee

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Part I

Introduction on Stroke

General Facts of Stroke

1

Chan-Hyuk Lee and Seung-Hoon Lee

Abstract

Stroke is the second leading cause of death, causing substantial physical and socioeconomic burden in the world. The decrease in stroke incidence occurred in developed regions, with the increasing trend in developing countries. This has been attributed to rapidly aging population and poor dietary behaviors in developing countries. The incidence of hemorrhagic stroke is higher in Asian than in Western populations. The incidence of aging-related stroke is higher for males than females. However, the fact that females have a longer life expectancy and strokes are more common in older ages has contributed to the result that the incidence is higher for females than for males. The incidence of stroke in females increases substantially after menopausal transition due to estrogen deficiency.

Ischemic stroke is defined as neurological symptoms resulting from focal brain ischemia or necrosis by abrupt occlusion of the cerebral vessels. A patient is diagnosed with a transient ischemic stroke (TIA) if the symptoms are relieved completely within 24 hours, or ischemic stroke if the symptoms persist for more than 24 hours. In fact, the limitation of 24 hours for TIA is not based on the scientific evidence but chosen arbitrarily. In this chapter, we introduce new proposals for the definition of TIA and ischemic stroke, distinguished according to the duration and lesion.

Several stroke classification systems with different criteria tailored to each purpose were introduced. Oxfordshire Community Stroke Project (OCSP) Classification System is fairly easy to identify the subtype of stroke just based on pre-contrast brain CT, whereas OCSP has the disadvantage of not being able to treat based on the cause of the stroke. In contrast, other classification systems based on the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification system divided stroke cases by the cause of the stroke. TOAST classification system can help develop effective treatment plan, but there is a risk of the overestimation of undetermined category.

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1.1 Introduction

Stroke has various symptoms, progression, and prognosis depending on severity and location of insulted lesions. Different treatment methods are

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applied depending on the stroke mechanism. Therefore, in order to understand the stroke properly, it is necessary to grasp the general overview before looking into the details. We have placed contents corresponding to the general overview of the stroke in the first chapter of the textbook, so that readers can understand the following topics more effectively. First, epidemiologic differences according to the region and sex were discussed. Next, we describe the definition of stroke, and then introduce some representative stroke classifications. The stroke classification is described in more detail in the Stroke Revisited series, Chap. 11, so readers are encouraged to refer to the textbook. The authors hope this chapter will help readers understand the general characteristics of stroke.

1.2 Burden of Stroke

According to the World Health Organization (WHO), stroke is the second leading cause of death in the world and is the third leading cause of disability [1]. Globally, 30,000 women and 25,000 men die each year with stroke, and 1 in every 19 people in the United States dies of stroke [2]. Stroke is a disease with high incidence and prevalence. According to the World Stroke Organization, around 15 million new strokes are diagnosed every year worldwide. As of 2013, 25.7 million people worldwide suffer from stroke, of which 10.3 million are the first diagnosis [3]. The incidence of stroke varies from country to country. The trend shows that developed countries are declining in incidence, while the rates of stroke in developing countries are increasing [4]. This is due to the rapid growth of the elderly population as a result of economic development in developing countries and the increased risk factors such as diabetes and hyperlipidemia due to dietary habits which are different from the past.

It can be seen more clearly in the stroke trend of Republic of Korea [5]. Republic of Korea has experienced rapid economic growth since the 1970s, and developed from a developing to an advanced country in only 30 years. Such rapid economic growth and accompanying dietary and lifestyle changes have also affected stroke trends. Stroke mortality is decreasing compared with the past, while the incidence of stroke is increasing, especially in ischemic stroke (Fig. 1.1). This is a good example of a change in the stroke pattern as the economy develops from developing to advanced country.

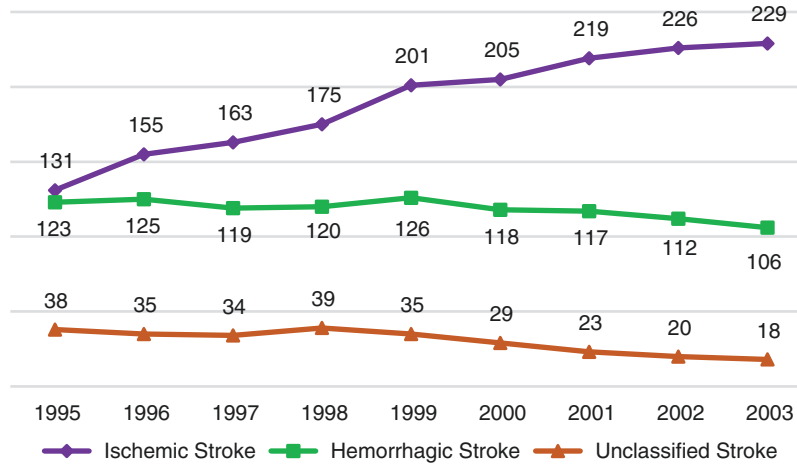

Fig. 1.1 The incidence per 100,000 of stroke according to the stroke classification in the Republic of Korea (1995–2003). Adapted with permission from Journal of Stroke, Copyright Korean Stroke Society

1.3 Epidemiologic Differences According to the Region and Sex

Stroke distribution varies by region and country. According to the neurology in 2013, the Chinese have a relatively high rate of hemorrhagic stroke compared to Caucasians [6]. PISCIS (Proyecto Investigacion de Stroke en Chile: Iquique Stroke Study), which was community-based prospective project in Latin America population, also showed a high rate of hemorrhagic stroke in Hispanic-Mestizo race [7]. As mentioned above, the stroke distribution varies by region and country. Moreover, stroke mortality and morbidity are still higher than other diseases, which results in a great burden on socioeconomic aspects. Considering the cost of treatment, rehabilitation, and secondary prevention of recurrent strokes, the importance of primary prevention is increasing more than ever. Stroke can be prevented adequately if you manage the risk factors of the stroke in advance and guide patients to take appropriate exercise and a balanced diet together.

Stroke has a different distribution depending on sex. The incidence of age-related stroke is higher for males than females. However, females have a longer life expectancy and strokes are more common in older ages, so the incidence is higher for females than for males. In the United States, between 1993 and 2003, the stroke mortality rate for people under 45 years of age was similar for males and females [8]. However, males are at higher stroke mortality rates between the ages of 45 and 74. After 75, the stroke mortality rate of females is higher than males (Fig. 1.2). In addition, the prevalence of stroke was higher in females than in males. Several hypotheses have been proposed regarding the tendency for females to increase in prevalence and mortality as age increases. The role of estrogen is the most widely accepted hypothesis. The rapid reduce of estrogen after menopause is thought to be a cause of stroke [9, 10]. Considering that the elderly themselves are independent risk factors for stroke, postmenopausal estrogen reduction in females is equivalent to the disappearance of another barrier for stroke. Therefore, females who are postmenopausal are more exposed to stroke risk than males, and more active efforts are needed to prevent stroke. It is also a part of this effort to promote females in the global stroke campaign organized by the World Stroke Agency with the slogan "I am Woman."

1.4 Definition of Stroke

The concept of Stroke goes back to BC. In 400 BC, Hippocrates defined nontraumatic brain injury as "apoplexy". After about 2000 years, it was maintained without conceptual change. In 1689 William Cole first introduced the term "stroke". Since the World Health Organization (WHO) referred to the "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death" in 1976, stroke has begun to be established systematically [11]. Since then, the definition of stroke has been redefined several

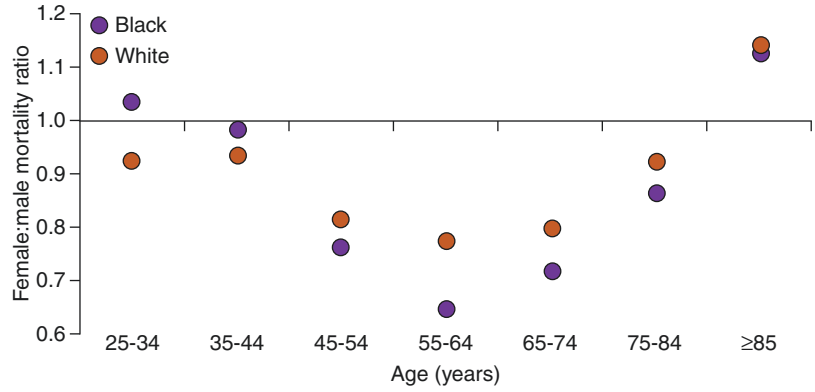

Fig. 1.2 Female-to-male mortality ratio according to age-related stroke in the United State (1999~2003). Adapted with permission from Lancet Neurology, Copyright Elsevier

times since the rapid development of neuroscience and imaging techniques.

The ischemic stroke, a subclass of stroke, has had much more controversy among researchers than the rest of the classification, such as hemorrhagic stroke. This is because the ischemic stroke conceptually overlaps with transient ischemic attack (TIA), which is a transient cerebral ischemic condition. The ischemic stroke presented in the International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) is as follows: "An ischemic condition of the brain, producing a persistent focal neurological deficit in the area of distribution of the cerebral arteries. The formation of an area of necrosis in the cerebrum caused by an insufficiency of arterial or venous blood flow. Infarcts of the cerebrum are generally classified by hemisphere, lobe, arterial distribution, and etiology" [12].

The newly revised ICD-11 defines ischemic stroke as "acute focal neurological dysfunction caused by focal infarction at single or multiple sites of the brain. Evidence of acute infarction may come either from (a) symptom duration lasting more than 24 hours, or (b) neuroimaging or other technique in the clinically relevant area of the brain". The term does not include infarction of the retina [13]. TIA is defined as "a brief episode (generally within 24 hours) of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction" [14].

However, the authors suggest that it is unreasonable to distinguish between ischemic stroke and TIA on a 24-hour basis. In other words, the guideline is "arbitrary" that patients with ischemic stroke should show neurologic deficits lasting longer than 24 hours. Ischemic lesions based on the imaging can be identified even at a much shorter duration of neurological deficits than 24 hours. Conversely, researchers often encounter that neurological symptoms are permanent, but the ischemic lesions are not detected in the imaging study. In other words, TIA is a concept designed to warn the possibility of permanent neurological deficits by ischemic stroke and to awaken both the physicians and the patients.

In view of the etiologic and pathophysiological aspects, fundamentally, both of them are diseases on the same continuous spectrum. Therefore, it is practically impossible to divide the two by a specific time. Nevertheless, ICD-10 and 11 continue to differentiate between the two and cause conceptual confusion among researchers. We would like to suggest a different concept of ischemic stroke and TIA from the above critical point. Considering the persistence of neurological symptoms and the presence of ischemic lesions in the imaging, it can be classified into three different concepts as shown in Fig. 1.3.

In Fig. 1.3, area A, is an ischemic stroke with persistent neurological deficits and lesions on imaging studies such as Brain CT or MRI. Neurological deficits might persist but not be confirmed by imaging. If the clinical diagnosis is a meaningful, it is appropriate to classify it as an ischemic stroke. Area B is a lesion-positive TIA (LPTIA), which is rapidly disappearing neurological deficit, but lesions are confirmed by imaging. Area C is a lesion-nega-

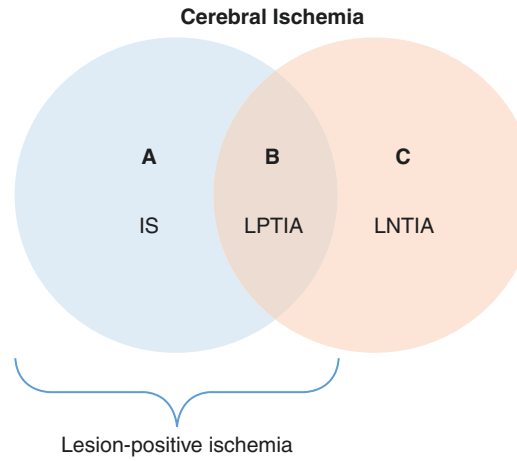

Fig. 1.3 New concept of TIA and stroke. Cerebral ischemia can be classified into three types (A, B, C) according to persistence of neurological symptoms and imaging findings, and A and B can be bound to lesion-positive ischemia. *IS* ischemic stroke, *LPTIA* Lesion-positive transient ischemic attack, *LNTIA* lesion-negative transient ischemic attack

tive TIA (LNTIA), a neurological deficit rapidly disappears and no lesion is detected on imaging. A and B, where lesions are identified, can be grouped into one concept called lesion-positive ischemia. In summary, ischemic stroke refers to "a condition in which sudden and focal neurological deficits caused by cerebral hemodynamic failure are sustained without rapid improvement." Imaging findings might suggest an ischemic stroke, but it is problematic to regard it as absolute evidence. TIA can be described as "a neurological deficit that is completely recovered in a short time, regardless of whether the ischemic lesion is confirmed on imaging," and it is not reasonable that specific time is one of the criteria that distinguishes the two concepts. This should be diagnosed in consideration of each clinical situation. We listed the existing definition of ischemic stroke and TIA, and the definition suggested by the authors (Table 1.1).

Table 1.1 The existing and new definition of ischemic stroke and TIA

Existing definition	
Ischemic stroke	Acute focal neurological dysfunction caused by focal infarction at single or multiple sites of the brain. Evidence of acute infarction may come either from (a) symptom duration lasting more than 24 hours, or (b) neuroimaging or other technique in the clinically relevant area of the brain. The term does not include infarction of the retina.
TIA	A brief episode (generally within 24 hours) of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction.
New definition	
Ischemic stroke	A condition in which sudden and focal neurological deficits caused by cerebral hemodynamic failure are sustained without rapid improvement. Most of the lesions are confirmed by imaging, and rarely, lesions are not identified.
TIA	A neurological deficit that is completely recovered in a short time, regardless of whether the ischemic lesion is confirmed on imaging.

TIA transient ischemic stroke

1.5 Classification of Stroke

Stroke is caused by cerebral blood flow obstruction of various causes. Depending on the etiology of the stroke, it has different pathophysiology, which means that different treatment is needed. In other words, the prognosis of the patient depends on the proper treatment, and the treatment depends on the cause of the stroke. Therefore, classification of stroke has been one of the challenges facing researchers.

After classifying stroke using the Harvard Stroke Registry at Harvard University in 1978, various classifications have been introduced [15]. We introduce some key stroke classifications. The first classification to be described is the ASCO Stroke Classification (*A* atherosclerosis, *S* small vessel disease, *C* cardiac disease, *O* other) [16, 17]. The ASCO Stroke Classification classifies only ischemic stroke, taking into consideration the potential likelihood of each stroke and the tests that support it. The next classification is the Oxfordshire Community Stroke Project (OCSP) classification developed by epidemiological study in Oxfordshire, England [18]. In the United Kingdom, primary care physicians are responsible for all stroke patients and only precontrast brain CT is used for image evaluation. This classification was developed to be optimized for the public healthcare system in the United Kingdom. Primary care physicians can be easily accessed to the classification because each case can be categorized solely based on basic physical examination and location and size of the lesions on brain CT (Table 1.2). Unlike stroke of undetermined etiology (SUE) of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, which is presented in the next section, there is no ambiguity in classification, so patients can be treated by clear guidelines. On the other hand, it is a disadvantage of this classification that it is difficult to treat based on the mechanism, because it is not classified on the basis of the etiology.

Last, we introduce the TOAST classification. This is currently the most widely used classification

Table 1.2 OCSP classification

Subtype	Details
Lacunar infarct (LACI)	Typical lacunar syndromes (4 types). Faciobrachial or brachiocrural deficits.
Total anterior circulation infarct (TACI)	If the following three symptoms are combined: 1. Higher cortical dysfunction (e.g., dysphasia, dyscalculia). 2. Homonymous visual field defect. 3. Ipsilateral motor and/or sensory deficit (2 or more body parts among face, arms, or legs). ∗ If there is a conscious impairment and the test cannot be carried out, it is assumed that there is a deficit.
Partial anterior circulation infarct (PACI)	1. Two of the three symptoms of TACI are relevant. 2. Higher dysfunction only. 3. Focal motor/sensory deficit.
Posterior circulation infarcts (POCIs)	Two of the three symptoms of TACI are relevant. 1. Ipsilateral cranial nerve palsy + contralateral motor and/or sensory deficit 2. Bilateral motor and/or sensory deficit. 3. Impaired conjugate eye movement. 4. Cerebellar dysfunction without ipsilateral long tract sign. 5. Isolated homonymous visual field defect.

OCSP Oxfordshire Community Stroke Project

in the world and classified into five categories. Each of these are large artery atherosclerosis, small vessel occlusion, cardioembolism, stroke of other etiology, and stroke of undetermined etiology. Three subtypes were further classified in the undetermined cause (Table 1.3). Compared to other classifications, TOAST is capable of causal assessment and criteria of the classification is quite clear. However, there are some problems in that classification. First, the criteria proposed by TOAST are arbitrary. For example, the criteria of large artery atherosclerosis for stenosis of more than 50% in the proximal vessel of the lesion has no specific basis for reference and are not scientific. Depending on the nature of the thrombus, it could be a stable thrombus even if the size is large. Even small thrombosis, if the contents are unstable (ulcerated plaque, intra-plaque

Table 1.3 TOAST classification

Subtype	Details
Large artery atherosclerosis (LAA)	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.
Small vessel occlusion (SVO)	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.
Cardioembolism (CE)	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-hour 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.
Stroke of other etiology (SOE)	Stroke caused by nonatherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders and other rare causes of stroke after diagnostic testing. Other categories must be excluded.
Stroke of undetermined etiology (SUE)	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 10172 in Acute Stroke Treatment, *CT* computed tomography, *MRI* magnetic resonance imaging

hemorrhage, etc.), the fragments of the thrombus might migrate to the distal area. The criteria that the size of the lesion should be within 1.5 cm in diameter proposed by the small vessel occlusion is also arbitrary, and there is a possibility that researchers might make errors in determining the treatment options. Another subtype to point out is 2 or more etiologies, one of the subcategories of stroke of undetermined etiology. TOAST classification assesses whether the ischemic stroke mechanism meets arbitrary criteria, and classifies it into "2 or more etiologies" if two or more criteria are met at the same time. It completely excludes clinicians from detecting the cause of stroke by combining various factors (neurological symptoms, medical history, history of drug use, changes in clinical symptoms, imaging findings, etc.). It also reduces the chance of treatment by focusing on clinically suspected causes. These simple and clear criteria are easy to use, but should be kept in mind that they might interfere with the proper care of patients. Rather than suggesting specific figures that divide each stroke subtype, somewhat vague criteria that allow physicians to actively judge could be more helpful. Stroke classifications are described in detail in the Stroke Revisited series, Chap. 11. Also, we have covered the details of stroke classification in the remainder of this textbook.

1.6 Conclusion

We have covered in this chapter what we need to know in order to define the basic concept of stroke, such as definition, classification, mechanism, and diversity of stroke. As you have already seen in this chapter, stroke is not a stereotypical disease that can be defined as one. Rather, it shows the most complex and diverse characteristics among all diseases that humans can suffer. Researchers around the world are struggling to conquer a stroke with this complexity, but it is still far from reality. The shortcut for overcoming stroke begins with an understanding of its nature. The authors hope that this chapter will be a valuable first step for readers to understand the nature of stroke.

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Cerebral Vascular Anatomy

2

Hyoung Soo Byoun and Gyojun Hwang

Abstract

The brain is about 2% of the body's weight, weighing between 1250 and 1450 g. The heart sends 15% of all blood to the brain, and 20% of total oxygen is consumed by the brain. Strokes occur due to problems with blood supply to the brain, and these can include hemorrhage, infarction, and transient ischemic attack. The emergent and proper management for strokes should be performed immediately and can prevent or minimize the otherwise devastating consequences. A fundamental concept of territories of the brain supplied by cerebral vessels and the functions of these territories is essential for effective therapeutic approach to stroke. At this point, defining and understanding cerebrovascular anatomy is the cornerstone to safe and successful treatment of stroke.

This chapter addresses the basic anatomical structures, courses, relationships, and functions of the cerebral vessels.

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2.1 Introduction

The cerebral blood flow is supplied by the internal carotid arteries (ICAs) and vertebral arteries (VAs) [1]. The ICAs take charge of the anterior circulation and the VAs take charge of the posterior circulation, sending 80 and 20% of the cerebral blood flow. The circle of Willis is an anastomotic system of arteries located at the base of the brain connecting anteroposterior and bilateral flows. The right innominate artery, left common carotid artery (CCA), and subclavian artery originate from the aortic arch. The right innominate artery is then divided into right CCA and right subclavian artery. The right VA originates from right subclavian artery and the left VA from the left subclavian artery. The CCA bifurcates to the ICA and the external carotid artery (ECA) at the level of the C4 vertebral body. Then, the anterior cerebral artery (ACA) and middle cerebral artery (MCA) are separated from the ICA. After branching of the posterior inferior cerebellar artery (PICA) from both VAs, the basilar artery (BA) is formed by the union of two VAs. As it ascends superiorly, the BA ramifies the anterior inferior cerebellar artery (AICA) and superior cerebellar artery (SCA), and is divided into two posterior cerebral arteries (PCAs).

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2.2 Internal Carotid Artery

The ICA separates from the CCA at the level of fourth cervical vertebrae, and passes through the carotid canal into the cranium [2]. The diameters of the CCA, carotid bulb, and proximal ICA are approximately 7.0 mm, 7.5 mm, and 4.5 mm, respectively [3]. The ICA penetrates the petrous bones, the cavernous sinus, and the dura, and finally separates into the ACA and MCA.

The ICA segment is divided into seven segments: cervical, petrous, lacerum, cavernous, clinoid, ophthalmic, and communicating segments from the bottom (Fig. 2.1).

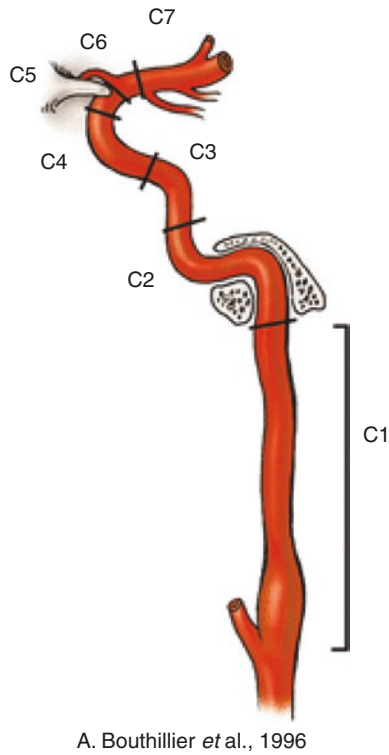

Fig. 2.1 The classification scheme of the internal carotid artery. C1, cervical; C2, petrous; C3, lacerum; C4, cavernous; C5, clinoid; C6, ophthalmic; and C7, communicating segment. Adapted with permission from Essential Neurovascular Anatomy, Copyright Springer Nature [4]

2.2.1 Segments of the ICA

2.2.1.1 Cervical Segment

The cervical segment of the ICA is the section from the CCA bifurcation to the carotid canal of the temporal bone. The ICA is initially located at the posterolateral portion of the ECA and then courses medially to the ECA as it ascends toward the carotid canal. The ICA lies anteromedial to the internal jugular vein. The glossopharyngeal nerve, vagus nerve, accessory nerve, and hypoglossal nerve course between the ICA and the internal jugular vein [5]. There is no important branch arising from this segment.

2.2.1.2 Petrous Segment

The petrous segment of the ICA enters the skull base through the carotid canal and courses in the petrous temporal bone. This segment subdivides into the short vertical segment, genu, and long horizontal segment. The sympathetic chain and venous plexus surround the petrous segment [6]. The caroticotympanic artery and vidian artery arise from this segment.

2.2.1.3 Lacerum Segment

The lacerum segment of the ICA is a section from the end of the petrous segment to the petrolingual ligament (Fig. 2.1).

2.2.1.4 Cavernous Segment

The cavernous segment of the ICA begins from the petrolingual ligament and enters the cavernous sinus. It consists of the posterior genu, horizontal segment, and anterior genu. The meningohypophyseal trunk, inferolateral trunk, and capsular arteries of McConnell arise from the cavernous segment of the ICA (Figs. 2.1 and 2.2).

The meningohypophyseal trunk arises from the posterior genu of the cavernous segment of the ICA. It ramifies three branches including the tentorial arteries, inferior hypophyseal artery, and lateral clival artery. The tentorial arteries course medially and superiorly along the margin of the tentorial incisura or run laterally and inferiorly

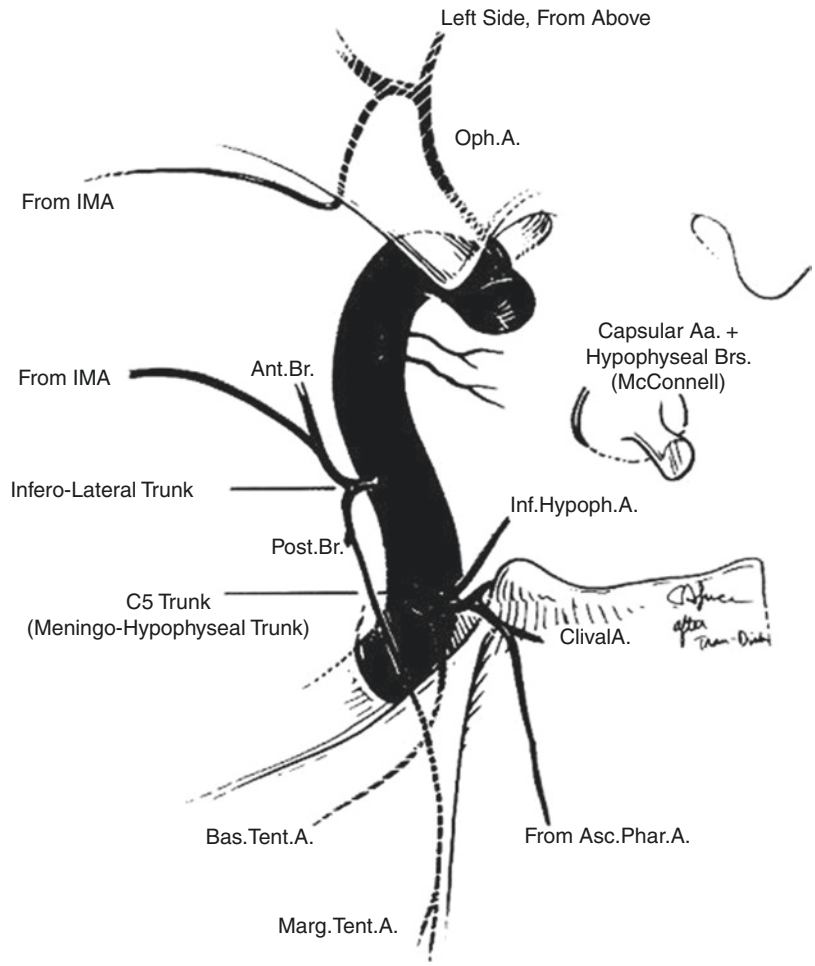

Fig. 2.2 The branches of cavernous internal carotid artery segments. Adapted with permission from Neurology, Copyright Wolters Kluwer Health [7]

into the tentorium. Near the petrous ridge and sigmoid sinus, they connect with the middle meningeal artery and dural arteries of the posterior fossa. The inferior hypophyseal artery which anastomoses with the superior hypophyseal artery and its contralateral flow supplies the pituitary gland. The clival artery supplies dura covering the clivus and has a connection with the ascending pharyngeal artery of the ECA.

The inferolateral trunk that arises from the lateral aspect of the horizontal ICA segment supplies the oculomotor nerve, trochlear nerve, gasserian ganglion of the trigeminal nerve, abducens nerve, dura mater of the cavernous sinus, and tentorium. It connects with several branches from the ECA including branches of the internal maxillary artery and the ascending pharyngeal artery.

The capsular arteries of McConnell arise from the medial aspect of the cavernous segment of the ICA and supplies the pituitary gland irregularly. They are too small to be seen during angiography in the normal state. Medially directed aneurysms of cavernous segments of the ICA can present in these arteries. They can penetrate the diaphragm sellae and occupy the sellae to cause subarachnoid hemorrhage (if ruptured) and hypopituitarism. These branches of the cavernous segment serve as important collaterals in the ICA occlusion.

2.2.1.5 Clinoidal Segment

The clinoidal segment of the ICA is the section from proximal dural ring to distal dural ring. It is the shortest section of the ICA. There is no branch arising from the clinoidal segment of the ICA.

2.2.1.6 Ophthalmic Segment

The ophthalmic segment of the ICA is the section from the distal dural ring to the origin of the posterior communicating artery. The ophthalmic artery and superior hypophyseal artery arise from this section (Fig. 2.1). The ophthalmic artery has important branches including the central retinal artery, the anterior and posterior ethmoidal arteries, lacrimal branch, recurrent meningeal branch, and branches supplying muscles and orbital content. They may receive collateral flows from the ECA when the ICA is occluded [8]. A connection between the facial or superficial temporal artery and the lacrimal branch can serve as an important collateral route. The recurrent meningeal branch can collateralize with the middle meningeal artery or the inferior lateral trunk of the cavernous segment of ICA.

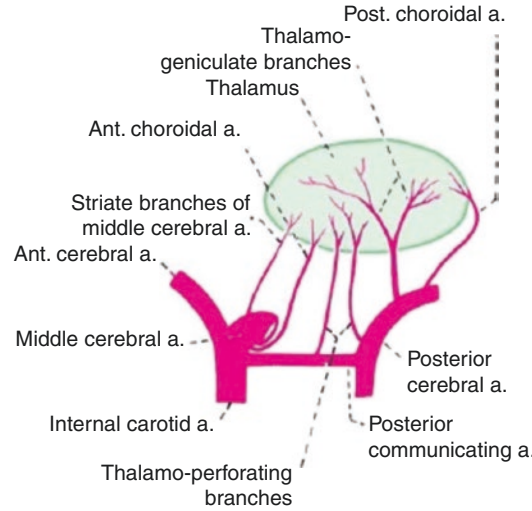

Fig. 2.3 Perforating branches of the thalamus. Adapted with permission from brainkart@com

2.2.1.7 Communicating Segment

The communicating segment of the ICA is a section from the origin of the posterior communicating artery (PCom) to the bifurcation of the ICA. The PCom and anterior choroidal arteries (AChA) arise from this section (Fig. 2.1).

The anterior thalamoperforator arteries (the most prominent branch of the anterior thalamoperforators is called premamillary artery or tuberothalamic artery), seven to ten in number, come from the superolateral aspect of the middle third of the PCom (Fig. 2.3). They supply the anterior portion of the thalamus, mammillothalamic tract, ventral amygdalofugal pathway, internal medullary lamina, posterior aspect of the optic chiasm, the proximal portion of the optic radiations, the posterior hypothalamus, and cerebral peduncle [9]. Twenty percent of people have fetal-type PCom which is a common variant. In individuals with fetal type PCom, the P1 segment of the PCA is absent or hypoplastic [10, 11]. The AChA arises from the posterior wall of the ICA between the origin of the PCom and the ICA bifurcation (Fig. 2.4). It is divided into two main segments: cisternal segment and intraventricular segment. The cisternal segment courses posterior medially below the optic tract and superomedially below the temporal lobe uncus then it turns laterally. After it curves around the cerebral peduncle in the crural cistern, it continues toward the lateral geniculate body. It turns sharply toward the choroidal fissure near the lateral geniculate body, and then, it enters the temporal horn through the choroidal fissure and the intraventricular segment begins. The sharp angle of the AChA at the choroidal fissure is known as the "plexal point." The intraventricular segment continues along the choroidal plexus and curves around the pulvinar of the thalamus anteriorly. The AChA supplies the

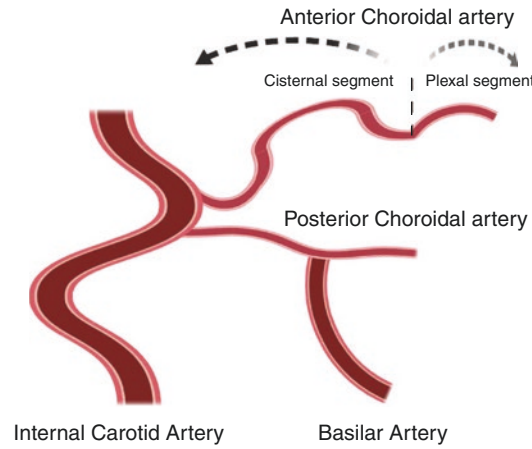

Fig. 2.4 The schematic illustration of angiographic feature of the anterior choroidal artery. *ICA* internal carotid artery, *BA* basilar artery, and *PCoA* posterior communicating artery

uncus, piriform cortex, tail of the caudate nucleus, hippocampus, amygdala, thalamus, lateral geniculate body, optic tract, genu and posterior limb of internal capsule, cerebral peduncle, choroid plexus, and subthalamic nucleus. Occlusion of the AChA causes clinical symptoms which include variable degrees of hemianesthesia, contralateral hemiplegia, and hemianopsia with memory loss and somnolence [12].

2.2.2 Anatomic Variants of the ICA

Agenesis of the ICA has been reported rarely. Unilateral agenesis of the ICA is more common than bilateral agenesis. Due to the development of the collateral circulations or alternative routes, clinical symptoms may not occur. This agenesis can be confirmed by absence of the carotid canal.

The aberrant ICA is thought to be associated with atresia or regression of the cervical portion of the ICA. It usually occurs bilaterally and may be misdiagnosed as a middle ear mass on axial images. Pseudoaneurysm and severe bleeding may occur due to biopsy of the misdiagnosed lesion.

2.2.3 Carotid-Basilar Anastomoses

Transient segmental connections between the primitive carotid and hindbrain circulations including the trigeminal, otic, hypoglossal, and proatlantal intersegmental arteries, present during development of fatal craniocerebral circulation (Fig. 2.5). These vessels course parallel with the cranial nerves and are named according to these nerves except for the extracranial proatlantal intersegmental arteries. Normally, these vessels disappear as the PComs develop. However, if these vessels are not obliterated and persist into adulthood, they are termed carotid-basilar anastomoses.

The persistent trigeminal artery is the most common of four carotid-basilar anastomoses. It arises from the posterior genu of the cavernous ICA. It curves laterally and posteriorly around the dorsum sella, following the trigeminal nerve

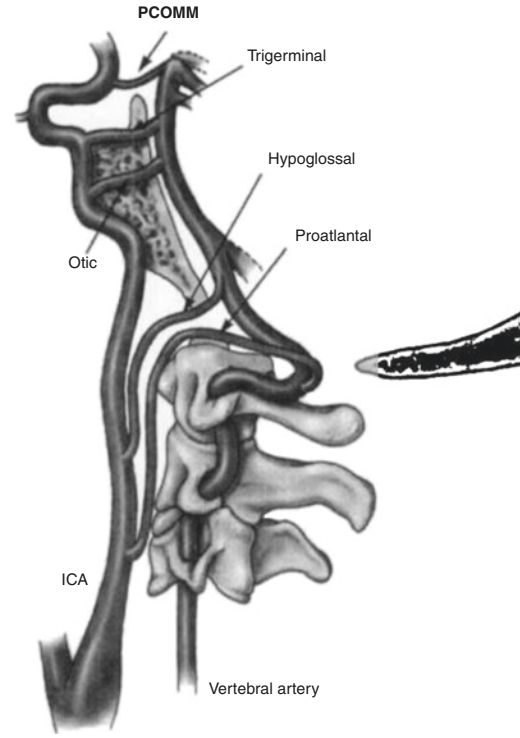

Fig. 2.5 Carotico-basilar anastomoses. Adapted with permission from American Journal of Roentgenology, Copyright American Roentgen Ray Society [13]

(parasellar course) or directly posteriorly to pierce the dorsum sellae to anastomose with the basilar artery (intrasellar course). The persistent trigeminal artery is frequently associated with other vascular abnormalities including aneurysm. The primitive otic artery arises from the petrous segment of the ICA. It emerges from the internal auditory meatus and joins the BA. The persistent otic artery is extremely rare. The persistent hypoglossal artery, the second most common anastomosis, arises from the cervical segment of the ICA at the level of C1 or C2. After that it curves posteromedially to the hypoglossal canal and passes through the hypoglossal canal to join the BA without passing the foramen magnum. In cases of persistent hypoglossal artery, the PCom is absent and the ipsilateral VA is hypoplastic. The proatlantal intersegmental artery arises from ICA (type 1) or ECA (type 2) at the level of C2 or C3, and runs posterolaterally and superiorly outside of the intervertebral foramen. Then, it passes through the foramen magnum and joins the VA.

2.3 Anterior Cerebral Artery

The ACA supplies the medial aspects of cerebral hemisphere, lentiform nucleus, and base of the frontal lobe (Fig. 2.6). The ACA is divided into three segments [14, 15]:

- A1: precommunicating segment (horizontal)
- A2: postcommunicating segment (vertical)
- A3: distal segment

The A1 segment extends horizontally from the ICA bifurcation to the origin of the anterior communicating artery (ACom). Divided from the ICA, it courses medially toward the interhemispheric fissure over the optic nerve or optic chiasm and below the anterior perforated substance.

If the A1 segment is hypoplastic or absent, the opposite A1 supplies both ACA territories through the ACom. The ACom complex has variations according to the relative size of the A1 segment and the ACom. If the diameter of the A1 segments is 1.5 mm or less, it is defined as hypoplastic. The ACom varies in diameter up to 3.4 mm, in length up to 7 mm. The greater the diameter of the ACom, the more asymmetry of the A1 segments occurs. Asymmetry of the A1 segments may affect aneurysm formation in the ACom [16, 17].

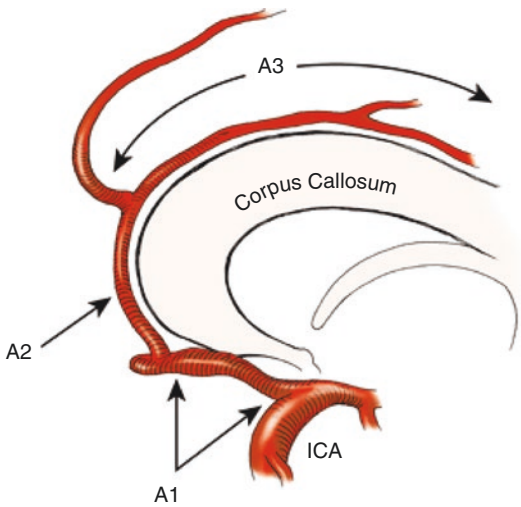

Fig. 2.6 The segments of anterior cerebral artery. Adapted with permission from Essential Neurovascular Anatomy, Copyright Springer Nature [4]

The A2 segment is the section from the origin of the ACom to the junction where the rostrum of corpus callosum and genu of corpus callosum meet. It courses upward within the interhemispheric fissure, anterior to the lamina terminalis and rostrum of corpus callosum.

The A3 segment begins at a point where the ACA is divided into the pericallosal artery and callosomarginal artery around the genu of corpus callosum. The callosomarginal artery courses over the cingulate gyrus and within the cingulate sulcus posteriorly. The pericallosal artery runs posteriorly above the corpus callosum with various lengths.

2.3.1 Perforating Branches

The medial lenticulostriate artery arises from the A1 segment, runs posterosuperiorly through the anterior perforated substance (Fig. 2.7). It supplies anterior hypothalamus, septum pellucidum, the medial part of the anterior commissure, the pillars of the fornix, and the anterior aspect of the striatum [14, 19].

The recurrent artery of Heubners arises from the proximal portion of the A2 segment (34–50%), A1 segment (17–45%), or ACom (5–20%) (Fig. 2.7). It runs back on the course of its parent vessel. It courses laterally above the A1 and M1 segments and supplies the head of the caudate nucleus, anterior limb of the internal capsule, anterior portion of the hypothalamus, and globus pallidus. Then, it terminates in the lateral aspect of the anterior perforated substance [20].

Inferiorly directed small perforating branches from A1, proximal A2, and ACom supply the optic chiasm and nerve. Also, perforating branches from the ACom are directed toward the anterior cingulum, corpus callosum, fornix, and septal region. The anterior basal perforating branches of the ACom complex supply the hypothalamic region. If these vessels are injured, neurologic and psychiatric syndromes will be generated [14, 21, 22].

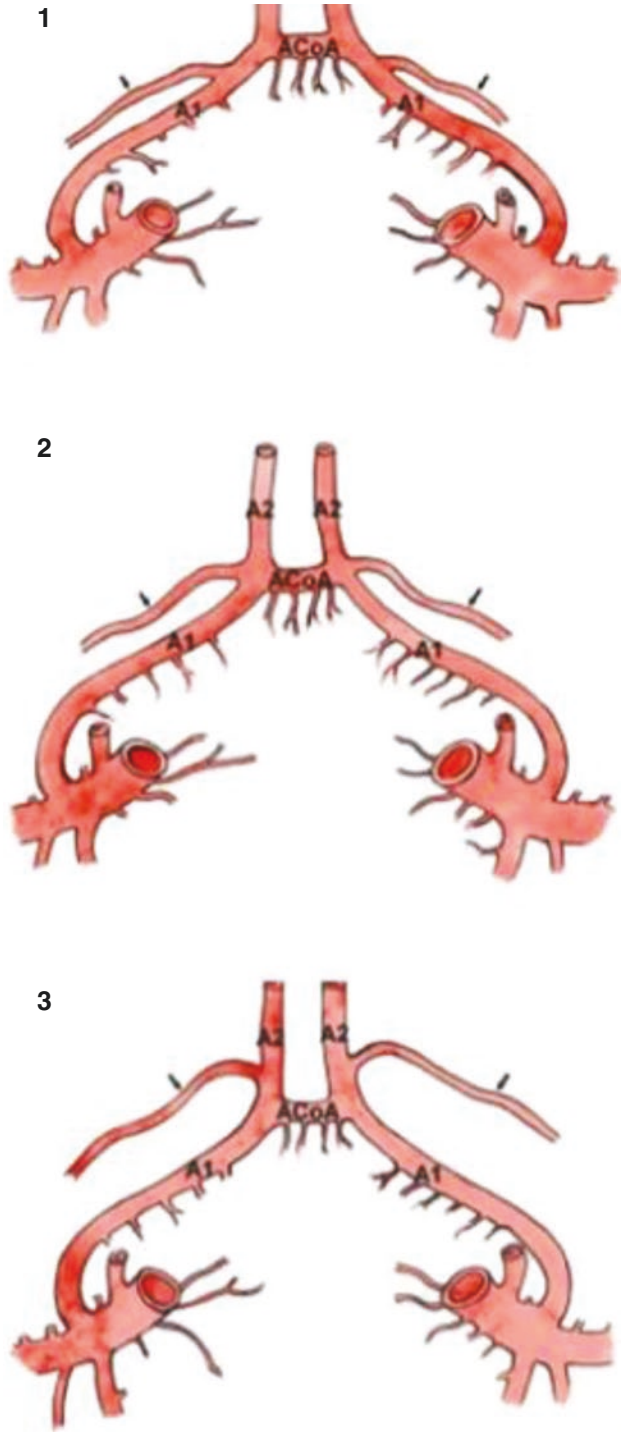

Fig. 2.7 The areas of origin of the recurrent artery of Heubner. Adapted with permission from BioMed Research International [18]

2.3.2 Cortical Branches

The cortical branches are named according to the territory perfused (Fig. 2.8). Normally, cortical branches do not arise from the A1 segment. First cortical branches arise from the proximal A2 segment. These vessels supply the orbital surface of the frontal lobe (orbitofrontal artery). Second cortical branches also arise from the proximal A2. The most prominent branch of these is called the frontopolar artery arising below the rostrum or genu of corpus callosum and coursing anteriorly to the frontal pole. The anterior, middle, and posterior internal frontal artery and precentral arteries which are ramified from the callosomarginal artery supply the medial surface of the hemisphere above the corpus callosum of frontal and precuneus as well as the adjacent convexity. The superior and inferior parietal arteries arising from the pericallosal artery represents continuation of the main ACA trunk supplying the medial surface above the corpus callosum of the parietal lobe.

2.3.3 Anomalies of the ACA

The ACA in rare cases arises from the region that located a few millimeters above the intradural ICA. In this situation which is called infraoptic origin of the ACA, the ACA courses medially below the optic nerve and then curves superiorly to the AComA. This anomaly is associated with other anomalies including aneurysm, agenesis of hypoplasia of the A1, and carotid agenesis. Accessory ACA arises from the ICA and courses under the optic nerve to supply the medial and basal area of the frontal lobe. Azygous ACA that is a single unpaired ACA is formed due to the embryonic median artery of the corpus callosum remaining. It is associated with an increased risk of aneurysm or other anomalies. Bihemispheric ACA is similar to azygous ACA. However, it has one hypoplastic A2 and the other dominant A2 divides into branches that supply both hemispheres.

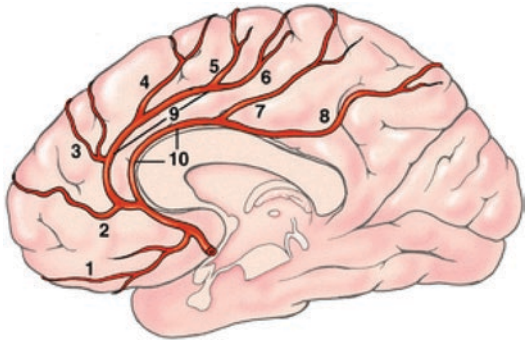

Fig. 2.8 The distal branches of anterior cerebral artery. (1) Orbitofrontal artery; (2) frontopolar artery; (3) anterior internal frontal artery; (4) middle internal frontal artery; (5) posterior internal frontal artery; (6) paracentral artery; (7) superior parietal artery; (8) inferior parietal artery; (9) callosomarginal artery; and (10) pericallosal artery. Adapted with permission from Essential Neurovascular Anatomy, Copyright Springer Nature [4]

2.4 Middle Cerebral Artery

After the ACA is separated at the ICA bifurcation, the MCA passes through the sylvian fissure and insula, and supplies a wide area on the surface of the cerebrum (Fig. 2.9). The MCA are divided into four segments [23–25]:

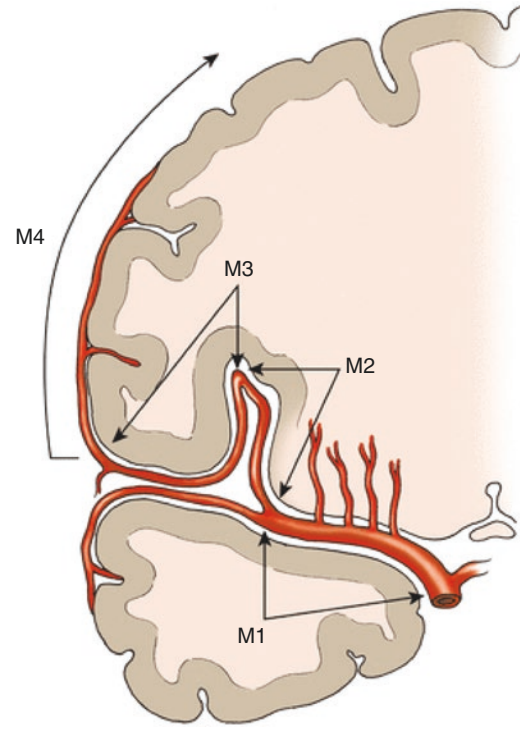

Fig. 2.9 The middle cerebral artery. Adapted with permission from Essential Neurovascular Anatomy, Copyright Springer Nature [4]

- M1: horizontal segment
- M2: insular segment
- M3: opercular segment
- M4: cortical segment

The M1 segment is the horizontal section from the ICA bifurcation to the limen insulae and courses below the anterior perforated substance. It is divided into prebifurcation and postbifurcation segments at a point where the MCA is divided into superior and inferior divisions. The MCA main trunk can be divided into four patterns such as a single trunk with no main division, a bifurcation, a trifurcation, or multiple trunks. Of these, the bifurcation pattern is the most common (up to 90%). Near the limen insulae, the postbifurcation segment curves upward in a gentle angle, forming "genu."

The M2 segment extends from the genu to the top of the circular sulcus of the insula. It consists of six to eight major stem arteries. In bifurcation pattern, superior and inferior division of the M2 segments course in posterosuperior and posteroinferior directions at the genu, respectively. The M3 segment begins at the top of the insula and turn laterally within the sylvian fissure (opercular turn). After exiting the sylvian fissure, the M4 segments become visible on the lateral convexity of the hemisphere and they spread to the outer part of frontal, parietal, temporal occipital lobe, and widely supply the cerebral cortex.

2.4.1 Perforating Branches

The lateral lenticulostriate arteries mainly arise from the posterosuperior aspect of the M1 segment and its remaining vessels arise from the M2 segment. The lateral group of the lateral lenticulostriate arteries have a slightly larger diameter than the medial group. Lateral groups have a recurrent curve before entering the anterior perforated substance. Lateral lenticulostriate arteries make a sharp posterior and medial turn in the cisternal portion from their origin to assume a more lateral curve as they enter the anterior perforated substance. They supply the lateral aspect of the anterior commissure, corona radiata, head and body of caudate nucleus, lateral segment of globus pallidus, putamen, and superior part of internal capsule [26–28] (Fig. 2.9).

2.4.2 Cortical Branches

The cortical arteries of MCA supply most of the lateral surface of the cerebral hemisphere and are named according to the territory perfused (Fig. 2.10). There are the orbitofrontal artery, prefrontal artery, precentral artery, central artery, anterior parietal artery, posterior parietal artery, and angular artery which supply the upper part of the MCA territory based on Sylvian fissure. The temporooccipital artery, posterior temporal artery, middle temporal artery, anterior temporal artery, and temporopolar artery supply the lower part of the MCA territory.

The orbitofrontal artery supplies the inferior surface of the frontal lobe. The prefrontal artery supplies much of the lateral aspect of the frontal lobe anterior to the sylvian triangle. The orbitofrontal and prefrontal arteries exhibit the fanciful appearance of a candelabra. They usually supply the Broca speech area, the frontal eye fields, and premotor strip on the dominant hemi-

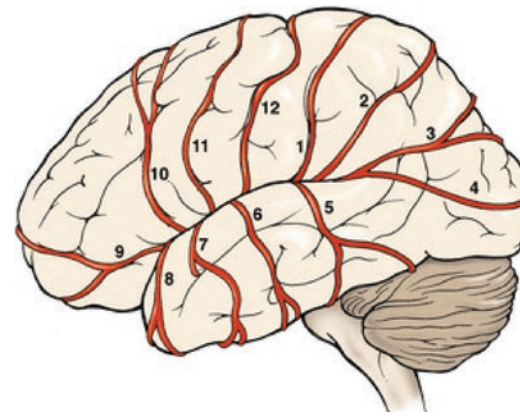

Fig. 2.10 The cortical branches of middle cerebral artery. (1) Anterior parietal artery; (2) posterior parietal artery; (3) angular artery; (4) temporooccipital artery; (5) posterior temporal artery; (6) middle temporal artery; (7) anterior temporal artery; (8) temporopolar artery; (9) orbitofrontal artery; (10) prefrontal artery; (11) precentral artery; and (12) central artery. Adapted with permission from Essential Neurovascular Anatomy, Copyright Springer Nature [4]

sphere. The precentral artery courses superiorly on the posterior part of the frontal lobe or the anterior edge of the parietal operculum. The central artery courses posterosuperiorly along the central sulcus toward the superior margin of the hemisphere. The anterior parietal artery initially courses along the postcentral sulcus, then courses in the intraparietal sulcus. The posterior parietal artery courses posterosuperiorly and shows the anterior border of the supramarginal gyrus. The angular artery appears at the most posterosuperior portion of the lateral sulcus and crosses transverse temporal gyrus (Heschl's gyrus). The temporooccipital artery courses posteriorly to supply the superior temporal gyrus and lateral surface of the occipital lobe. The posterior temporal artery crosses the superior, middle, and inferior gyrus posteroinferiorly to supply the posterior part of the temporal lobe. The medial temporal artery supplies the middle part of the temporal lobe. The anterior temporal artery that arise from the M1 segment usually supplies the lateral aspect of the anterior temporal lobe.

The region named "the watershed zone" occupies the border between the MCA territory and the territories of the adjacent cerebral arteries, meaning that it is at the interface of different circulations. This region is vulnerable to ischemic injury particularly in the hypo-perfused condition.

2.4.3 Anomalies of the MCA

Accessory M1 arises from the ACA and parallels the M1. It is associated with aneurysm formation and should be distinguished from other anomalies such as duplicated M1 and a large recurrent artery of Heubner. Duplicated M1 that arises from ipsilateral ICA runs parallel with ipsilateral M1. It is also associated with the aneurysm formation. Fenestration of the M1 is rarely found and should not be misdiagnosed as an M1 dissection.

2.5 Posterior Cerebral Artery

The BA is divided into the two PCAs at the front of midbrain, interpeduncular cistern near dorsum sellae or suprasellar cistern below the base of the third ventricle (Fig. 2.11).

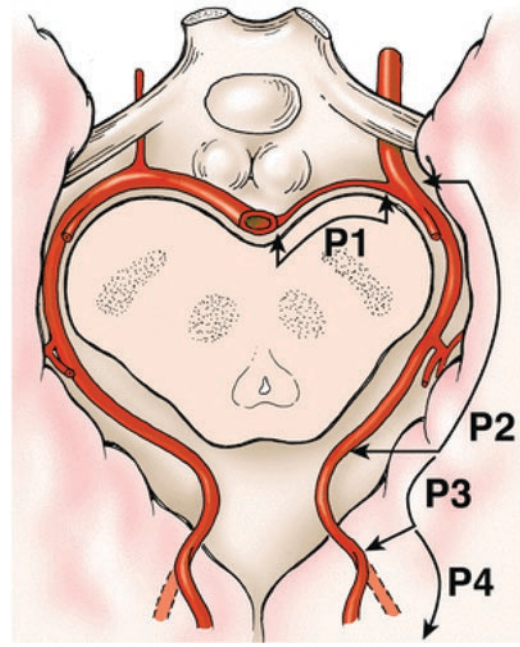

Fig. 2.11 The posterior cerebral artery. Adapted with permission from Essential Neurovascular Anatomy, Copyright Springer Nature [4]

The PCA consists of four segments:

- P1: precommunicating segment
- P2: ambient segment
- P3: quadrigeminal segment
- P4: calcarine segment

The P1 segment is a section from basilar bifurcation to the junction with the PComA. It curves around the front of the midbrain in the interpeducular cistern and locates above the oculomotor nerve. The P2 segment extends from the junction with the PComA to the posterior portion of the midbrain between the midbrain and the hippocampal gyrus. Above the tentorium cerebellum and trochlear nerve, it courses parallel to the basal vein of Rosenthal and optic tract in the ambient cistern. The P3 segment curves medially within the perimesencephalic cistern. Both P3 segments approach each other behind the colliculi with varying distances. Then, it courses laterally from the level of the quadrigeminal plate to the calcarine fissure. The P4 segment begins at the anterior part of the calcarine fissure. It is divided into the medial and lateral occipital arteries within the

calcarine fissure and includes cortical branches that arise from the distal PCA [29].

2.5.1 Perforating Branches

The posterior thalamoperforating arteries, up to eight in number, arise from the posterior or superior aspect of the P1 segment (Fig. 2.3). They course posteriorsuperiorly and pass through the posterior perforated substance, the interpeduncular fossa, and the medial walls of the cerebral peduncles. Usually, the posterior thalamoperforating arteries arise from both P1 segments. Both posterior thalamoperforating arteries may arise from one side as a common trunk (the artery of Percheron). In this case, if the common trunk is occluded, thalamic infarction may occur on both sides. The proximal 2–3 mm of the P1 segment are most often free of vessels. Therefore, when treating aneurysm in this area, the risk of perforating artery injury is relatively small.

The thalamogeniculate arteries, 2–12 in number, arise from the posterior or posterosuperior aspect of the P2 segment primarily, as well as the P3 segment [30].

The posterior thalamoperforating arteries and thalamogeniculate arteries together, supply the posteromedial aspect of thalamus, subthalamic nucleus, the substantia nigra, red nucleus, oculomotor and trochlear nuclei, posterior portion of the internal capsule, and the cisternal segment of the oculomotor nerve [9].

The perpendicular perforating arteries arise (up to six in number) from the P1 and P2 segments. They course directly to the cerebral peduncles and supply the corticospinal and corticobulbar tracts, substantia nigra, red nucleus, and tagmental and cisternal portions of the oculomotor nerve.

2.5.2 Ventricular Branches

The medial posterior choroidal arteries (PChAs) arise from the P2 segment primarily, but also the P1 segment, or parietooccipital artery. They course around the ambient cistern, then curve superomedially and run forward to enter the roof of the third ventricle. They extend anteriorly within the velum interpositum toward the foramen of Monro and terminate at the choroid plexus of the lateral ventricle. Cisternal branches of the medial posterior choroidal arteries supply the medial geniculate body, habenula, midbrain, pineal gland, posterior thalamus, and tectal plate.

The lateral PChAs, up to nine in number, arise from the P2 segment or various cortical branches of the PCA. Their origin is more distal than the medial PChAs. They pass through the choroidal fissure to enter the lateral ventricle posteriorly at the level of the atrium. Then, they curve laterally around the pulvinar of the thalamus within the lateral ventricle. The lateral PChAs anastomoses with the medial PChAs and branches of the AChA [31].

2.5.3 Cortical Branches

The anterior and posterior temporal arteries arise from the P2 segments (Fig. 2.12). The anterior temporal artery courses anterolaterally under the hippocampal gyrus. The posterior temporal artery courses posterolaterally toward the occipital lobe. They anastomose with temporal branches of the middle cerebral artery and supply the inferior aspect of the temporal lobe. Passing through the calcarine fissure, the posterior cerebral artery is divided into the medial and lateral occipital arteries. The lateral occipital artery is further divided into the anterior, middle, and posterior inferior temporal arteries supplying the inferior surface of the temporal lobe. The medial occipital artery is divided into the parietooccipital artery and the calcarine artery. The parietooccipital artery, the largest terminal branch of the PCA, courses in the parietooccipital sulcus and curves laterally to approach the parietooccipital sulcus. The calcarine artery runs deep within the calcarine sulcus. It supplies the primary visual cortex. The splenial artery arises from the parietooccipital artery or calcarine artery. It anastomoses with the branches of the pericallosal artery and the medial PChA.

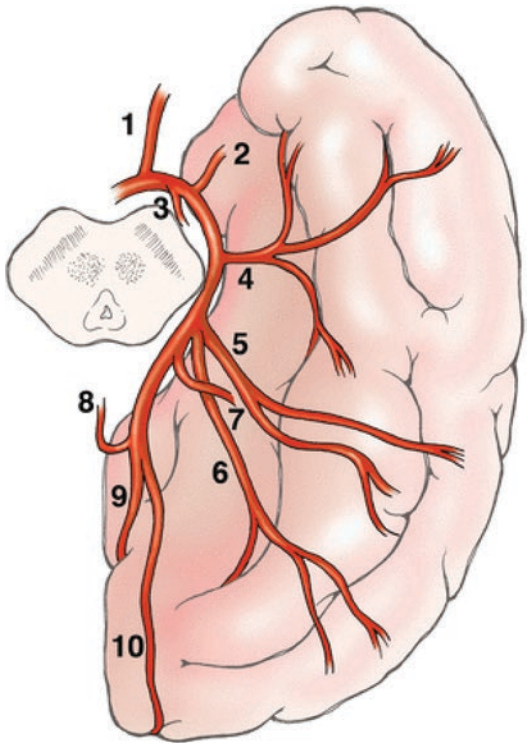

Fig. 2.12 The major branches of posterior artery. (1) Posterior communicating artery; (2) hippocampal artery; (3) posteromedial choroidal artery; (4) anterior temporal artery; (5) middle temporal artery; (6) posterior temporal artery; (7) posterolateral choroidal artery; (8) splenial artery; (9) parietooccipital artery; and (10) calcarine artery. Adapted with permission from Essential Neurovascular Anatomy, Copyright Springer Nature [4]

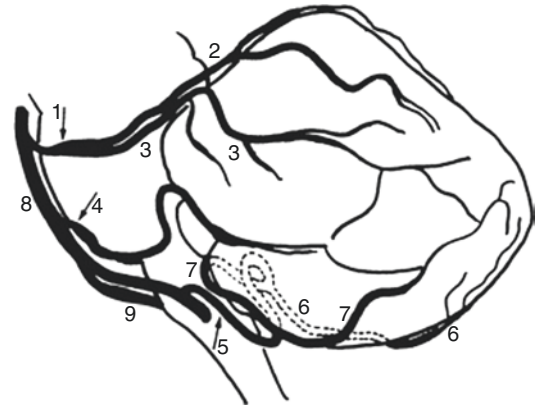

Fig. 2.13 The schematic illustration of the cerebellar arterys. (1) Superior cerebellar artery (SCA); (2) medial branch of SCA; (3) lateral branch of SCA; (4) anterior inferior cerebellar artery (AICA); (5) posterior inferior cerebellar artery (PICA); (6) medial branch of PICA; (7) lateral branch of PICA; (8) basilar artery; and (9) vertebral artery. Adapted with permission from Vascular Supply and Territories of the Cerebellum, Copyright Springer Nature [32]

2.6 Basilar Artery

Both VAs join and become the BA at the pontomedullary junction. The BA is approximately 32 mm in length and 4 mm in diameter in adults, until it is divided into two PCAs in the prepontine cistern. It courses along a shallow median groove on the pons.

2.6.1 Cerebellar Branches

The SCA arises from proximal portion of the basial bifurcation. It is divided into four segments including the anterior pontomesencephalic, lateral pontomesencephalic, cerebellomesencephalic, and cortical segments (Fig. 2.13). The anterior pontomesencephalic segment courses below the oculomotor nerve between the dorsum sellae and the upper brainstem. The lateral pontomesencephalic segment begins at the anterolateral margin of the brain stem, then it curves around the cerebral peduncle posterolaterally below the trochlear nerve and above the trigeminal nerve. It is divided by the tentorium cerebelli at distal portion to form the cerebellomesencephalic segments. It courses within the cerebellomesencephalic fissure and is divided into two cortical branches (medial and lateral). The lateral branch of the SCA supplies superolateral aspect of cerebellar hemisphere, superior cerebellar peduncle, dentate nucleus, and brachium pontis, and the medial branch supplies the superomedial aspect of the cerebellar hemisphere, superior aspect of vermis, inferior colliculi, and midbrain [33].

The AICA arises from the proximal basilar artery and curves laterally, posteriorly, and inferiorly around the pons near the abducens nerve. It is divided into four segments including the anterior pontine, lateral pontine, flocculopeduncular, and cortical segments (Fig. 2.13). The anterior pontine segment is located between the clivus and the belly of the pons. The lateral pontine seg-

ment begins at the anterolateral margin of the pons and passes through the cerebellopontine angle. In this segment, it locates the anteromedial portion of the facial nerve and vestibulocochlear nerve. The flocculopeduncular segment courses above the flocculus and along the middle cerebellar peduncle toward the apex of the cerebellopontine fissure. The cortical segment goes toward the petrosal surface of the cerebellum. The AICA supplies the anterior inferior aspect of the cerebellum, flocculus, middle cerebellar peduncle, inferolateral aspect of pons, and superior portion of medulla. It terminates near the petrosal surface. The labyrinthine artery that mainly arises from the AICA supplies the structures of the internal auditory canal including the facial and vestibulocochlear nerves [34, 35].

2.6.2 Perforating Branches

Numerous pontine perforating arteries arise from the BA within the prepontine cistern. The median and paramedian branches arise perpendicularly from the posterior wall of the BA and penetrate the pons posteriorly to reach to the floor of the fourth ventricle. The circumferential branches arise from the posterolateral wall of the basilar artery and curve around the lateral aspect of the pons. They give off many perforating branches perpendicularly to the pons and ventrolateral portion of cerebellum [36].

2.7 Vertebral Artery

The VA, which is the first branch of the subclavian artery, is divided into four segments:

- V1: extraosseous segment
- V2: foraminal segment
- V3: extraspinal segment
- V4: intracranial segment

The V1 segment arises from the superior or posterior aspect of the subclavian artery and courses superoposterioly toward the transverse foramen of the C6. The V2 segment runs vertically to the transverse foramen of the second cervical vertebra and passes through laterally through the transverse foramen of the C2 in an inverted L-shape. Then it turns again superiorly to the transverse foramen of the C1. Passing through the transverse foramen of the C1, the V3 segment makes a posteromedial curve around the atlantooccipital articulation. Then, it turns sharply anteriorly and superiorly to pierce the dura. After piercing the dura, the V4 segment enters the skull via the foramen magnum and each V4 segment joins together at the pontomedullary junction to become the BA. Usually, the left VA is larger in diameter than right one [37].

2.7.1 Intracranial Branches

The PICA is the largest and most important vessel among the VA branches and has the most variations. Eighty to ninety percent of the PICA arise from the intracranial VA and the others arise from the extracranial VA. The PICA is divided into five segments and two loops (Fig. 2.13). After separating from the vertebral artery, the PICA curves posteriorly around the inferior margin of the olive within the medullary cistern to be the anterior medullary segment. It runs between or above the root of the glossopharyngeal, vagus, and accessory nerves. The lateral medullary segment courses between the accessory rootlets. The tonsillomedullary segment extends from the level of accessory nerves around the caudal half of the tonsil and forms the caudal loop. The telovelotonsillar segment extends from the midlevel of the tonsil to the exit from the cleft located between the tela choroidea and inferior medullary velum superiorly and the superior pole of the tonsil inferiorly, and forms a cranial loop. Then, it terminates upon separating into the vermian branch (medial branch) and the tonsilohemispheric branch (lateral branch). The PICA supplies the lower medulla and the inferior aspects of the fourth ventricle, tonsils, vermis, and inferolateral cerebellar hemisphere. If territories of the PICA are occluded, a lateral medullary syndrome or Wallenberg syndrome is generated. Numerous medullary perforating

branches arise from the anterior, lateral, posterior medullary segments. Therefore, medullary functions can be spared in case of more distal PICA infarctions [38].

The anterior spinal artery arises from the V4 segment. Each anterior spinal artery courses inferomedially to unite with each other. After combining, it descends along the anteromedian sulcus of the spinal cord. The anterior spinal artery gives off small perforating vessels to the anterior aspect of the medulla and anterior two thirds of the spinal cord. The lateral spinal artery arises from the V4 segment or posterior inferior cerebellar artery. It originates lateral to the medulla, and descends anterior to the posterior spinal nerve roots and posterior to the dentate ligament. It supplies the accessory nerve, the lateral and posterior aspects of medulla and spinal cord, and C1–4 spinal nerves.

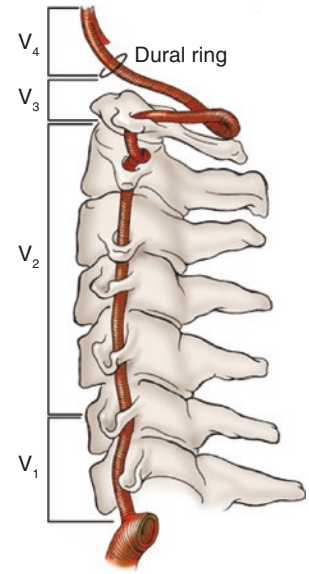

Fig. 2.14 The vertebral artery. Adapted with permission from Essential Neurovascular Anatomy, Copyright Springer Nature [4]

2.8 External Carotid Artery

The ECA is anatomically related to many important structures of the head and neck. Initially, it locates at the anterior and medial portion of the ICA. Running cranially, it is in the posterolateral portion of the ICA to ramify over the structures of the face (Fig. 2.14).

The ECA consists of eight main arteries which include the superior thyroid artery, ascending pharyngeal artery, lingual artery, facial artery, occipital artery, posterior auricular artery, internal maxillary artery, and superficial temporal artery.

2.8.1 Superior Thyroid Artery

The superior thyroid artery is the first branch of the ECA. It courses inferiorly to anastomose with the branches of the contralateral superior thyroid artery and ipsilateral inferior thyroid artery and supplies the thyroid gland, parathyroid gland, larynx, and related structures (Fig. 2.15).

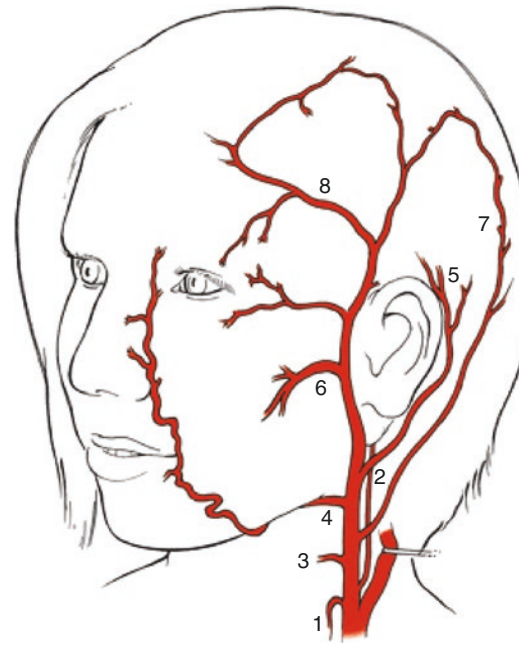

Fig. 2.15 The branches of external carotid artery. (1) Superior thyroid artery; (2) ascending pharyngeal artery; (3) lingual artery; (4) facial artery; (5) posterior auricular artery; (6) maxillary artery; (7) occipital artery; and (8) superficial temporal artery. Adapted with permission from Essential Neurovascular Anatomy, Copyright Springer Nature [4]

2.8.2 Ascending Pharyngeal Artery

The ascending pharyngeal artery arises from the posterior portion of the proximal ECA or arises from the cervical segment of the ICA. It occasionally has a common trunk with the occipital artery. The ascending pharyngeal artery is divided into the pharyngeal trunk, neuromeningeal trunk, inferior tympanic branch, and musculospinal branch.

The pharyngeal trunk consists of the superior, middle, and inferior pharyngeal branches, and supplies the nasopharynx, oropharynx, and hypopharynx, respectively. The superior pharyngeal branch passes through the artery of foramen rotundum to anastomose with the inferolateral trunk of the ICA.

The neuromeningeal trunk consists of the hypoglossal and jugular branches. The hypoglossal branches supply the neural structure of the hypoglossal canal and various dural territories of the posterior fossa, and have bilateral connections between the vertebral artery and the ascending pharyngeal artery behind the C2 body (arcade of the odontoid process). Furthermore, they form the collateral anastomosis with the meningohypophyseal artery. The jugular branches enter through the jugular foramen and run posterolaterally. It supplies the adjacent dura and sends branches running along the course of the sigmoid sinus.

The inferior tympanic artery courses between the pharyngeal trunk and the neuromeningeal trunk. It anastomoses with the stylomastoid branch of the occipital artery running with the facial nerve, middle meningeal artery, and caroticotympanic branch of the ICA in the middle ear.

The musculospinal branch supplies the accessory nerve, superior sympathetic ganglion, and cervical muscle and anastomoses with the vertebral artery, ascending cervical artery, and deep cervical arteries.

2.8.3 Lingual Artery

The lingual artery is the second branch of the ECA coursing anteriorly. It supplies the tongue, mouth floor, and suprahyoid area. Ten percent of the lingual artery makes a common linguofacial trunk with the facial artery. The facial artery and lingual artery achieve hemodynamical balance. Therefore, if one is hypoplastic, the other will be prominent to supplement the lack of blood flow.

2.8.4 Facial Artery

The facial artery is the third branch moving toward the anterior direction that arises from a just distal portion to the origin of the lingual artery. It courses inferolaterally around the body of the mandible. Then, it turns anterosuperiorly to supply the face, palate, lip, and cheek. The facial artery maintains hemodynamic balance with the branches of the ECA such as the ascending pharyngeal artery, internal maxillary artery, and accessory meningeal artery. Because it anastomoses with the branch of the ophthalmic artery branch, it can be an important supplementary collateral in case of occlusion of the ipsilateral ICA.

2.8.5 Occipital Artery

The occipital artery is one of the posteriorly directed branches of the ECA and it courses posterosuperiorly between the occipital bone and C1 vertebra to supply the extensive musculocutaneous structures, meninges, and scalp.

Normally, the occipital artery anastomoses with the ipsilateral vertebral artery in the C1 and C2 spaces and with the deep cervical artery at the C3 and C4 level. Sometimes, there is a connection between the musculospinal branch of the ascending pharyngeal artery.

Among the branches of the occipital artery, the stylomastoid artery and transmastoid artery are the endocranial branches. As the stylomastoid artery supplies the facial nerve and structures in the middle ear, caution is needed during embolization. The transmastoid artery is the source of high flow vascular lesions or tumors in the posterior fossa.

2.8.6 Posterior Auricular Artery

The posterior auricular artery courses posteriorly and arises from distal portions of the occipital artery to supply the superficial structures of the outer ear such as the scalp around the ear, ear, and external auditory meatus. Sometimes, it ramifies the stylomastoid artery that supplies the chorda tympani nerve.

2.8.7 Superficial Temporal Artery

The superficial temporal artery is the thermal artery that supplies the frontal and parietal areas of the scalp, ear, lateral aspect of the orbit and parotid gland. Sometimes, it has important anastomoses with the palpebral and lacrimal arteries.

2.8.8 Internal Maxillary Artery

The internal maxillary artery is the largest ECA branch. It terminates by ramifying numerous branches that supply structures deep in the face and nose, within the pterygopalatine fossa. The middle meningeal artery that arises from the proximal portion of the internal maxillary artery is the largest branch. It enters the skull via the foramen spinosum by curving at a right angle and supplying the dura of the frontal, temporal squamous, parietal area and near the sigmoid and transverse sinuses. The accessory meningeal artery is a small but important branch that arises from the middle meningeal artery. It passes through the foramen ovale or sphenoid emissary foramen to enter the cranial space. It mainly supplies the extracranial structures and additionally the trigeminal ganglion, cavernous sinus, and adjacent dura near the foramen ovale. It anastomoses with the inferolateral trunk of the ICA. The sphenopalatine artery passes through the foramen spinosum to supply the nose. It is mainly associated with posterior epistaxis. The distal branches of the internal maxillary artery including the artery of the foramen rotundum, the vidian artery, and the palatovaginal arteries have numerous anastomoses with other ECA branches and the ICA and its branches.

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Part II

Clinical Science: Large Artery Atherothrombosis

Concept of Large Artery and Small Vessel

3

Seung-Hoon Lee

Abstract

In the TOAST classification of ischemic strokes, large-artery atherosclerosis and small-vessel occlusion are major subtypes. However, the meaning of "large artery" and "small vessel" is unclear. Histologically, the arterial system of the human body comprises of elastic and muscular arteries, arterioles, and capillaries. Among them, muscular arteries are distributed to each organ in the body and are present in the subarachnoid space of the brain. Arterioles usually have a diameter of 10–100 μm and are mostly located in the brain. "Large arteries" and "small vessels" under the TOAST classification system are not found in the histological classification of arteries. This discrepancy causes a major hurdle in the understanding of stroke pathophysiology. In this chapter, we will thoroughly explore the different concepts of large arteries and small vessels and provide a basis to understand the stroke pathophysiology.

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The TOAST classification system of ischemic strokes is based on its pathophysiology and includes some unique subtypes, such as large-artery atherosclerosis and small-vessel occlusion, that are uncommon in other classifications [1]. It is important to understand the meaning of "large artery" and "small vessel." Histologically, the arterial system of the human body comprises of elastic and muscular arteries, arterioles, and capillaries, determined by their size and proximity from the heart and does not include large arteries or small vessels, the strokes of which are the main subtypes in the TOAST system. Therefore, early career physicians and physicians-in-training of neurology intuitively assume that "large arteries" mean aorta and muscular arteries, while "small vessels" mean arterioles and capillaries. Such intuitive assumptions may not be correct, and because these words are key to the proper understanding of stroke pathophysiology, they must be clearly defined. Nevertheless, most textbooks and articles on stroke pathophysiology have not provided any obvious explanation of the terms.

The paper by Adams Jr. et al., Stroke 1993 on TOAST classification described large-artery atherosclerosis as "clinical and brain imaging findings of either significant (>50%) stenosis or occlusion of a major brain artery or branch cortical artery" [1]. In their description, large arteries referred to the major brain arteries and branches to the brain cortex, and their histolog-

S.-H. Lee (ed.), *Stroke Revisited: Pathophysiology of Stroke*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1430-7_3

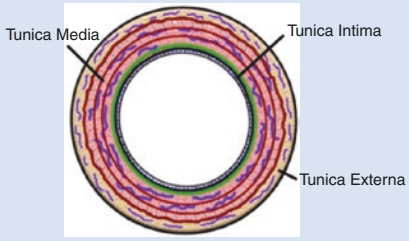
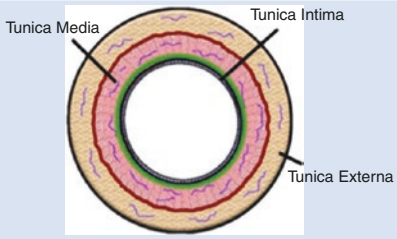
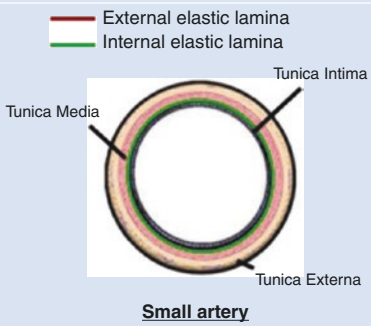
ical categories were not mentioned. Moreover, they described the strokes caused by small-vessel occlusion as "strokes are often labeled as lacunar infarcts in other classifications," without explaining the concept of small vessels. The global confusion on large arteries and small vessels must have begun here. To understand the pathophysiology of ischemic strokes, we must know the vessels involved and the pathological conditions they are involved in. In this chapter, we will thoroughly explore the different concepts of large arteries and small vessels and provide a basis to understand the stroke pathophysiology.

3.1 Histological Classification of Arteries

Table 3.1 describes the histological classification of the arterial system. The arteries from the heart to the individual organs are generally categorized as elastic and muscular arteries and arterioles [3, 4].

The elastic arteries are the aorta and pulmonary arteries, which begin directly from the heart. They are the largest in diameter among all arteries in the body. However, the vessel walls are relatively thin. They are abundant in elastin, and the elasticity is necessary to take blood from the

Table 3.1 The histological classification of the arterial system

Subtype	Details		
	Intima	Media	Adventitia
Elastic artery (conducting artery)			
 **Elastic artery**	A single layer of endothelial cells is supported by elastin-rich collagen IEL is not distinct	It consists of abundant concentrating layers of elastic laminae EEL is not distinct	It contains elastic and collagen fiber, vasa vasorum, and nervi vascularis
Muscular artery (distributing artery)			
 **Muscular artery**	It is relatively thin with well demarcated IEL It is made up of an endothelium	It is consisted mainly by smooth muscle fibers It is separated from tunica adventitia by prominent EEL	It consists of elastic and collagen fibers There is few fibroblasts, vasa vasorum and nervi vascularis
Arteriole (local regulating artery)			
 **Small artery**	It is very thin and consists of only a single layer of endothelium	It consists of one to six layers of smooth muscle cell There is no EEL	It is about the same size as tunica media

IEL internal elastic laminar, *EEL* external elastic laminar. Adapted from EC cardiology [2]

heart and deliver it. The tunica intima is composed of a single layer of endothelial cells and is supported by elastin-rich collagen. The tunica media is thick and has concentric sheets of elastin, but the smooth muscle cells are few. The tunica adventitia has a vasa vasorum for its own blood supply. The internal and external elastic lamina (IEL and EEL) are not found in elastic arteries.

The muscular arteries are the blood vessels distributed in the individual organs of our body, which course through the subarachnoid space in the brain. The tunica media contains many smooth muscle cells that can shrink and relax while supplying blood to the organs, and the elastin component is less. The tunica intima is composed of a single layer of endothelial cells, while the tunica adventitia is thick and composed mainly of collagen and elastin. Muscular arteries characteristically have distinct IEL and EEL.

Arterioles usually have a diameter of 10–100 μm and almost always course through the brain tissue. The three layers of tunica intima, media, and adventitia are intact but are much thinner compared to muscular arteries. The tunica media consists of 1–6 layers of smooth muscle cells, and the tunica adventitia has almost the same thickness as tunica media. The IEL is intact, but there is no EEL.

In the histological classification of the arterial system, large arteries and small vessels are not present. In addition, it is unclear why one of the terms has "arteries" and the other "vessels." It might have been an attempt to include venous diseases, but that is unlikely. It can be concluded that the concept of large arteries and small vessels in the arterial classification are clinical, and not histological.

3.2 Differentiation of Large Arteries and Small Vessels

Dr. Leonardo Pantoni et al. published an interesting research in 2006 [5]. Considering that small vessels have been defined poorly for clinical neurologists, they conducted a survey on the definition of a small vessel among principal investigators responsible for the top neuropathological centers around the world. The answers for the definition of small vessels had the agreement of less than 50%. This result is surprising because the respondents to this survey were prominent experts in the field of neuropathology. Their answers diversely ranged from the diameter of less than 50 μm to less than 500 μm and to only arterioles, etc. In view of the situation of no material agreement on the definition of large arteries and small vessels, we have clinically dealt with the diseases of those vessels.

Small vessels do not generally course through the subarachnoid space. As mentioned above, vessels present in the subarachnoid space are muscular arteries histologically [6]. Hence, it is reasonable to regard muscular arteries coursing through the subarachnoid space as large arteries. Moreover, these large arteries penetrate the brain parenchyma in a perpendicular fashion [7, 8]. They are also called as deep perforating arteries, which are the previously defined large arteries. Deep perforating arteries representatively include (1) posterior circulation: perforators to thalamus and brain stem arising from the posterior cerebral artery and the basilar artery, and (2) anterior circulation: lenticulostriate arteries to basal ganglia arising from the middle cerebral artery [9]. The lenticulostriate arteries have a diameter of 300–700 μm at the branching site on the middle cerebral artery, but the other perforators have a smaller diameter [9, 10]. After branching into the deep perforating arteries, the large arteries course through the subarachnoid space in the brain, and finally, penetrate the cerebral cortex [8]. These vessels are called superficial perforating arteries, which are the previously defined small vessels.

Large arteries coursing through the brain undergo progressive narrowing of the internal diameter with decreasing blood pressure, so the superficial perforating arteries have lower blood pressures and smaller diameters than the deep perforating arteries [11]. Small vessels do not have a vascular network with the adjacent small vessels without a collateral circulation [12]. Thus, regardless of the cause, if one small vessel is obstructed, lacunar infarction can occur because of no alternative blood supply.

The histological category of the clinical small vessels must also be determined. As the vascular microangiopathy of small vessels damaged by long-standing hypertension is called "arteriolosclerosis," there have been prejudices that the small vessels are arterioles [13]. However, as mentioned above, because the internal diameters of arterioles are 10–100 μm and of deep perforating and leptomeningeal arteries are approximately 50–800 μm, the small vessels are larger than arterioles. We can conclude that small vessels are histologically (1) "small" muscular arteries and (2) "large-sized" arterioles. As shown in Fig. 3.1, small vessels do not histologically belong to a single category and range from small-size arteries to large-size arterioles [14, 15]. Therefore, they are called "small vessels" rather than "small arteries," and it should be noted that the venous system is not included in the category of small vessels. From large arteries to small vessels, the lumen diameter dramatically reduces, but the blood pressure is almost constant as shown in Table 3.2 and Fig. 3.2 [11]. Hence, small vessels are the most vulnerable to long-standing hypertension. Chronic or long-standing hypertension leads to hypertensive microangiopathy (arteriolosclerosis), which ultimately causes lacunar infarction or intracerebral hemorrhage [14, 15]. Moreover, small vessels do not include capillaries. Disorders of the capillary circulation in the brain are generally not associated with strokes because the proportion of blood flow through the capillaries is too small to cause ischemia or hemorrhage. Chapter 6 describes cerebral microangiopathy in detail.

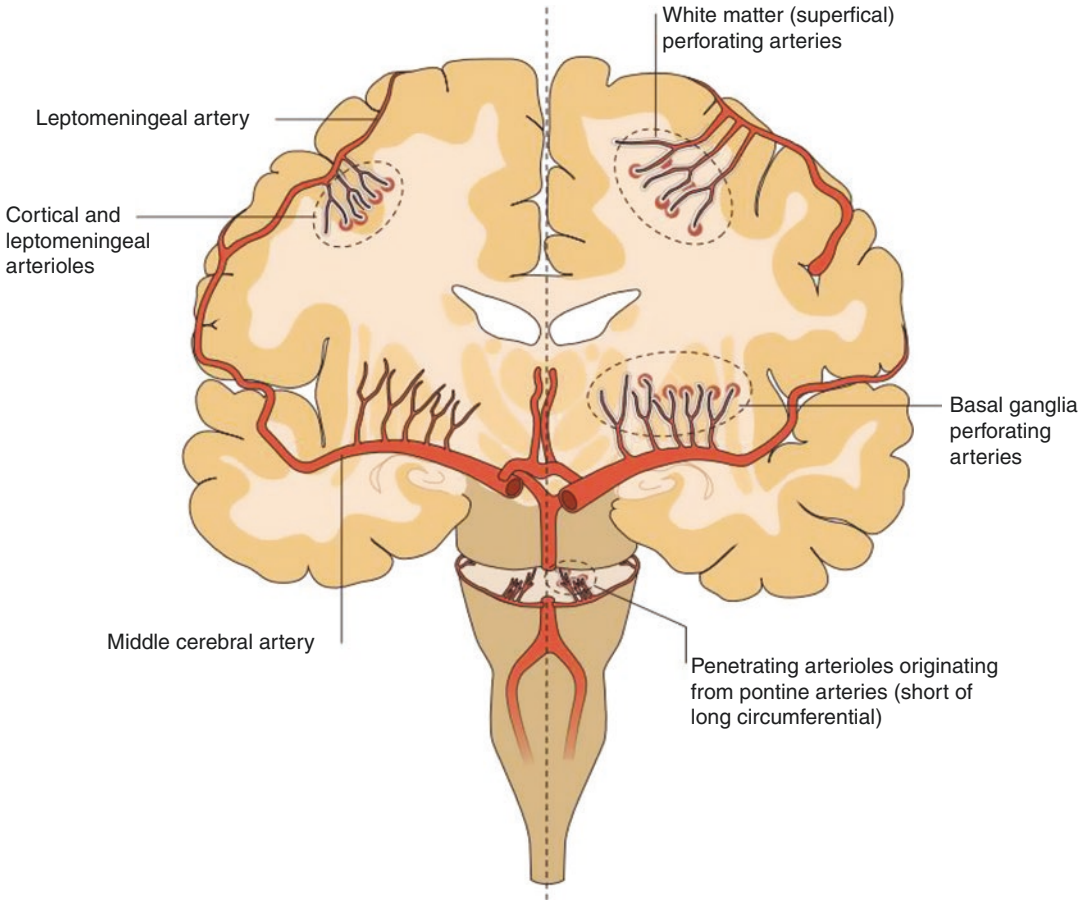


Fig. 3.1 Anatomical location of small vessel diseases. The red spots in the brain parenchyme is frequent regions of small vessel disease. Adapted with permission from Nature Reviews Neurology, Copyright Springer Nature [14]

Table 3.2 Diameter and arterial pressure at several cerebral arterial locations

Subtype	Diameter (mm)	SBP (mmHg)	DBP (mmHg)
Internal carotid	4.84	117	77
Basilar	3.45	113	73
Poserior cerebral	1.63	111	71
Distal medial striate	0.55	110	70
Prefrontal	0.96	95	61
Temporal branch of MCA	0.92	98	62
Lenticulostriate	0.58	113	73
Arterioles of lenticulostriate bed	0.19	102	65
Posterior parietal branch of MCA	1.04	85	54
Arterioles of posterior parietal bed	0.19	66	42

SBP systolic blood pressure, *DBP* diastolic blood pressure, *MCA* middle cerebral artery. Adapted with permission from Stroke & Vascular Neurology, Copyright BMJ Publishing Group Ltd. [11]

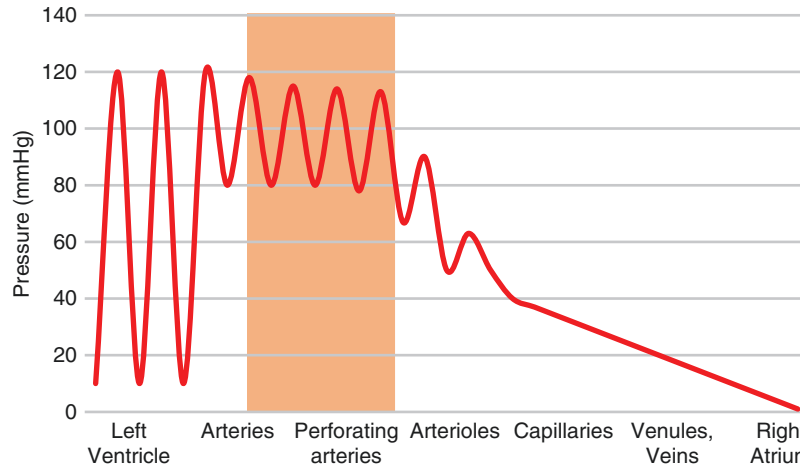


Fig. 3.2 Blood pressure in various blood vessels. The highlighting area shows blood pressure throughout the perforating arteries

3.3 Conclusions

The terms "large arteries" and "small vessels," used in the clinical classification of ischemic strokes, have caused confusion among physicians in neurology. This is because they have not been covered in basic medical contexts, such as anatomy and histology. Large arteries refer to the extracranial cerebral arteries (carotid and vertebral arteries) and intracranial muscular arteries coursing through the subarachnoid space, while small vessels refer to the deep perforating arteries and superficial perforating arteries that penetrate the brain tissue. Histologically, small vessels are the small-size muscular arteries and large-size arterioles and are most vulnerable to high blood pressure. Long-standing hypertension may result in cerebral microangiopathy (arteriolosclerosis), ultimately leading to lacunar infarction or intracerebral hemorrhage. The descriptions of large arteries and small vessels would aid in understanding stroke pathophysiology.

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Pathophysiology of Large-Artery Atherosclerosis

4

Seung-Hoon Lee

Abstract

Large-artery atherosclerosis (LAA) is one of the major three causes of ischemic stroke, together with cardioembolism and small-vessel occlusion, accounting for approximately 20–30% of all cases, albeit by race and ethnicity. Pathophysiology of coronary atherosclerosis responsible for acute coronary syndrome is well established, and recent development of knowledge about atherosclerosis is mostly from studies on coronary diseases. Researches on cerebral atherosclerosis causing stroke has not been enough to fully elaborate its pathophysiology, but there are a lot of similarities and differences as compared to the pathophysiology of coronary atherosclerosis. In this chapter, I will describe mechanisms of LAA-related stroke in detail.

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4.1 Atherosclerosis: A General Concept

4.1.1 Formation of Atherosclerosis

Atherosclerosis is a chronic inflammatory disease in which an initial endothelial damage leads to deposition and denaturation of lipids in the vessel walls for several years, as shown in Fig. 4.1. The vascular endothelial cell dysfunction can be caused by various vascular risk factors, such as hypertension, diabetes, and smoking, resulting in increased permeability among the endothelial cells and invasion of monocytes, which plays a crucial role in the development of early-stage atherosclerosis. Meanwhile, low-density lipoprotein (LDL) cholesterols penetrate to the vascular walls and lodge in the internal extracellular matrix. If the risk factors are not properly corrected, LDL cholesterol particles continue to be accumulated due to sustained vascular stresses and begin to form a lipid mass inside the vessel walls. Then, the LDL cholesterols are transformed by modification such as oxidization, which is a very strong pro-inflammatory material, causing a further exacerbation of inflammation during the process of atherosclerosis.

The monocytes that penetrate into the subendothelial areas are subsequently differentiated into the macrophages by the macrophage colony-stimulating factor. The macrophages show two distinct subtypes that are markedly differentiated

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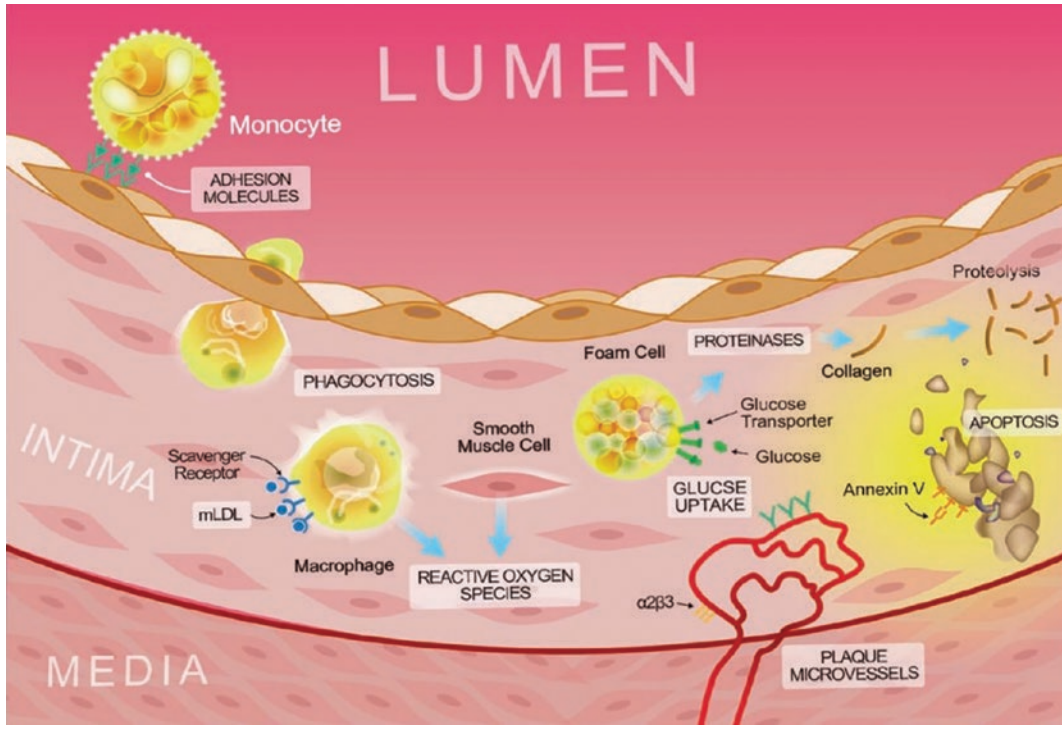

Fig. 4.1 Progression of atherosclerosis. LDL: low-density lipoprotein

by polarization in stages of atherosclerosis, M1 and M2 (Fig. 4.2): M1 macrophages generally have a pro-inflammatory function, but in contrast, M2 macrophages have an anti-inflammatory function [1]. In the early stage of atherosclerosis, macrophages are differentiated to M1, and by presenting surface pattern recognition receptors that recognize modified LDL, they are subsequently transformed into foam cells through uptake of lipids. The foam cells further aggravate inflammatory status by releasing pro-inflammatory cytokines and growth factors. In the meantime, the vascular smooth muscle cells (VSMCs) move from the media to the intima, producing extracellular matrix material that is important for the formation of fibrous caps. The foam cells may be removed in the form of apoptosis by M2 macrophages, which is called efferocytosis. If this process is active enough, overall inflammation process can be reduced. However, when the inflammation process is more severe than M2-related efferocytosis, the M2 macrophages ingest apoptotic cells too excessively, stress to the endoplasmic reticulum inside the M2 macrophages are increased, resulting in dysfunction of efferocytosis. Then, inflammatory factors, coagulation factors, and matrix metalloproteinases (MMPs) are released, which induce a structural instability of atheromatous plaques and ultimately, a rupture of the plaques. After the ruptures, von Willebrand factors (vWFs) and collagen from the lesions stimulate the platelets in the blood, which form a thrombus by adhesion and aggregation of the platelets, causing a thromboembolism to organs of the body such as brain. The plaque instability or vulnerability increases with fewer VSMCs and more undifferentiated new blood vessels (angiogenesis) in the necrotic plaque cores.

4.1.2 Classification of Atherosclerosis

Atherosclerosis has various morphological features, depending on the location of blood vessels, the degree of exposure to risk factors, and

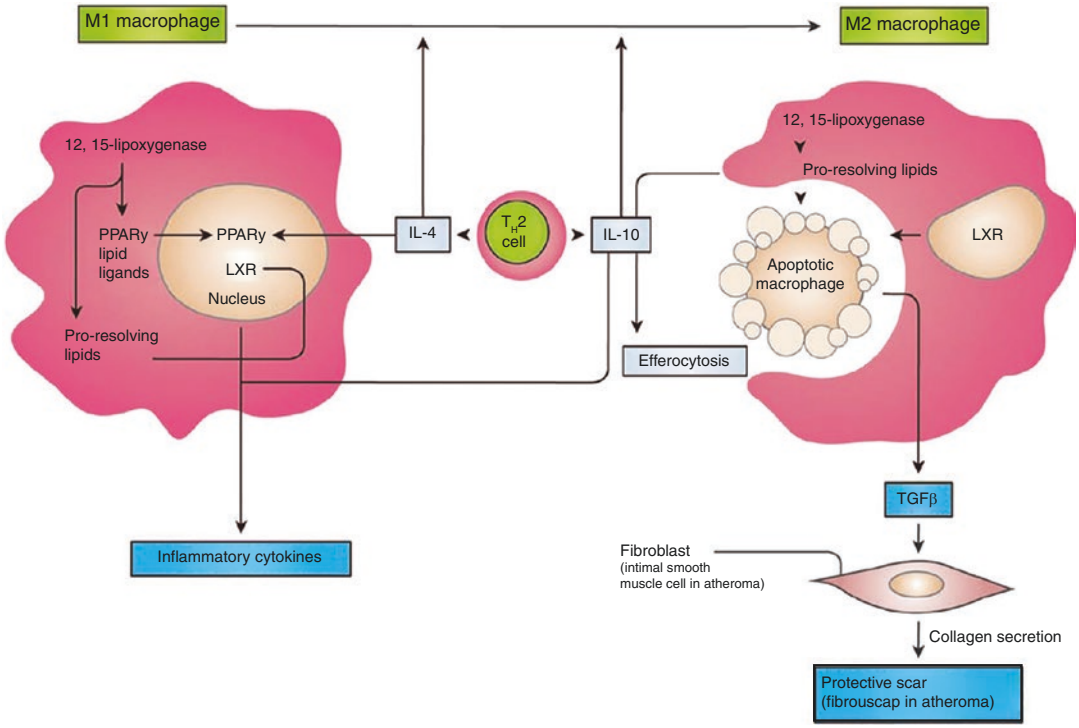

Fig. 4.2 The M1 and M2 subtypes of macrophage with differential functions according to atherosclerotic stage

the process stages. Therefore, classification of the lesions is indispensable to understand its pathophysiology. In 1958, WHO first classified arteriosclerosis into four categories: fatty streak, atheroma, fibrous plaque, and complicated lesion [2]. In the mid-1990s, the American Heart Association (AHA) recommended new classification criteria for atherosclerotic plaques, which was established after some minor modifications (Table 4.1, Fig. 4.3) [3–5]. However, there might be a caveat: this is a pathophysiological classification for the coronary arteries, and it is not clear whether it can be applied to all arteries in our bodies, including cerebral arteries. Because the nature of atherosclerosis is not considered to be significantly different between the cerebral arteries and coronary ones, application of this classification for understanding of stroke mechanism would be plausible. As described in this classification, atherosclerotic plaque lesions responsible for the thrombosis are plaque ruptures, an erosion of the plaque, and a calcified nodule (Figs. 4.4 and 4.5), and I will explain the thrombosis mechanisms from these lesions in this chapter [6].

4.1.2.1 Plaque Rupture

Plaque rupture is observed in the form of a rupture of the necrotic core and the fibrous cap, which are usually infiltrated with macrophages and T cells [3]. The extracellular matrix of the fibrous cap is mostly composed of collagen type I, biglycan and decorin, and VSMC is rarely found. Thrombus found on the ruptured lesion is mostly composed of platelets—so we called it as white thrombus by its color, which turns red-colored thrombus in the form of red blood cells embedded in fibrin layers (lines of Zahn) distal to the center of the thrombus. This is the evidence that platelets are activated early due to rupture of the plaque, and that clotting factors are activated subsequently after stagnation of blood. Rupture of the fibrous cap occurs in the shoulder area of the plaque, which is generally considered the weakest part of the plaque. Secretion of proteolytic enzymes from macrophages and the shear

Table 4.1 The AHA classification of atherosclerotic lesions

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

An updated version of the modified AHA classification published in 2016, which was based on the original AHA classification published in the mid-1990s. *AHA* American Heart Association

stress and tension on the plaque may act as a basal mechanism for the rupture. In addition, dying macrophages or VSMC-derived microcalcifications (>5 μm) inside the fibrous caps may induce detachment from plaques under blood pressure, resulting in rupture of the plaques.

4.1.2.2 Plaque Erosion

Plaque erosion refers to atherosclerotic lesions that can cause blood clots without rupture, exposing the VSMCs and the proteoglycan matrix with a slight peeling of the endothelial lining. These lesions usually occur during the intimal thickening or early- or late-stage fibroatheroma, and they are less inflammatory than the ruptured plaques. The plaque rupture causes positive remodeling, whereas the plaque erosion causes negative remodeling. Usually, large calcifications are rarely observed in the plaque erosion, and only microcalcifications are observed at about 40% [7]. The tissue at the thrombosis-occurring site of the plaque erosion was identified as activated VSMCs embedded to a proteoglycan-rich substrate composed mainly of collagen type III, hyaluronan, and versican. This is in contrast to the fibrous caps mainly composed of collagen type I in the ruptured or stable plaques. Plaque erosion may cause more microembolization to

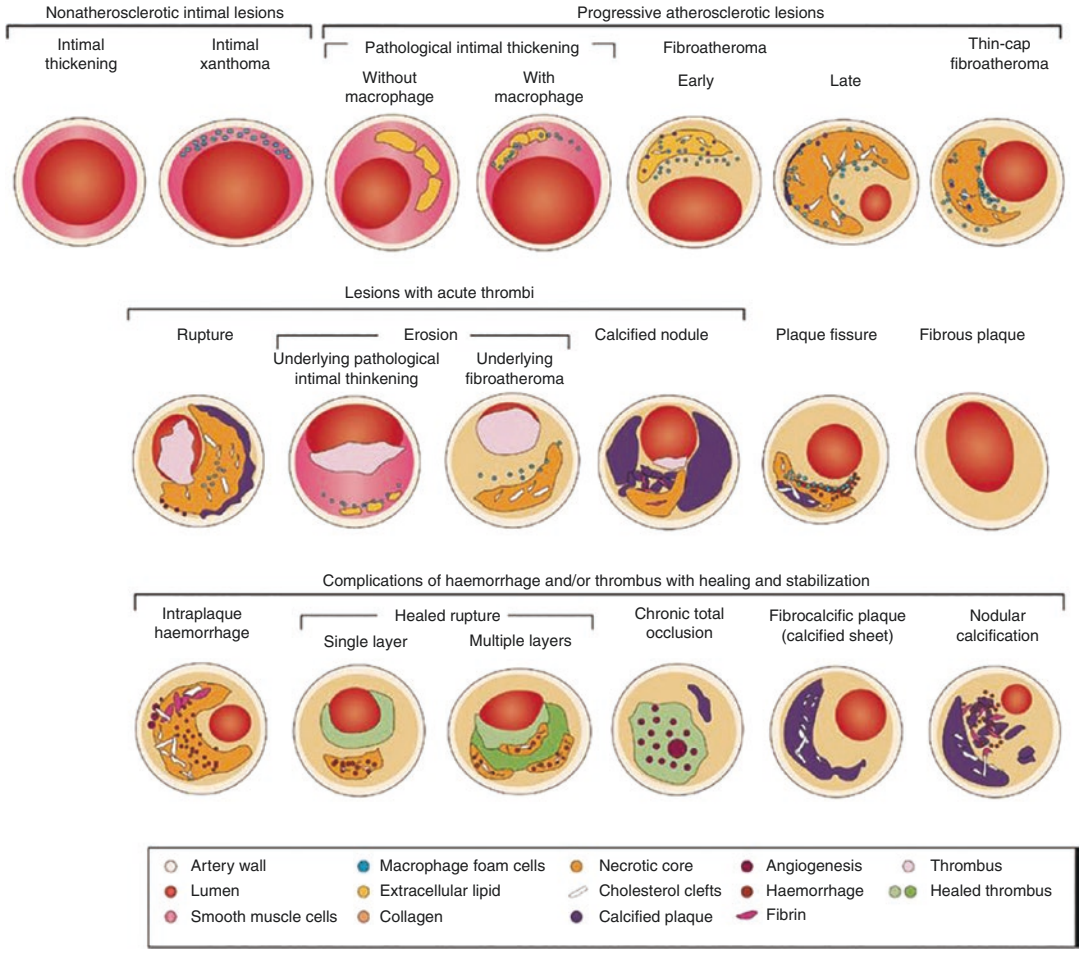

Fig. 4.3 Schematic figures showing composition and morphology of atherosclerotic lesion according to the classification suggested by the American Heart Association

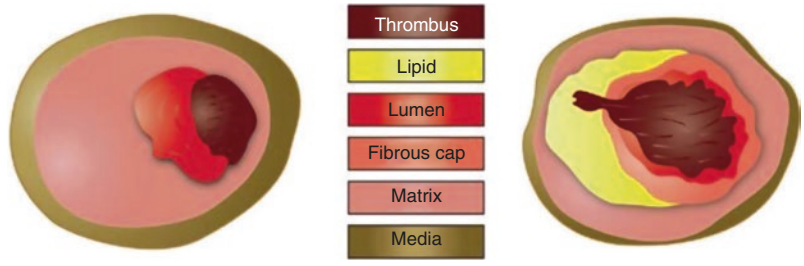

Fig. 4.4 The characteristics of plaque erosion and plaque rupture

Plaque erosion

Lipid poor
Proteoglycan and glycosaminoglycan rich
Non-fibrillar collagen breakdown
Few inflammatory cells
Endothelial cell apoptosis
Secondary neutrophil involvement
Female predominance
High triglycerides

Plaque rupture

Lipid rich
Collagen poor, thin fibrous cap
Interstitial collagen breakdown
Abundant inflammation
Smooth muscle cell apoptosis
Macrophage predominance
Male predominance
High LDL

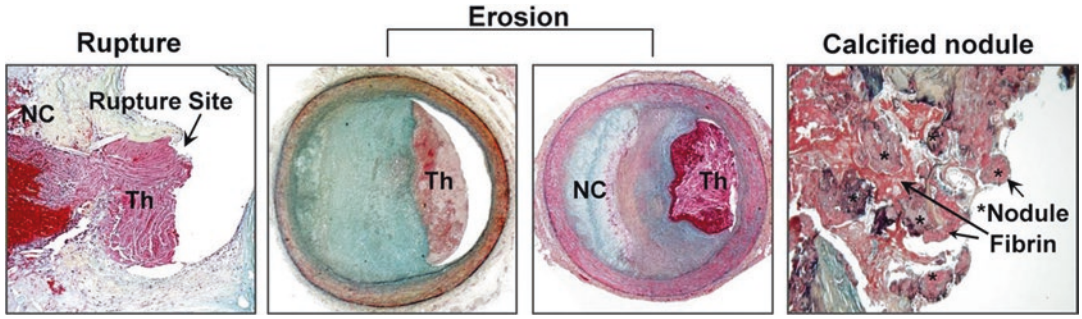

Fig. 4.5 Pathology of the coronary plaques of three different morphologies (rupture, erosion, and calcified nodule). Ruptured plaques have thin fibrous cap which is critical site of rupture. In case of rupture, the luminal thrombus (Th) has communication with the lipid-rich necrotic core (NC). Surface erosions usually occur in area lacking surface endothelium. In rare cases of erosion with necrotic core, the necrotic core does not communicate with the luminal thrombus. Calcified nodules are fibrocalcific plaques protruding into lumen with disruption. Adapted with permission from Heart, Lung and Circulation, Copyright Elsevier [6].

the distal regions than that the plaque ruptures (artery-to-artery embolism). It was reported that tobacco smoking rather than blood lipid levels are correlated with the incidence of plaque erosion, but it needs to be more verified [7].

4.1.2.3 Calcified Nodule

Among thrombosis-related atherosclerotic lesions, calcified nodules are the least common form: only 5% of thrombosis in coronary arteries are caused by these lesions—even so with advanced calcifications [8]. Because cerebral arteries show lower incidence of arterial calcification than coronary arteries, the attributable fraction of calcified nodules for cerebral infarction is likely to be much lower. The mechanism by which thrombosis develops on the calcified nodules is uncertain, and it was hypothesized as follows: when calcified tissue membranes break down due to blood pressure, fibrin accumulates around the destroyed lesions, and eventually erupt up to the luminal surface [9]. Fibrin is relatively common even in non-erupted calcified nodules but not communicated to the lumen, which may come from the surrounding damaged capillaries. Eruptive calcified nodules are common in asymmetrically shaped lesions, and these eruptions may stimulate platelet activation. Calcified nodules are more observed in older people. These lesions should not be confused with the nodular calcification: the nodular calcification can destroy the structure of the media, but not invade to the adventitia, and is not associated with thrombosis.

4.2 Large Artery Atherosclerosis: Intracranial Versus Extracranial

LAA causing ischemic stroke can be divided into two types: atherosclerosis in intracranial arteries and those in extracranial arteries. Intracranial arteries mean all cerebral large arteries in the intracranial space, and extracranial arteries mean large arteries in the extracranial area, but relevant to ischemic stroke: parts of aorta (ascending and arch), common carotid artery, internal carotid artery, and vertebral artery. Internal carotid artery and vertebral artery run through both extracranial and intracranial space, so these arteries belong to both categories according to their locations. Extracranial artery and intracranial artery not only differ in embryological origin but also in histologic findings. Due to their structural differences, clinical features of atherosclerosis and thromboembolism is a little different from those of coronary artery. This will be explained in detail below.

4.2.1 Epidemiology of Intracranial Atherosclerosis

First, we need to look at the burden of intracranial atherosclerosis in the general population. A European population study indicated that by age 65, 80–97% had pathological evidence of intracranial atherosclerosis [10]. In addition, according to the Rotterdam Scan Study, calcification of intracranial internal carotid arteries confirmed by CT scan was found in 82% [11]. A clinicoradiologic study in patients with ischemic stroke, 45–62% of patients were identified to have intracranial plaques or stenoses [12]. The prevalence of symptomatic intracranial stenosis has been reported to be 20–53%, depending on the subjects, methods, and races [13]. In particular, intracranial atherosclerosis is much more prevalent in Asian (Korea, Japan, China and etc.) and African-American individuals than in Caucasian whites [14]. According to the Northern Manhattan Study, intracranial atherosclerosis was found only in 9% for white individuals as compared with 17% for African-American, and 15% for Hispanic [15]. East Asia studies have shown that the prevalence is up to 30–40% [16, 17].

4.2.2 Histologic Comparisons of Normal Arteries

Extracranial arteries belong to elastic arteries, because elastin is profuse in tunica media. In contrast, intracranial arteries are classified as muscular arteries, because they have little elastic fibers [18]. In terms of internal carotid arteries, a transition from elastic artery to muscular artery occurs in carotid bifurcation due to differences in embryological development. Compared to extracranial arteries, intracranial arteries are characterized by a thin tunica media and adventitia, no external elastic lamina, but an intense internal elastic lamina. External elastic lamina exists to the petrous portion of the internal carotid artery but disappears at the cavernous portion, which may be associated with frequent occurrence of atherosclerotic stenosis at this site.

In extracranial arteries, vasa vasorum plays an important role in the survival of vascular cells, but intracranial arteries do not have vasa vasorum from 1.5 cm after dural penetration: the function of vasa vasorum, delivery of oxygen and nutrients, is replaced by luminal diffusion from the cerebrospinal fluid [18]. Due to the thin media and adventitia, and the absence of external elastic lamina, the intracranial artery can carry out this process. Given that the vasa vasorum may play an important role in atherogenesis, a later onset of intracranial atherosclerosis is likely related to the absence of vasa vasorum.

4.2.3 Pathologic Comparisons of Atherosclerosis

Aging in the intracranial arteries gradually reduces the elastic fibers and muscle components and replaces them with collagen tissue. Initially, intimal thickening, reduplication, and splitting of the thick internal elastic lamina occur, together with fibrosis and hyalinization of the media and adventitia [18]. At this time, there was little lipid in the vessel wall. Intracranial atherosclerosis is predominantly found as fibrous plaques, with less frequent fatty streaks or complicated lesions. Plaque ruptures or calcified nodules, representative complicated atheromatous lesions causing thrombosis, are found at internal carotid arteries, basilar artery, and proximal segments of vertebral arteries, but rarely in old age. In the proximal segment of distal internal carotid arteries or middle cerebral arteries, fibrous plaques rather than calcification and plaque rupture are predominant [19]. However, uncontrolled exposure to risk factors can result in complicated plaques with high-lipid content, intraplaque necrosis or hemorrhage, neovascularization, macrophage and T lymphocyte infiltration, which can lead to thrombosis-related stroke.

The progression of atherosclerosis differs in occurrence timing and rate of intracranial arteries from those of extracranial arteries. Aortic atherogenesis increases linearly, whereas intracranial atherogenesis occurs very late, but dete-

riorates very rapidly in the 1950s and 1960s, and then slowly in the 1970s and 1980s. This is quite contrast to the coronary atherogenesis, which is rapidly deteriorating in the 1930s and relieving from the 1940s to the 1970s [18]. The sites of atherosclerosis development in the intracranial arteries are mainly anterior circulation: internal carotid arteries are the most common, followed by middle cerebral arteries, basilar artery, vertebral arteries, posterior cerebral arteries, and anterior cerebral arteries. In Asian countries, middle cerebral arteries are known to be the most common site, with ICA being the next most frequent.

4.3 Thrombus Formation in Large Artery Atherosclerosis

Thrombus or blood clot is the final product of the coagulation process and consists of two components: (1) a plug agglomerated with platelets and (2) a fibrin-derived meshwork structure to secure the platelet plug firmly. Thrombosis is basically a result of a defense mechanism against bleeding, but when it occurs inside the lumen of blood vessels without bleeding, we generally call it thrombosis. It may occur that a thrombus suddenly obliterates cerebral blood vessels leading to cerebral infarction, but it can be originated from an atherosclerotic lesion or from the heart with dysfunctions such as atrial fibrillation.

In general, the conditions for development of thrombi are firstly illustrated as "Virchow's triad": (1) damage to vascular endothelial cells: trauma or arteriosclerosis, (2) abnormal blood flow: loss of laminar flow due to stagnation of blood flow in veins or turbulence in arteries, and (3) hypercoagulability. The thrombi can be classified into white thrombi, which are mainly composed of aggregated platelets, and red thrombi, which are mainly composed of red blood cells and fibrin, depending on its composition (Fig. 4.6) [20]. Both types of thrombi can result in ischemic stroke, but the type of thrombus may influence the patient's early course, effect on acute treatment, and prognosis and secondary prevention. Therefore, in order to properly diagnose and treat ischemic strokes, it

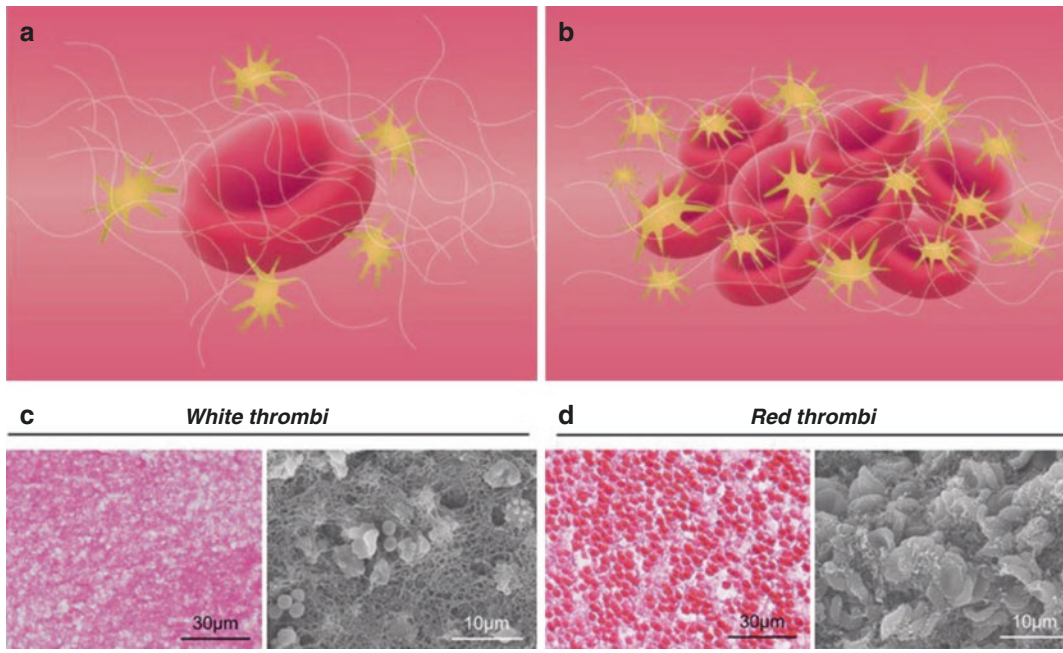

Fig. 4.6 Schematic figures and scanning electron microscopy images of white thrombi (**a**, **c**) and red thrombi (**b**, **d**). Adapted with permission from Stroke, Copyright Wolters Kluwer Health [20].

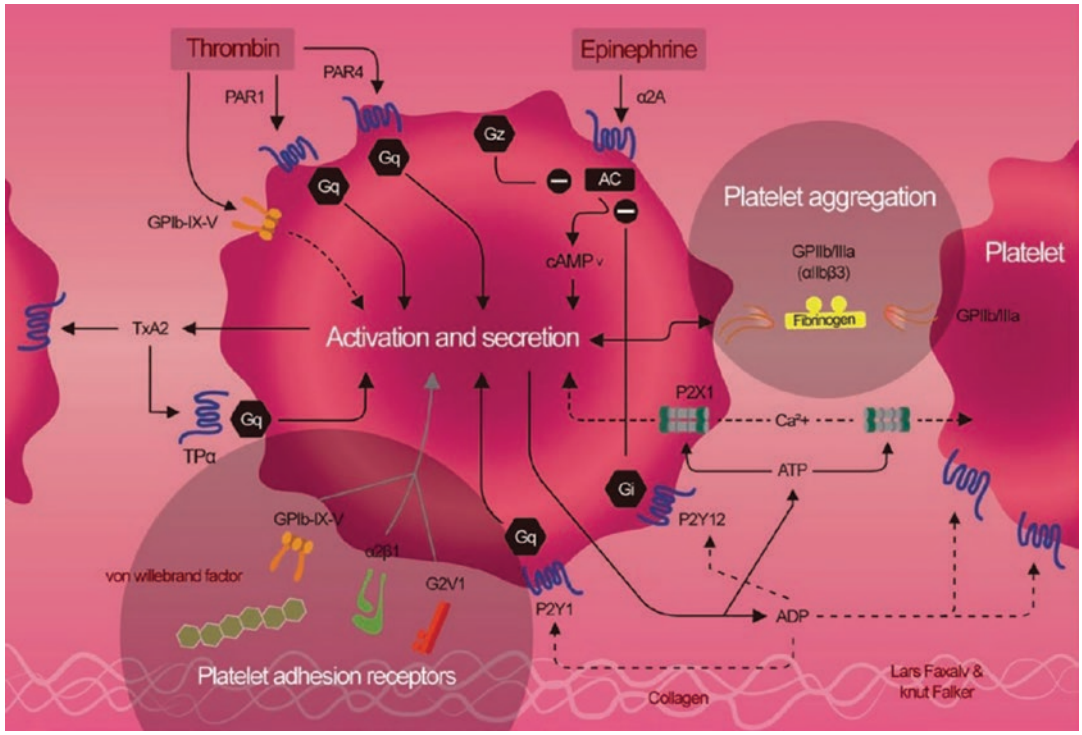

Fig. 4.7 Mechanism of platelet activation

is of note to understand the mechanisms, components, and related factors of thrombus development [21].

4.3.1 The Formation of Platelet Thrombus

Endothelial cells, collagen in subendothelial layer, and tissue factor (TF) are important for the maintenance and homeostasis of the vascular system. In particular, endothelial cells form the inner lining of blood vessels and produce three thromboregulators (nitric oxide, prostacyclin, and ectonucleotidase CD39) that inhibit blood clot formation.

4.3.1.1 Two Independent Pathways for Platelet Activation

There are two well-known substances that cause platelet activation: collagen and TF. When rupture of vessel walls causes bleeding to the surrounding tissue, collagen and TF are exposed to the blood and begin to form blood clots to stop the further bleeding (Fig. 4.7). Collagen promotes platelet aggregation and activation, while TF initiates thrombin formation, leading to further activation of platelets and conversion from fibrinogen to fibrin. The two pathways can be activated predominantly in either situation, with the same result—platelet activation.

Collagen exposed to blood due to vascular damage causes platelets to adhere to the endothelial cells (platelet adhesion) through interactions between collagen and glycoprotein VI of platelets or between vWFs attached to collagen and glycoprotein Ib-V-IX of platelets. Glycoprotein VI acts as the most important promoter for early platelet activation and platelet granule secretion. Platelet activation here is not due to thrombin.

TF activates the TF pathway, the second most important pathway for early platelet activation. Platelet activation here is closely related to thrombin, but not to vascular endothelial rupture, vWFs, and glycoprotein VI. Originally, TF is present as two forms, either in an inactive form on the vessel wall or in an activated form inside the vessel wall. The inactivated TF form is

activated by protein disulfide isomerase, and forms a complex with factor VIIa, which in turn activates factor IX, producing thrombin along the proteolytic pathway. Thrombin activates platelets by breaking down protease-activated receptor 4 (Par 4 in mice, Par 1 in humans) on the platelet surface. As a result, activated platelets secrete adenosine diphosphate (ADP), serotonin and thromboxane A2, which in turn amplify the signal for thrombin formation, activating other platelets.

4.3.1.2 Thrombus Propagation

Platelet integrin αIIbβ3 (also known as glycoprotein IIb/IIIa) is activated and serves to platelet–platelet interaction and to draw platelets into thrombi. Integrin αIIbβ3 requires protein disulfide isomerase to be activated [22]. Platelets adhering to damaged endothelial cells promote structural changes in αIIbβ3, resulting in increased affinity with fibrinogen or vWFs as ligands of αIIbβ3. In addition, activated platelets secrete alpha granules and dense granules, which are critical for the formation of thrombi. Alpha granules contain a variety of proteins for thrombus formation, while dense granules contain ADP and calcium ions. As a result, the secreted ADP attaches to the P2Y1 and P2Y12 receptors on the platelets to further promote platelet activation.

4.3.2 Blood Coagulation

The coagulation pathway in blood plasma consists of the following three pathways that are sequentially activated (Fig. 4.8).

4.3.2.1 Contact Activation Pathway (Intrinsic Pathway)

The contact activation pathway begins with the formation of an initial complex after high-molecular-weight kininogen (HMWK), prekalli-

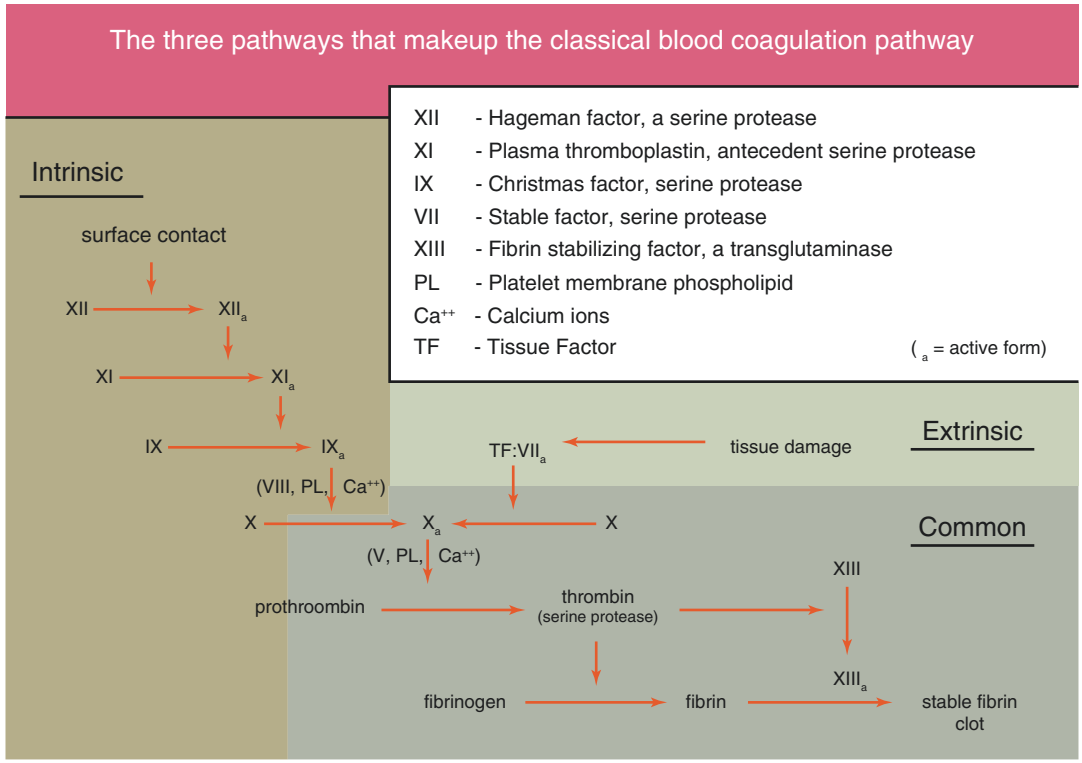

Fig. 4.8 Cascades of clotting factor activation: contact activation pathway, tissue factor pathway, and common pathway

krein, and factor XII (Hageman factor) encounter collagen. As prekallikrein changes to kallikrein, factor XII is activated by XIIa. Factor XIIa converts factor XI to XIa, and in turn, factor XIa converts factor IX to IXa. Factor IXa forms a tenase complex with a cofactor, factor VIIIa, which activates factor X to Xa. The contact activation pathways are very powerful for coagulation in laboratory environments, but are not necessary in vivo for initiation of blood coagulation. Activation of Factor XII is important as the starting point of the contact pathway, whose deficiency is identified by a prolonged partial-thromboplastin time (PTT). However, this does not necessarily mean that patients lacking factor XII have hemorrhagic disease, so the importance of factor XII and XI is to be more clarified.

4.3.2.2 TF Pathway (Extrinsic Pathway)

The most important role of the tissue factor pathway is the "explosive increase in thrombin" by including feedback mechanisms, the most important component of the entire coagulation pathway. TF, as mentioned earlier, is a membrane protein with various roles. TF is consistently expressed in fibroblasts, pericytes in outer layers of vessels, and smooth muscle cells of vascular walls, and part expressed in cells which are not related to blood vessels as well. TF interacts with some nano- or microparticles (<1000 nm) in blood. During the thrombus formation, platelets attach to endothelial walls and become activated, expressing an adhesion molecule called P-selectin. P-selectin binds to microparticles expressing a receptor called P-selectin glycoprotein ligand 1 (PSGL-1), allowing microparticles expressing TF derived from monocytes to be caught to thrombi. As such, TF derived from blood plays an important role in the expansion of fibrin in thrombi.

Because only activated TF is associated with blood clotting activity, it is necessary for the inactivated TF (latent or encrypted form) present in the endothelial cells to become active in order to participate in blood coagulation. Although molecular mechanisms of TF activation have not been clearly identified, it is believed that TF activation needs release of disulfide bonds in the cysteine group of TF protein. This bond is separated by protein disulfide isomerase, which is released from activated endothelial cells or platelets. In other words, protein disulfide isomerase is involved in both fibrin production and platelet activation for thrombus formation.

Of the various coagulation factors, factor VIIa is higher in the amount than other coagulation factors. Factor VII is activated by thrombin, XIa, XII and Xa. When blood vessels are damaged, factor VIIa enters fibroblasts or monocytes containing TF and binds to TF to form complexes. This complex activates factors IX and X. Activation of X by the complex can be inhibited immediately by tissue factor pathway inhibitors (TFPI). Factor Xa and the cofactor factor Va form a prothrombinase complex, which converts prothrombin to thrombin. Thrombin affects various coagulation factors, such as factor V and factor VIII. Activated factor VIIIa, as mentioned above, acts as a cofactor for factor IXa, creating a tenase complex. Collectively, this process amplifies thrombin formation.

4.3.2.3 Common Pathway

Basically, thrombin exists from the initial aggregation of platelets and performs a lot of functions besides simply converting fibrinogen into fibrin, as the most important coagulation factor. Thrombin activates factors VIII and V and also activates protein C under the presence of thrombomodulin. Activated protein C inhibits VIII and V to compromise blood clotting. Thrombin also activates factor XIII to crosslink fibrin monomers into polymers. The common pathway acts to maintain coagulation tendency with sustained activation of factors VIII and IX until suppressed by anticoagulation mechanisms.

4.3.2.4 Cofactors and Modulators

Cofactors include calcium, phospholipids and vitamin K. Calcium and phospholipids as components of platelet cell membranes act as cofactors in the functions of the tenase complex and the prothrombinase complex. Calcium is also reported to play a role in the activation of other coagulation factors. Vitamin K is an essential component of the hepatic gamma-glutamyl carboxylase, which

attaches carboxyl groups to the glutamic acid residues of factors II, VII, IX, X and proteins C, S, and Z. In this process, vitamin K itself is oxidized. An enzyme called Vitamin K epoxide reductase (VKORC) returns vitamin K back to active state. VKORC is a pharmacologically important enzyme because it is a target of warfarin. Warfarin blocks VKORC, causing vitamin K deficiency and preventing clotting factors from being activated.

Modulators include protein C, antithrombin, TFPI, plasmin and prostacyclin (PGI2). First, as a major anticoagulant, protein C is activated by thrombin bound with cell surface protein thrombomodulin. Activated protein C inactivates factor Va and VIIIa along with cofactors S and phospholipids. Decreased levels of protein C or S cause various thrombosis, including ischemic stroke. Antithrombin is a serine protease inhibitor (serpin) that breaks down the serine proteases such as thrombin, factors IXa, Xa, XIa, and XIIa. It is always activated in the body, and the effect is enhanced when heparan sulfate is present or when heparin is injected from the outside. Its quantitative deficiency may also lead to various thrombosis, including ischemic stroke. Second, TFPI limits the action of TF. Third, in the liver, plasmin is produced by the decomposition of plasminogen. This process is catalyzed by tissue plasminogen activator (t-PA), which is synthesized and secreted from vascular endothelial cells. Plasmin decomposes fibrin into fibrin degradation product (FDP), which acts to inhibit the formation of excess fibrin. For the initial treatment of ischemic stroke, the method of injecting recombinant t-PA for thrombolysis has been widely used worldwide. Finally, prostacyclin (PGI2) is secreted from endothelial cells to activate the platelet Gs protein-linked receptor. This in turn activates adenylyl cyclase and increases cyclic adenosine monophosphate (cAMP) synthesis. cAMP lowers intracellular calcium levels, inhibits platelet activation, and inhibits the secretion of granules that induce secondary platelet/coagulant activation.

4.4 Conclusions

In this chapter, I carefully looked into the pathophysiology of LAA, one of the three major causes of ischemic stroke. Atherosclerosis results from chronic inflammatory processes due to innate immunity inside the vascular walls of large arteries, and monocytes and LDL cholesterol play a critical role in the pathogenesis. Atherosclerotic lesions responsible for thrombosis are plaque rupture, plaque erosion, and calcified nodule according to the AHA's morphological classifications: the plaque rupture is the most common lesion for acute coronary syndrome, but in terms of ischemic stroke, the attributable risk need to be clarified. Platelet activation is the main mechanism of LAA-derived thrombi, whose propagation is dependent on the coagulation factor cascades in the plasma [3]. This knowledge of pathophysiology on the LAA-related thrombosis is the key to prevent future stroke or coronary disease in patients with atherosclerosis.

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5 Pathophysiology of Stroke Resulting from Large-Artery Atherothrombosis

Jae Guk Kim and Soo Joo Lee

Abstract

Atherosclerosis is the most common cause of the local disease within the large extracranial and intracranial arteries that supply the brain. Cerebral infarction due to large-artery atherothrombosis primarily caused by rupture of the plaque, thrombus formation, occlusion, and hypoperfusion. The atherosclerotic plaque that is easy to rupture consists of a lipid core, an intra-plaque hemorrhage, and thin fibrous capsule. The atherothrombotic lesion in large extracranial and intracranial arteries cause symptoms by reducing blood flow beyond obstructive lesions, and by serving as the source of intra-arterial emboli. The cerebral infarction varies according to the stability, the location of the plaque, and the degree of the stenotic vessel. Occasionally, the atherosclerotic plaque at the entrance of the penetrating artery gradually becomes larger and may cause occlusion. The atherothrombotic strokes of large artery can be divided into four mechanisms as follows: in situ thrombosis, artery-to-artery embolism, hemodynamic infarct, and branch atheromatous disease. The ischemic strokes can be expressed in two or more complex mechanisms, not actually one.

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5.1 Introduction

Atherosclerosis is the most common cause of in situ arterial disease within the extracranial and intracranial arteries that supply the brain. White platelet-fibrin and red erythrocyte-fibrin thrombi are often superimposed upon the atherosclerotic lesions, or they may develop without severe vascular disease in patients. The atherothrombotic lesions in cervical and cerebral large arteries cause symptoms by reducing blood flow beyond obstructive lesions, and by serving as the source of intra-arterial emboli. At times a combination of mechanisms is working. Severe stenosis can promote the formation of thrombi which can break off and cause embolization, and the reduced blood flow caused by the arterial obstruction makes the circulation less competent at washing out and clearing these emboli [1].

Thrombosis refers to obstruction of a blood vessel due to in situ occlusive process within a blood vessel. The obstruction may occur acutely or gradually. In many cases, underlying pathology such as atherosclerosis may cause narrowing of the diseased vessel [2]. This may lead to restriction of blood flow gradually, or in some cases, platelets may adhere to the atherosclerotic

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plaque forming a clot leading to acute occlusion of the vessel. Identification of the specific localized vascular lesion, including its nature, severity, and localization, is important for treatment because specific therapy may be effective (e.g., surgery, angioplasty, intra-arterial thrombolysis). In most patients, it should be possible clinically to determine whether the local vascular disease is within the carotid or vertebral-basilar circulation and whether the disorder affects large or small penetrating arteries. Delivery of adequate blood due to a blocked or partially blocked artery depends upon many factors, including blood pressure, blood viscosity, and collateral blood flow. Local vascular lesions also may throw emboli off, which can cause transient symptoms. In patients with thrombosis, the neurologic symptoms often fluctuate, remit, or progress in a stuttering pattern. Although the formation of atherothrombotic plaque must be a long and gradual process over many years, the clinical symptoms usually occur acutely and tend to cluster in time. For example, stroke tend to occur sooner after transient ischemic attack rather than later, perhaps as a result of recent breakdown and instability of atherothrombotic plaque [3, 4].

Occlusion secondary to atheromatous plaque occurs by three mechanisms. First, thrombus may occur on atheroma lesions that cause in situ occlusion. Second, embolization of a part of plaque and thrombi may occlude more distal arteries. Third, the origin of small artery may be blocked by the growth of plaque in the parent of artery. In the other situation without occlusion, when atheromatous plaque growth cause severe stenosis of arterial lumen and hypoperfusion of distal brain region, that may lead to hemodynamic (watershed) infarction following severe hypotension or hypoxia. The atherothrombotic stroke of large artery can be summarized in the following four mechanisms: in situ thrombosis, artery-to-artery embolism, hemodynamic infarct, and branch atheromatous disease [1]. The ischemic strokes can be often expressed in two or more complex mechanisms, not actually one (e.g., hemodynamic failure and arterial-artery embolism, or atherosclerosis and arterial-artery embolism).

5.2 Territorial Infarct

Knowledge of the vascular territories is important, because it enables you to recognize infarctions in arterial territories, in watershed regions and also venous infarctions. It also helps you to differentiate infarction from other pathology.

The intracranial circulation can be divided into anterior and posterior circulation, on the basis of internal carotid artery and vertebral artery supply respectively [1]:

- Anterior circulation (carotid artery territory)
  - Anterior choroidal artery
  - Anterior cerebral artery (ACA)
    - Medial lenticulostriatal arteries
  - Middle cerebral artery (MCA)
    - Lateral lenticulostriatal arteries
- Posterior circulation (vertebral artery territory)
  - Posterior cerebral artery (PCA)
  - Basilar artery
  - Superior cerebellar artery (SCA)
  - Anterior inferior cerebellar artery (AICA)
  - Posterior inferior cerebellar artery (PICA)

The presence of acute infarction with stenosis or occlusion of the relevant artery is essential for diagnosis of infarct resulting from large-artery atherothrombosis. Since the original TOAST classification scheme was developed in the early 1990s, advances in stroke evaluation and diagnostic imaging have allowed more frequent identification of potential vascular and cardiac causes of stroke. An evidenced-based modification of the TOAST criteria called SSS-TOAST was developed [5]. The SSS-TOAST system divides each of the original TOAST subtypes into three subcategories as “evident,” “probable,” or “possible” based upon the weight of diagnostic evidence as determined by predefined clinical and imaging criteria. In a further refinement, an automated version of the SSS-TOAST called the Causative Classification System (CCS) was devised to improve its usefulness and accuracy for stroke subtyping [6].

In this classification criteria of cerebral infarction commonly used in clinical practice [6],

atherothrombotic stroke of large artery becomes evident when the following criteria are met; (1) either occlusive, or stenotic (≥50% diameter reduction or <50% diameter reduction with plaque ulceration or thrombosis or plaque with ≤50% diameter reduction that is seated at the site of the origin of the penetrating artery supplying the region of an acute lacunar infarct) vascular disease judged to be due to atherosclerosis in the clinically relevant extracranial or intracranial arteries. (2) The absence of acute infarction in vascular territories other than the stenotic or occluded artery (Table 5.1).

Table 5.1 Causative classification system (CCS) of ischemic stroke etiology: diagnostic criteria of large-artery atherothrombotic stroke

Level of confidence	Criteria
Evident	1. Either occlusive or stenotic (≥50% diameter reduction or <50% diameter reduction with plaque ulceration or thrombosis) vascular disease judged to be caused by atherosclerosis in the clinically relevant extracranial or intracranial arteries, and 2. The absence of acute infarction in vascular territories other than the stenotic or occluded artery.
Probable	1. History of ≥1 transient monocular blindness (TMB), TIA, or stroke from the territory of index artery affected by atherosclerosis within the last month, or 2. Evidence of near-occlusive stenosis or non-chronic complete occlusion judged to be caused by atherosclerosis in the clinically relevant extracranial or intracranial arteries (except for the vertebral arteries), or 3. The presence of ipsilateral and unilateral internal watershed infarctions or multiple, temporally separate, infarctions exclusively within the territory of the affected artery
Possible	1. The presence of an atherosclerotic plaque protruding into the lumen and causing mild stenosis (<50%) in the absence of any detectable plaque ulceration or thrombosis in a clinically relevant extracranial or intracranial artery and history of ≥2 TMB, TIA, or stroke from the territory of index artery affected by atherosclerosis, at least 1 event within the last month, or 2. Evidence for evident large-artery atherosclerosis in the absence of complete diagnostic investigation for other mechanisms

Source: Ay H, Benner T, Arsava EM. A computerized algorithm for etiologic classification of ischemic stroke: the causative classification of stroke system. Stroke 2007; 38:2979 [6]

5.3 In Situ Thrombosis and Artery-to-Artery Embolism

In Situ Thrombosis Atheromatous plaque may promote platelet adhesion, activation, and aggregation, which can stimulate the blood coagulation pathway and produce mural thrombus form an early stage [2]. The atheroma and atherothrombotic plaque gradually grows because of repeated event of mural thrombosis layering one on top of the other, finally the arterial lumen may be occluded. The intraluminal thrombus can then propagate to the proximal portion of artery or distal portion of the artery. But it usually propagates no further than the next branching point of the artery. The balance of pro-thrombotic and anti-thrombotic factors may determine whether a thrombus superimposed on atheromatous plaque or an occlusive embolus grows, lysed or become incorporated into the arterial wall and produce the gradually enlarging atherothrombotic plaque. As with acute myocardial infarction, it is not uncommon to have a severe cerebral infarction due to cervical carotid artery occlusion. The rupture of an unstable atherosclerotic plaque results in a fatal occlusion. However, symptomatic acute in situ atherothrombotic occlusion rather than artery-to-artery embolism does not often appear as a cause for ischemic stroke or transient ischemic attack in the carotid system. For example, internal carotid artery can be better observed than middle cerebral artery (Figs. 5.1, 5.2, and 5.3). This may be because atheroma affects the larger arteries and it take a very large plaque to occlude them or because the collateral blood flow is better distal to larger arteries [7, 8]. In situ thrombotic occlusion is not common in other intracranial arteries. Because intracranial arterial stenosis progresses for a long time and collateral blood

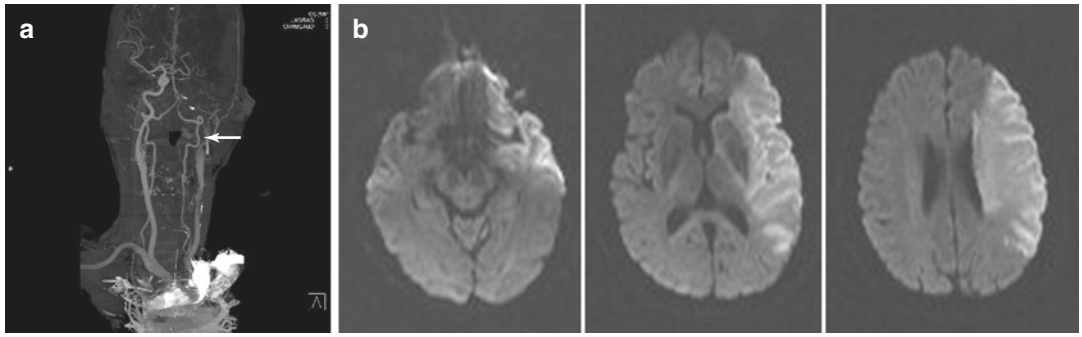

Fig. 5.1 In situ thrombosis, internal carotid artery (ICA). (**a**) Occlusion of left proximal ICA on CT angiography. (**b**) Acute infarct of insular and striatocapsular region, frontotemporal cortex and subcortical white matter area on diffusion-weighted image

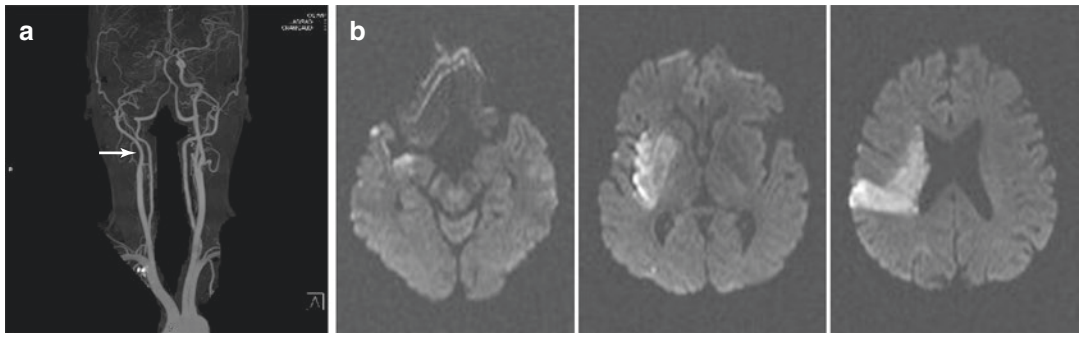

Fig. 5.2 In situ thrombosis, internal carotid artery (ICA). (**a**) Occlusion of right proximal ICA with faintly visible right distal ICA on CT angiography. (**b**) Acute infarct of insular, basal ganglia, and some frontotemporal cortex on diffusion-weighted image

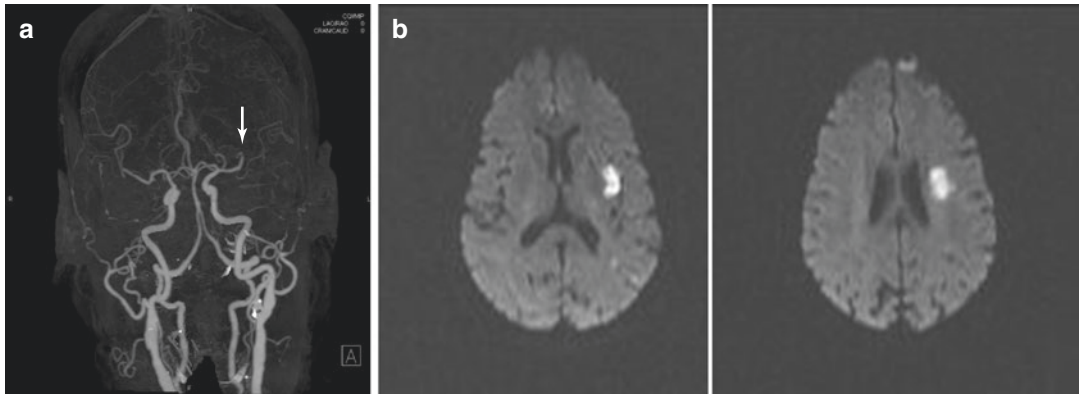

Fig. 5.3 In situ thrombosis, middle cerebral artery (MCA). (**a**) Occlusion of left MCA (M1) on CT angiography. (**b**) Acute infarct of insular and striatocapsular region on diffusion-weighted image

flow is well developed, cerebral infarcts involving whole area of the arterial territory usually occur in the rare. Infarcts usually occur in deep areas such as striatocapsular or border zone area. Symptoms are also mild and may appear as TIA. On the other hand, in situ atherothrombotic occlusion may be more common in the posterior circulation such as basilar artery but even here

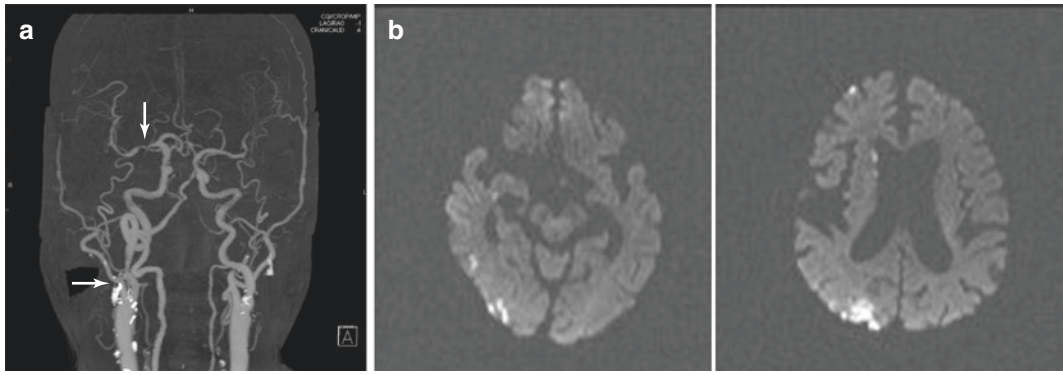

Fig. 5.4 Artery-to-artery embolism. (**a**) Severe stenosis at right ICA and focal stenotic lesion of MCA on CT angiography. (**b**) Acute scattered infarct of right occipitotemporal area and small frontal cortex on diffusion-weighted image

artery-to-artery embolism is also often found. Figures 5.1, 5.2, and 5.3 show cases with in situ thrombosis.

Artery-to-Artery Embolism One of the most common aspects is the ulcer or rupture of the surface of the plaque, resulting in distal embolism, which blocks the blood vessels at the distal end, resulting in cerebral infarction. Atheroma and/or thrombus may become emboli to obstruct a smaller distal artery, usually at a branching point. Emboli consist of platelet–fibrin particles, combined red thrombi, cholesterol crystals, and other debris from plaque, calcified particles, and any combinations. Depending on the size and nature of emboli, the embolus can be lyzed, fragmented, and then swept on into microcirculation. In other case, emboli permanently can block the distal artery and produce antegrade and retrograde thrombosis form platelets. In most cases, severe vascular stenosis is accompanied by perfusion defects, which may be due to the inability of blood clot wash-out if perfusion is impaired. Cerebral infarction due to this mechanism can be suspected as multiple small cerebral cortical infarctions suggesting embolism in diffusion-weighted images and microemboli can be observed by monitoring with transcranial Doppler ultrasound.

Emboli can be delivered to the brain or eye through blood vessels. An embolus from a plaque at the origin of the internal carotid artery normally goes to the eye or anterior two-third cerebral hemisphere. On occasion, it may go to the occipital cortex if blood can flow from the internal carotid artery via posterior communicating artery to the posterior cerebral artery. If the artery is already occluded, then an embolus may travel via the collateral circulation and impact in an unexpected area. The emboli from cervical arteries seldom seem to enter the small perforating arteries of the deep brain to cause lacunar infarct. It may be a consequence of the fact that the perforating arteries arise at 90-degree angle from the parent artery. For example, Fig. 5.4 shows case with artery-to-artery embolism.

5.4 Hemodynamic (Watershed) Infarction

Reduced cerebral blood flow secondary to large atheroma may develop when plaque growth causes severe stenosis of arterial lumen and hypoperfusion of distal brain region. That may lead to border zone infarct following severe hypotension or hypoxia.

The reduction of arterial blood pressure can be systemic or local. In either case, if perfusion pressure falls, cerebral arterioles dilate. When this vasodilatation is maximal, autoregulation stops, and if pressure is further reduced, cerebral blood flow also decreases. In such situation, the boundary or watershed zones between arterial territories become to be oligemic. The distribution of brain

damage caused by profound hypotension is determined by the balance between the vulnerability of regional brain tissues and the degree of collateral blood flow.

The combination of cardiac disease or arterial hypotension of the other causes and severe carotid arterial stenosis are principal risk factors for hemodynamic watershed infarcts [9, 10]. These stenotic lesions are composed of stable fibrous sheets with many fibrous tissues and fewer lipid centers and are predominantly caused by severe stenosis of the extracranial and intracranial carotid arteries and middle cerebral artery. When the vascular stenosis progresses to a level that is almost obstructed, hemodynamic end-diastolic blood flow is reduced (hypoperfusion), and the degree of development of the leptomeningeal collateral determines the extent of the blood flow disturbance. The lesion may become larger due to changes in blood pressure or position such as dehydration or excessive blood pressure drop. In the early diffusion-weighted images, there is a high risk of progression if the perfusion defect appears large in the perfusion-weighted image.

The onset and progression of hemodynamic stroke is characteristic. Unlike embolic stroke that occur suddenly or atherothrombotic and lacuar stroke that often occur in a stuttering pattern of discrete steps, many hemodynamic strokes gradually worsen over hours to days. Some hemodynamic strokes also progress in a stepwise pattern. Syncope at the onset is seen more commonly in hemodynamic stroke than in other types.

Watershed infarctions are of two types as follows: cortical watershed infarct and internal watershed infarction. These infarctions that occur in cortical border zones mostly commonly affect the watershed between those cortical portions perfused by the middle cerebral artery and those portions perfused by anterior cerebral artery or posterior cerebral artery. Internal watershed infarction occurs in the cerebral white matter border zones between medullary arteries in superficial pial arteries and the deep penetrating arteries that are branches of the basal cerebral arteries. Figure 5.5 shows example case with hemodynamic infarct.

5.5 Branch Atheromatous Disease

Small deep brain infarcts are often caused by two different vascular pathologies: (1) atheromatous occlusion at the orifice of large caliber

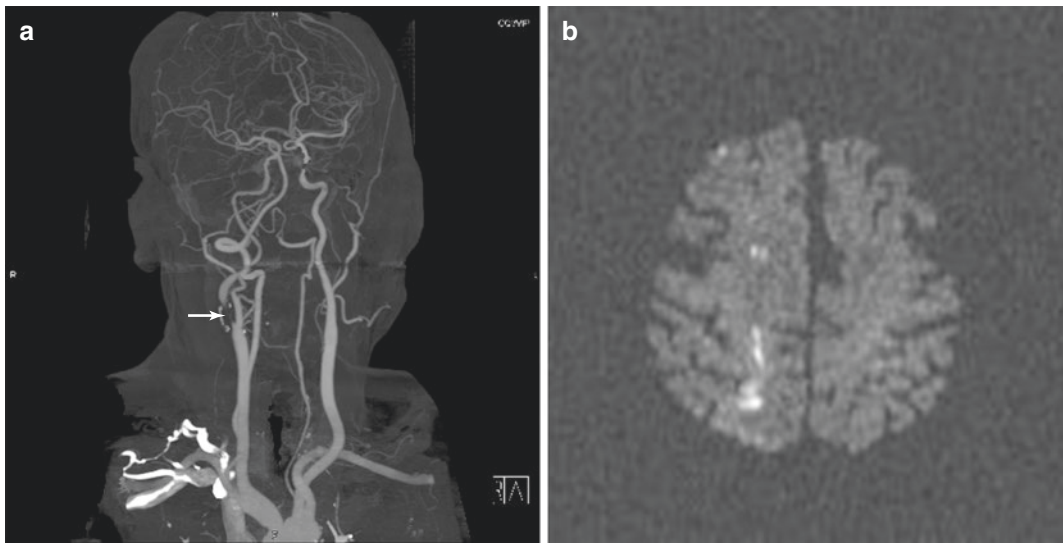

Fig. 5.5 Hemodynamic infarct. (**a**) Severe stenosis at right proximal ICA on CT angiography. (**b**) acute linear infarct of frontoparietal cortex on diffusion-weighted image

penetrating arteries termed branch atheromatous disease and (2) lipohyalinotic degenerative changes termed lipohyalinotic degeneration (lacunar infarct). The type of pathology that causes small deep infarcts involves the large arteries that give rise to penetrating artery branches rather than intrinsic disease of the branches themselves. The orifices of these penetrating arteries branches could be obstructed by atherosclerotic plaque lesions. Caplan described the vascular pathology in these branches, and named the condition intracranial branch atheromatous disease [11]. The location and mechanism of the pathology within the parent arteries are following. The orifices of the penetrating branches can be blocked by atheroma in the parent artery, atheroma can originate in the parent artery and extend into the branch (so-called junctional atheromatous plaques), or microatheroma can arise at the origin of the branch itself. Thrombus may be sometimes superimposed on the atheroma and occasionally a microdissection may develop in the parent artery and spread into the first millimeters of the branch. It is now possible to image intracerebral branch atheromatous disease using high resolution MRI. Plaques in the middle cerebral artery and basilar artery can be shown to impinge upon or occlude penetrating branches by MRI techniques that show axial sections of the origins of branches from the parent arteries. The location within the parent artery is critical in blocking lenticulostriatal, thalamostriatal, and basilar artery branches. Figures 5.6 and 5.7 shows cases with branch atheromatous disease.

The lesion size may be less than 20 mm in diameter (similar to the size of the lacunar infarction) and mild stenosis of less than 30% in the corresponding vessel is found. It is more common in the basilar artery than in the middle cerebral artery. In the case of the middle cerebral artery, more than one ischemic lesion is observed in two or more images of the axial view, and the basal artery is a form in which the ischemic lesion extends to the basal surface. Although early lesions and symptoms may be misinterpreted as lacunar infarction, it is common to see progression of the neurological disorder as the lesion becomes larger than the lacunar infarction due to lipohyalinosis [12].

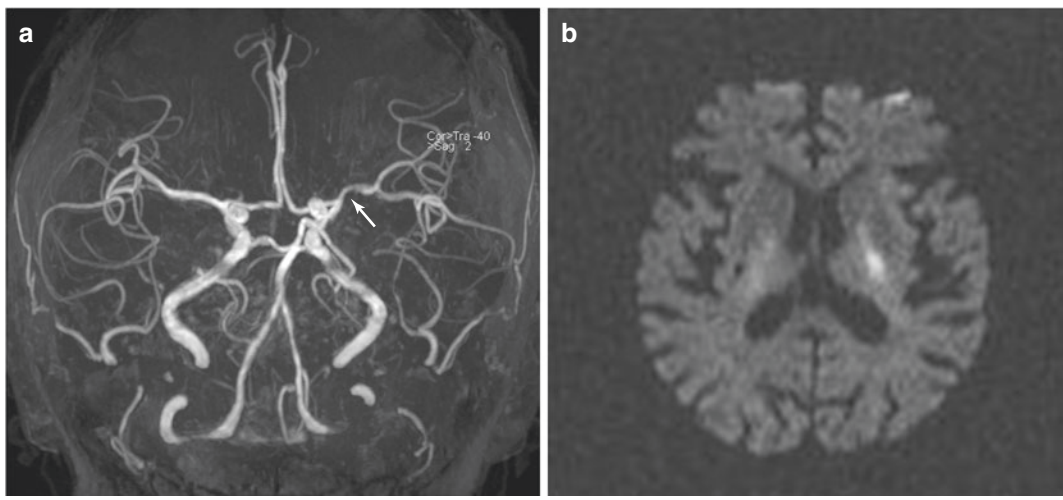

Fig. 5.6 Branch atheromatous disease, middle cerebral artery (MCA). (**a**) Mild focal stenosis at left proximal MCA on MR angiography. (**b**) Small capsular infarct on diffusion-weighted image

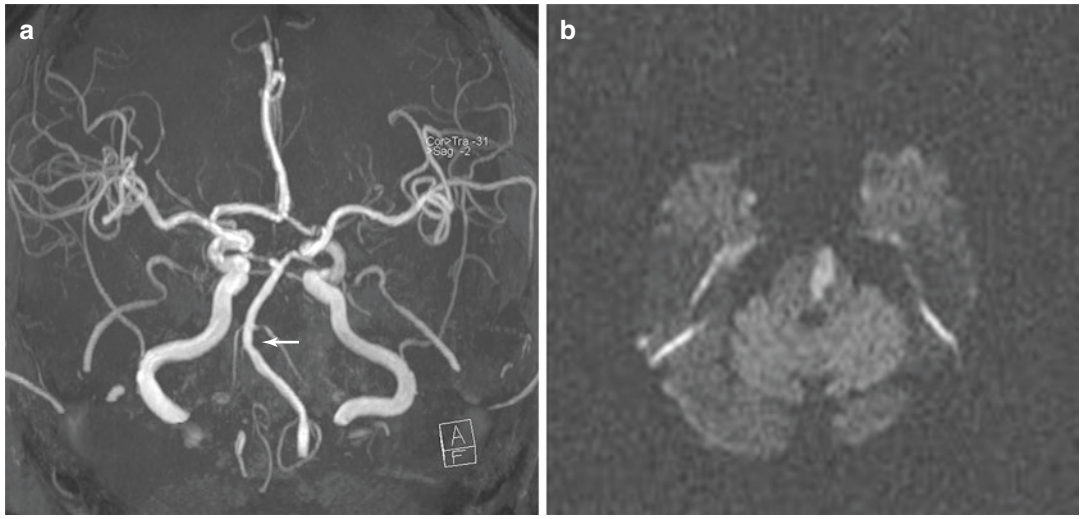

Fig. 5.7 Branch atheromatous disease, basilar artery. (**a**) Mild focal stenosis of basilar artery on MR angiography. (**b**) Acute infarct involving ventral surface of pons on diffusion-weighted image

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Part III

Clinical Science: Small Vessel Disease

Cerebral Small Vessel Disease

6

Seung-Hoon Lee

Abstract

Cerebral small vessel disease refers to a variety of diseases caused by the degeneration of small arteries, arterioles, capillaries, and venules in the brain. It is a syndrome of pathological, radiological, and clinical abnormalities or dysfunction associated with damage to small arteries and arterioles. Hypertension and old age are the most important risk factors for this disease. Meanwhile, arteriosclerosis, whose representative finding has been known as lipohyalinosis, is the fundamental vascular pathologic feature when the risk factors are improperly controlled for at least several years. Arteriosclerosis may cause acute strokes such as lacunar infarction, cerebral microinfarct, and intracerebral hemorrhage, and can also cause subclinical radiologic lesions such as lacunes, microbleeds, and white matter hyperintensities. These lesions are significant in terms of prevention because they can predict future strokes, dementia, depression, and vascular parkinsonism. This chapter covers the underlying pathologic findings, clinical types, risk factors, and pathophysiologic theories of SVD.

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Cerebral small vessels refer to small arteries, arterioles, capillaries, and venules in the brain. Arterial small vessels, except capillaries, are divided into two types: the first is the deep perforating arteries branching from the parent large arteries. These travel through the subarachnoid space in a perpendicular fashion, such as the lenticulostriate arteries. Second, is the small arteries (leptomeningeal perforators) that penetrate into the brain as the size decreases gradually from the superficial large arteries. Cerebral small vessel disease (SVD) is a syndrome of pathological, radiological, and clinical abnormalities or dysfunction caused by damage to these vessels. However, it is generally understood that SVD refers to old lacunes or white matter hyperintensities (WMHs) in the periventricular or subcortical areas, which are identified on brain magnetic resonance imaging (MRI). Here we can find some strange things. SVD refers to disease in the small "vessels," but WMHs are lesions on brain "tissue." For example, Takayasu's arteritis or coronary atherosclerosis are both abnormalities of blood vessels, not damage to tissues. In fact, even with the most advanced brain imaging, small vessels are not visible enough for clinical investigation, so we have little to see for direct evidence of the morphological abnormalities of actual small vessels. Even using 7T MRI, we can only just see the existence of lenticulostriate arteries, but not morphological status, such as vascular stenosis [1]. Accordingly, the term SVD is a misnomer,

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although the original nomenclature is not known. Personally, I consider the expression "microangiopathic cerebral lesions" to be much more accurate. For now, SVD is currently used to express the cerebral lesions caused by abnormalities of cerebral small vessels such as WMHs, lacunes, microbleeds, enlarged perivascular spaces (ePVS), microinfarcts, and brain atrophy that are found on brain computed tomography (CT) or MRI. In this situation, it is ironic that numerous articles or reviews on SVD do not include intracerebral hemorrhage (ICH), the most catastrophic result of cerebral microangiopathy.

SVD is often classified as symptomatic versus asymptomatic (or clinically silent) lesions. However, lacunes, microbleeds, and WMHs, largely known as asymptomatic lesions, are not completely asymptomatic. It may initially be asymptomatic, but can cause a variety of neurological dysfunction in advanced stages. Such neurological symptoms can be divided into those due to acute injury versus chronic, accumulated injury. Acute injuries comprise acute strokes, which include lacunar infarction (a type of ischemic stroke) and ICH (a type of hemorrhagic stroke). Both subtypes of acute stroke account for 20–40% of total strokes, although this can vary across the world [2]. Considering that proportions of other major subtypes, such as large-artery atherosclerosis and cardiac embolism, are similar to that of lacunar infarction, SVD accounts for the majority of strokes. The neurological symptoms of chronic, accumulated injury from SVD refer to higher cortical or subcortical dysfunction: (1) cognitive decline, including mild cognitive impairment and dementia; (2) emotional or psychological dysfunction, such as depression and psychosis; and (3) motor coordination problems, such as gait disturbance or vascular parkinsonism.

This chapter covers the underlying pathologic findings, clinical features, radiologic findings, risk factors, and pathophysiologic theories of SVD. SVD has been understood to occur passively by hypertensive end-organ damage. Recently, it was hypothesized that SVD can be actively acquired through endothelial injury, small vessel inflammation, blood–brain barrier (BBB) breakdown, and plasma protein extravasation [3]. This chapter will also discuss the possibilities and limitations of these new theories.

6.1 Underlying Pathologic Findings: Arteriolosclerosis

Pathologic findings of SVD have long been known as cerebral microangiopathies. Dr. Miller Fisher demonstrated microangiopathic findings by examining brains of patients with lacunar infarction and ICH using a serial section technique [4, 5]. With the advent of brain CT in the 1970s, the study of brain pathology almost completely ceased, and Fisher's body of work remains the most reliably cited literature on SVD pathology. He established pathological terms that are still in use, such as lipohyalinosis, microatheroma, etc., and proved that these lesions are caused by long-standing hypertension. In addition, as a neurologist, he classified the symptoms of patients with lacunar infarction and established a variety of lacunar syndromes. However, as the age of neuroimaging using CT and MRI has emerged, it is true that previous pathological knowledge has not been accurately retained, leading to some confusion. A survey of leading investigators in top class neuropathologic centers around the world showed a less than 50% agreement on the definition of small vessel [6]. To minimize confusion, one academic term to integrate these pathologic lesions has long been needed. There was an attempt to unite them under the term "arteriolosclerosis" by Dr. Leonardo Pantoni, but unfortunately no consensus was reached [7]. Indeed, this will be another misnomer. The term "arteriolosclerosis" refers to miniatherosclerosis in arterioles. However, according to the histologic classifications of arterial systems, microangiopathic findings responsible for SVD occur mainly in small arteries, rather than arterioles. The lenticulostriate arteries, which are typical of penetrating small arteries, have a diameter of 300–700 μm, whereas the arterioles typically range from 40 to 150 μm [8]. Furthermore, as mentioned later, arteriolosclerosis is an established histopathologic term indicating a concen-

tric microangiopathy in arterioles, so using this term only creates another confusion. Therefore, I suggest naming these lesions "arteriosclerosis" rather than arteriolosclerosis. In large arteries, we usually describe the vascular lesions responsible for ischemic stroke as atherosclerosis, so it would be easily differentiated from the term "arteriosclerosis." Collectively, arteriosclerosis in this chapter should be understood as a lesion that refers to all microangiopathic findings underlying SVD lesions, such as lipohyalinosis, microatheroma, microaneurysm, and fibrinoid necrosis (Fig. 6.1).

6.1.1 Lipohyalinosis

Dr. Fisher, while investigating the penetrating arteries that caused lacunar infarctions, observed foam cells in the subintimal layer and pink-staining fibrinoid material in the tunica media to thicken the vessel walls [4]. In some regions, these vessels were replaced by whorls, tangles, and wisps of connective tissue occluding the lumen (Fig. 6.2a) [9]. He named these vascular states segmental arterial disorganization, fibrinoid degeneration, or lipohyalinosis. Among them, lipohyalinosis generally described the pathologic features, and sometimes termed fibrohyalinosis or lipofibrohyalinosis. Lipohyalinosis describes the loss of smooth muscle cells in the tunica media, fibro-hyaline material accumulation, and foam cells, and leakage of plasma protein such as apolipoprotein E, alpha2-macroglobulin, and immunoglobulin G in asymmetric fashion in blood vessels of 40–300 μm (Fig. 6.2b–f) [10]. Contrary to lipohyalinosis, concentric stenosis of lumen due to concentric hyaline degeneration in smaller blood vessel levels, namely at the arteriole level (40–150 μm), is pathologically called "arteriolosclerosis." However, it should not be confused with arteriosclerosis, which denotes all microangiopathic changes to small vessels, as mentioned above.

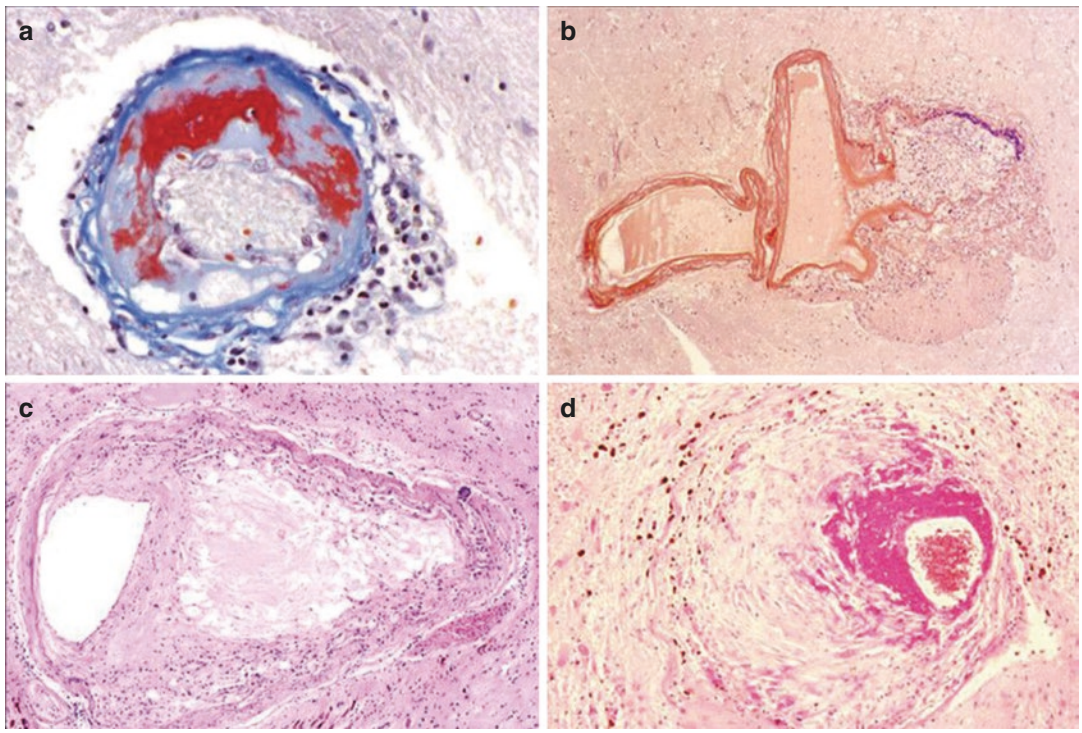

Fig. 6.1 Pathology of the cerebral small vessel disease. (**a**) Lipohyalinosis, (**b**) microaneurysm, (**c**) microatheroma, (**d**) fibrinoid necrosis. Adapted with permission from Lancet Neurology, Copyright Elsevier [7]

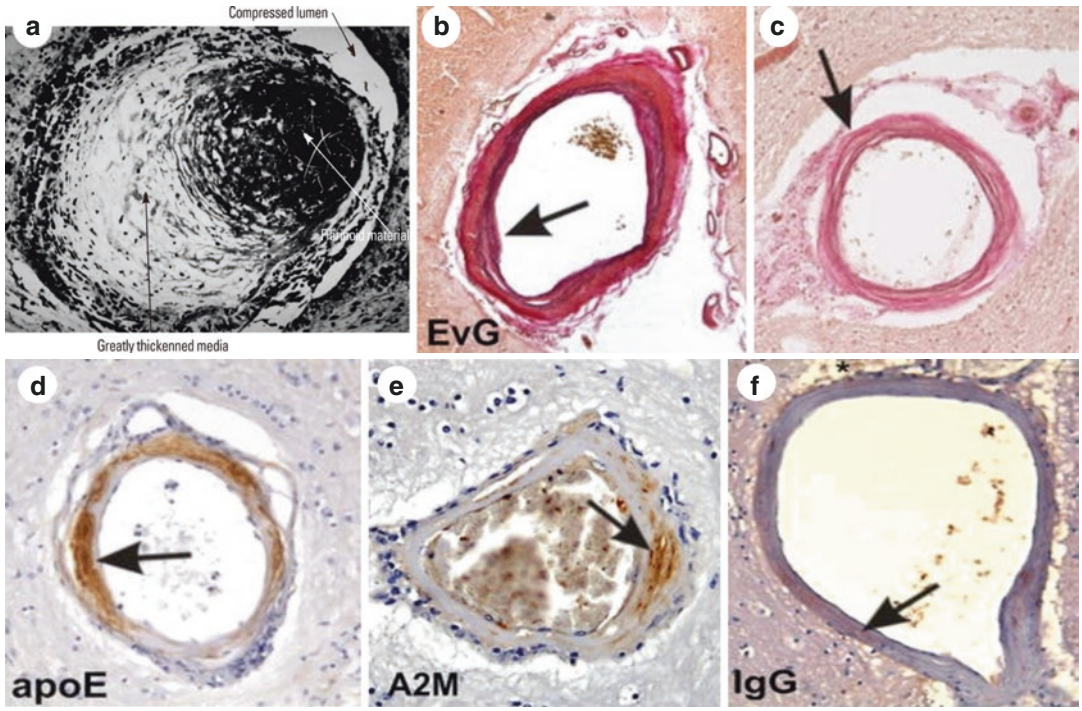

Fig. 6.2 Pathologic features of lipohyalinosis. (**a**) Whorls, tangles, and wisps of connective tissue, adapted with permission from Journal of Stroke, Copyright Korean Stroke Society. (**b**) Splitting of the internal elastic lamina, (**c**) fibrosis and fibrinoid necrosis, (**d**) plasma proteins apolipoprotein E, (**e**) alpha2-macroglobulin, and (**f**) immunoglobulin G shown within the affected vessel. Adapted with permission from Acta Neuropathologica, Copyright Springer Nature [10]

As one of the major underlying pathological characteristics of hypertensive microangiopathy or SVD, lipohyalinosis is the most common causative lesion of lacunar infarction and the most common background lesion of WMHs. Because of a strong association with lacunar infarction, there is a preconception that it may only be related to occlusion-type SVDs. However, lipohyalinosis is one of the most causative microangiopathies responsible for bleeding-type SVDs, such as microbleeds and ICH [11, 12]. In other words, it is important to understand that lipohyalinosis not only blocks small vessels, but also ruptures them.

6.1.2 Microatheroma

In penetrating arteries with relatively large diameters (200–800 μm), there may be some pathologic features with endothelial proliferation, splitting of internal elastic lamina and small plaque-like protrusion with accumulation of plasma proteins and macrophages, known as microatheroma (Fig 6.1c). This usually develops at the beginning of perforating arteries. When the microatheroma occurs at the junction where the brain branches from the large artery that travels across the subarachnoid space, it is also called a junctional atheroma (Fig. 6.3) [9]. Then, atherosclerosis in the branching site of a large artery may obstruct the blood flow of perforating arteries, often called “branch atheromatous disease.” In this case, it is reasonable to classify strokes with large-artery atherosclerosis, even if the sizes of the stroke lesions meet the definition of lacunar infarction. It is reasonable to classify SVD and its lacunar infarction only if the microatheroma is confined within the small vessel, so a complete differentiation between branch athero-

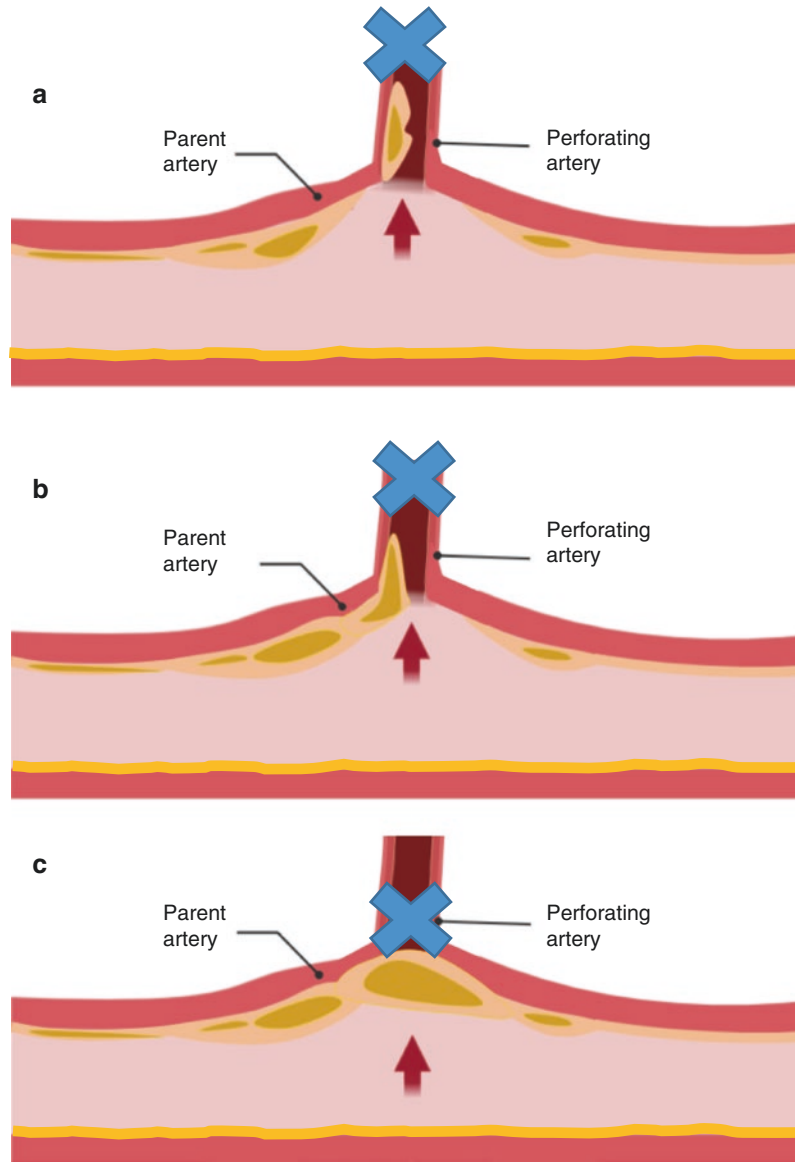

Fig. 6.3 Schematic illustrations of arterial pathology. (**a**) microatheroma blocked at the orifice of a branch; (**b**) junctional atheroma growing from the parent artery to the branch; (**c**) occlusion of perforating artery by atheroma of the parent artery

matous disease and lacunar infarction related to microatheroma or junctional atheroma would not be possible in a real clinical practice setting. Recently, however, it is increasingly possible to distinguish them with a high-performance 1.5T MR angiography or a 3T high-resolution MRI.

6.1.3 Microaneurysm

In 1868, Charcot and Bouchard found miliary saccular aneurysms connected to hemorrhages by autopsy of ICH brains and claimed that these lesions were a direct cause of ICH [13]. Because of this, these are also called "Charcot-Bouchard type microaneurysms." Then, in 1972, Dr. Fisher published a detailed analysis of the pathological findings of this type of lesion [11]. It differs in size from intracranial saccular aneurysms of large arteries within the subarachnoid space but is very similar in shape. Its diameter is approximately 300–1100 μm and protrudes approximately 40–160 μm from the blood vessel. It communicates with a parent arterial lumen through a nar-

row well-formed mouth and is not created by irregular tears or wall dissections. However, this lesion probably consists of an extremely thin layer of collagenous adventitial tissue, without a trace of muscle or elastic tissue except for the 100-μm stretch of wall adjacent to the parent artery. There is no definite endothelial lining. Hemosiderin-filled macrophages are often scattered in the region. If so, is this lesion a direct cause of ICH? In 1967, Cole and Yates found circumstantial evidence for the relationship between hypertensive hemorrhage and microaneurysms: microaneurysms existed in 46 of the hypertensives versus seven of the normotensives and had a common topographic distribution with the hematomas [14]. However, Dr. Fisher did not find evidence supporting aneurysms as the cause of the hemorrhages, asserting that the same type of hypertensive vascular disease (lipohyalinosis) under some circumstances evokes ischemia and under others tends toward bleeding [11]. Challa et al. (1992) used microradiography of sections stained histochemically for alkaline phosphatase and failed to find any aneurysm in 35 hypertensive brains, four with ICH, or in 20 normotensive brains [12]. Moreover, they showed that miliary microaneurysms were extremely rare in their routine examination of 2800 autopsies examined over one decade. Compared to lipohyalinosis, microaneurysms are uncommon findings. In addition, lipohyalinosis is a lesion capable of rupture as well as occlusion, and there are some mixed features, such as lipohyalinotic miliary aneurysm. Thus, it is reasonable to conclude that lipohyalinosis, a common cause of lacunar infarction, is the most causative lesion of ICH rather than microaneurysm.

6.1.4 Fibrinoid Necrosis

Fibrinoid necrosis is produced by the insudation of plasma proteins into the arterial wall, which includes fibrin or fibrinogen. The affected area is deeply eosinophilic and structureless (Fig 6.1a) or very finely granular, and may be segmented, as in lipohyalinosis. Extensive studies have shown that abrupt, marked elevations of blood pressure alone can cause fibrinoid change in a matter of minutes. Therefore, many lesions from fibrinoid necrosis are observed early in an acute hypertensive crisis or in hypertensive microangiopathy. There is much controversy about a direct association between fibrinoid necrosis with lacunar infarction or ICH.

6.1.5 Is Arteriosclerosis Found Only in the Brain?

In fact, all arteriosclerosis lesions are not characteristic lesions specific to the brain. They are common forms of hypertensive vessel changes and are observed in the kidney, heart, or retina. Why then are these pathological findings best known in the brain? The clinical manifestations of SVD, such as lacunar infarction, ICH, or dementia are common in the brain, so have been studied extensively. In the heart, these lesions may cause progressive dilated cardiomyopathy, and in the kidney, chronic kidney disease with low glomerular filtration rate. However, pathological correlations for non-brain clinical diseases have not been studied much in the past and there is still a lack of education on pathological background. SVD in the brain has been autopsied since the 1850s for people who died of ICH, and Fisher's historic achievements are far better known. The idea that SVD only occurs in the brain is therefore a misconception.

6.2 Clinical Manifestations of Small Vessel Disease

Regarding cerebral SVD, there has been a preconceived notion that the clinical impact of SVD is relatively small because lacunar infarctions are a subtype causing the least neurological deficit among strokes. However, as mentioned earlier, SVD is often overlooked as the most fatal cause of ICH. This is because most reviews dealing with SVD have focused on explanations of subclinical lesions, such as WMHs, lacunes, and microbleeds. In this chapter, we describe the clinical manifestations of SVD in two categories: (1)

lesions identified by acute stroke symptoms—lacunar infarction and ICH, and (2) lesions found on brain imaging without acute stroke symptoms—lacunes, WMHs, microbleeds, ePVS, and microinfarcts.

6.2.1 Lesions Identified by Acute Stroke Symptoms

6.2.1.1 Lacunar Infarction

Lacunar infarction is a subtype of stroke, based on TOAST classification, caused by small vessel occlusion (Fig 6.4a). Dr. Fisher analyzed lacunar infarctions using serial sections of human brains and found that most lacunar infarctions are due to obstruction of penetrating artery with a diameter less than 225 μm [4]. Cerebral infarctions in blood vessels larger than 300 μm was uncommon. Most of these blockages occur when fibrous connective tissue, resulting from lipohyalinosis-related denaturation, mechanically block the small arteries. As in large-artery atherosclerosis-related stroke, thrombosis originating from vessel lesions is rare in lacunar infarction. In lacunar infarctions occurring in small vessels of 300 μm or more, the probability of clot is increased by approximately 50%, and microatheroma is largely associated with such cases. Indeed, clear identification of lacunar infarction is difficult in some situations. Traditionally, it meant cerebral infarction due to occlusion of a penetrating small artery, but strokes due to large-artery atherosclerosis as a form of branch atheromatous disease are frequently classified as lacunar infarction because we do not conduct pathological examinations in actual clinical practice [15].

Only 50% of acute lacunar infarctions are observed on CT, but almost all can be seen on a diffusion-weighted sequence of MRI [16]. According to a recent clinical consensus, cerebral infarctions less than 2 cm on diffusion-weighted imaging are defined as lacunar infarctions [17]. With a single occluded small artery, deep brain

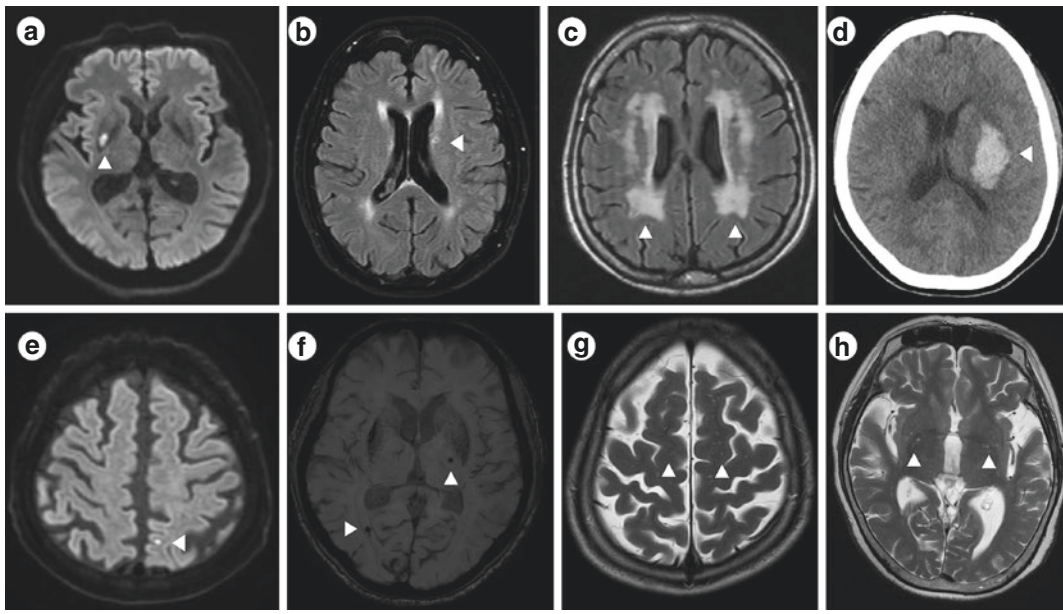

Fig. 6.4 Neuroimaging features of cerebral small vessel disease. White arrow heads show general types of the cerebral small vessel-related lesion. (**a**) Lacunar infarction in the right basal ganglia on DWI-sequence MRI, (**b**) lacune in the left corona radiata on FLAIR-sequence MRI, (**c**) white matter hyperintensities on FLAIR-sequence MRI, (**d**) intracerebral hemorrhage on CT, (**e**) Cortical microinfarct in left frontal lobe on DWI-sequence MRI, (**f**) Microbleeds in left internal capsule and right occipital lobe on SWI-sequence MRI, (**g**) enlarged periventricular spaces in bilateral frontal lobe, and (**h**) bilateral basal ganglia on T2-weighted MRI. DWI: diffusion-weighted imaging, MRI: magnetic resonance imaging, FLAIR: fluid-attenuated inversion recovery, CT: computed tomography, SWI: susceptibility weighted imaging

structures with poor collateral supply can be involved, such as the corona radiata, basal ganglia, internal capsules, thalamus, and pons. Its shape is round, ovoid, or tubular. Larger or tubular lesions are more likely to be caused by more proximal artery diseases, such as microatheroma [18]. However, in actual clinical practice, it is almost impossible to distinguish the causes of infarctions only by size and shape. It is not uncommon for emboli from the heart, parent arteries, or hypercoagulability to cause lacunar-like infarctions. However, a primate model study showed that less than 6% of emboli from internal carotid arteries move to lenticulostriate arteries, and most of them move on to cortical branches [19]. Despite this, in some cases of suspected embolism, lacunar syndrome or lacunar infarction requires more attention to identify the causes.

Because the lesion sizes are small, patients usually have one or two neurological deficits. Three or more deficits are extremely rare, and acute cognitive decline is not a symptom in most cases. Dr. Fisher has summarized several lacunar syndromes through clinico-pathologic studies (Table 6.1). Lacunar syndromes are useful to express the patients' status in a word, but is less useful in a contemporary context where advanced stroke imaging with MRI is available. As mentioned above, lacunar syndromes are often caused by large-artery atherothrombosis or cardioembolism, even in small-size hemorrhages.

In terms of the natural course of lacunar infarction, the acute lesion may become one of three chronic lesions: (1) small cavity (lacune) (Fig. 6.4b), (2) WMH lesion without cavity (if the stroke is mild at first) (Fig. 6.4c), and (3) no visible lesion [20]. The general prognosis of lacunar infarctions is excellent because the patient's symptoms are relatively mild and do not involve the cerebral cortex. In many cases, even without treatment, the disease will automatically improve without the need to visit emergency centers. However, it is important to remember that if the initial treatment is not appropriate, it is not uncommon for the neurological deficits to worsen during the acute stage (i.e., early neurological deterioration). Further, a better strategy for secondary prevention should be implemented during admission.

6.2.1.2 ICH

ICH is a type of hemorrhagic stroke, together with subarachnoid hemorrhage (SAH). The incidence of hemorrhagic stroke is approximately 15–40 people per 100,000 [21]. It accounts for approximately 15% of strokes (ischemic stroke, 85%), where ICH comprises approximately 10–15% and SAH approximately 5% of cases [22]. The incidence of ICH varies widely between ethnic groups and is known to be highest in Asian countries such as Korea, China, and Japan [21]. The Global Burden of Disease 2010 Study, which comprehensively analyzed various studies published from 1990 to 2010, indicated a 47% increase in ICH patients worldwide; compared to an 8% reduction in incidence and 38% reduction in mortality in high-income countries, the ICH incidence increased by 22% in middle- and low-income countries [23].

Table 6.1 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

ICH refers to a disease in which hemorrhage occurs spontaneously in the cerebral intraparenchymal area without trauma (Fig. 6.4d). Hypertension, cerebral amyloid angiopathy (CAA), arteriovenous malformation, arteriovenous fistula, cavernous hemangioma, moyamoya disease, brain tumor, cerebral venous thrombosis, and coagulopathies are important risk factors for ICH. Because of the influence of hypertension, hypertensive ICH has been used as a general term for communication, particularly for differentiation from ICHs caused by CAA. More accurately, ICH is a clinical manifestation of advanced SVD (a rupture of small vessels with arteriosclerosis) rather than hypertension itself. Among the microangiopathic features, lipohyalinosis is the most common and important causative lesion, as mentioned earlier. ICH is most common in the basal ganglia and thalamus because blood pressure is higher in deep brain structures than in the cerebral cortex. As for lobar ICH, a variety of causes including metastatic tumors or arteriovenous malformations can be involved, but it is certain that the most common cause is hypertension-related arteriosclerosis. Most clinical neurological deficits characteristic of ICH are identified as high density lesions on CT, so brain MRI is not necessary for initial ICH treatment. However, MRI is much more useful than CT for identifying associated vascular diseases, the burden of SVD, and the presence of microbleeds. Please refer to the textbook series "Stroke Revisited Volume 2: Hemorrhagic Stroke" for more details on ICH.

6.2.1.3 Cerebral Microinfarct (Fig. 6.4e)

Before the introduction of diffusion-weighted images, cerebral microinfarcts were not detectable, even when patients had relevant neurological dysfunction. However, thanks to the development of diffusion-weighted images and high-resolution MRI techniques, we can diagnose microinfarcts even when no neurological symptoms appear. Microinfarcts are usually found in the cortical or subcortical area and are defined as 1–5 mm in size [24]. A systematic review of neuropathological studies reported that cerebral microinfarct was found in 62% of patients with vascular dementia, 43% of Alzheimer's patients, and 24% of normal elderly patients without dementia aged 75 years or older [25]. In fact, when these lesions are identified, embolic infarction is usually suspected, but it can be caused by SVD or even by hemodynamic insult. When the SVD is related to microinfarcts, it may result from CAA-induced degeneration of leptomeningeal arteries [24]. However, the clinical effects and causes of cerebral microinfarct need to be further elucidated.

6.2.2 Lesions Found on Brain Imaging Without Acute Stroke Symptoms

6.2.2.1 Lacunes

Lacune is a neuropathologic term that is used in various situations and thus causes confusion. Dr. Fisher mentioned: "historically, the original SVD feature was the lacune (hole), which was derived from French for a small fluid-filled cavity that was thought to mark the healed stage of a small deep infarct" [4]. Since then, lacune has been the term for small cavitary lesions containing cerebrospinal fluid (CSF), regardless of relevant neurologic deficits. Lacunar infarction and lacune have been used interchangeably, so in recent years, a definite consensus has been established on the definition of these states. Lacunar infarction refers to a small acute infarction due to occlusion of a penetrating artery with a relevant neurological deficit, whereas lacune refers to a cavity lesion found by chance in brain imaging, regardless of neurological symptoms. Therefore, old, chronic, asymptomatic or subclinical lacune were also used alternatively. Although lacune is generally known to be a chronic change resulting from lacunar infarction, a residual lesion from a small hemorrhage can be possible [26]. Poirer et al. (1983) proposed to divide lacunes into three types using neuropathological studies: type I lacune, secondary to lacunar infarction (ischemic lacune); type II lacune, secondary to small hemorrhage (hemorrhagic lacune); type III lacune, ePVS [27]. This classification is not widely accepted, though it was a meaningful attempt to some extent in that type II lacune might suggest

microbleeds, which would be discovered on gradient-echo (GRE) MRI in the near future.

A typical lacune is found mainly in deep gray structures (e.g., basal ganglia and thalamus), subcortical white matter, and the pons. It is usually between 3 and 15 mm in diameter [17]. In most cases where it is less than 3 mm, the lesions are ePVS, and in cases larger than 15 mm, it is likely to be a territorial infarction by other mechanisms, such as large-artery atherosclerosis or embolism, rather than lacunes. The imaging criteria for lacunar infarction are a high-signal intensity lesion less than 2 cm on a diffusion-weighted sequence, whereas a lacune is a cavitary lesion less than 1.5 cm on T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences. This is because lacunar infarction may initially appear larger due to cytotoxic edema, but shrinks over time as it becomes chronic. Clear imaging criteria to distinguish them from ePVS are also required. Both lacunes and ePVS have CSF-filled small cavitary lesions (high signal on T2, low signal on FLAIR or T1) in common, but lacunes are larger (3–15 mm) and are more likely to have a high-signal intensity gliotic rim on FLAIR images. In addition, lacunes are found in distal portions of the parent artery, compared to ePVS. The prevalence of lacunes in adults varies considerably from report to report, but populations with vascular risk factors or a stroke history are likely to have more lacunes than normal elderly adults. There is a 28–94% chance of developing lacunes after lacunar infarctions [28, 29]. In other cases, the lesions become invisible or become WMHs.

6.2.2.2 WMHs

WMHs refer to symmetric, bilateral degeneration of cerebral white matter, especially the centrum semiovale or periventricular area. Although commonly found in cerebral white matter, these lesions may also occur in the pons or cerebellar white matter, and in severe cases, deep gray matter such as the basal ganglia and thalamus can also be involved. WMHs can be found as low-density lesions in CT but are more sensitively diagnosed as high-signal intensity in T2-weighted or FLAIR sequences on MRI. The etymology of the term WMH originates from MRI findings. The term used to refer to these lesions had not been unified, causing confusion in academic communications for a long time. For example, first there was the term “leukoaraiosis” that Dr. Hachinski originally used [30]. He developed a kind of compound word with Greek etymology, where leuko- means “white” and -araiosis means “rarefaction.” The word was popular for a time, but is now subsumed under WMHs.

WMHs are frequently found in normal older people, so a minimal amount of WMHs need not be considered pathological. Therefore, clinical grading of WMHs is necessary, though there are more than 19 reported image analysis methods [31]. Among them, the most readily available method is a grading scale that Fazekas et al. proposed by grading WMH in the centrum semiovale: grade 0: none or minimal; grade 1 (mild), punctate; grade 2 (moderate), early confluent; grade 3 (severe), confluent [32]. This method is quite easy and practical in that WMHs can be simply graded by visual inspection, and therefore is very useful for academic purposes as well as clinical practice. However, this method only evaluates WMH status in the centrum semiovale, disregarding the periventricular white matter, deep gray matter, and pons. Another disadvantage is its reliance on subjective judgment. As for the natural course, it is quite well known that WMHs progress more rapidly at moderate to severe grades (grade 2 or 3) than at minimal or mild levels [33, 34]. In other words, the status of WMHs is initially stationary, but with poor control of risk factors, conditions deteriorate rapidly after a certain period.

WMHs naturally affect cerebral function to various extents. They do not cause sudden and severe neurologic deficits as in stroke but induce chronic progressive cerebral dysfunction with insidious onset. If the lesions significantly affect white matter functions such as cognition, emotion, and sensorimotor coordination, there would be vascular cognitive impairment or dementia, depression or psychological dysfunctions, and gait disturbance or even vascular parkinsonism, respectively. Depending on the extent of the WMHs, the effects vary from person to person,

but the more severe the WMHs, the more likely deficits are. In addition, since it is a representative subclinical manifestation of SVD, WMHs are a crucial radiologic marker for future stroke occurrence or recurrence [35–37]. In particular, the predictability of stroke by SVD mechanisms (lacunar infarction or ICH) is relatively high. In addition, even with the same stroke, patients with more severe WMH have significantly worse outcomes [37]. In terms of ischemic stroke, severe periventricular WMHs were significantly associated with poor functional outcome at 3 months, independent of other factors, such as diabetes and age [37]. As for ICH, in Korea's ICH nation-wide cohort study by Kim et al., moderate-to-severe WMHs exhibited severe Glasgow Coma Scale (GCS) scores at admission (odds ratio, OR 2.45) and 30-day mortality (OR 2.52) [38]. Severe WMHs in white matter damage neurons and the physical structures of synapses, and in turn, reduce the activity or effectiveness of neurofunctional circuits. In addition, it is obvious that if stroke occurs in patients with advanced WMHs, the functional reservoir needed for patient recovery would be insufficient, thus long-term outcomes ultimately worsen.

The underlying pathologic findings of WMH are well established. In neural tissues, selective loss of neurons and oligodendrocytes, as well as demyelination and axon damage, is found, and lipohyalinosis is frequently observed in relevant penetrating arteries [39]. These findings suggest that WMHs may cause problems in the transmission of electrical signals through neural axons. Even without complete necrosis, as in a stroke, a partial pathological change would cause progressive damage in neurofunctional circuits for higher cortical functions. These pathological findings are traditionally explained by chronic hypoperfusion caused by advanced microangiopathies in small arteries. The centrum semiovale, receiving dual perfusion on both sides by basal penetrating arteries at the bottom of the cerebral cortex and leptomeningeal arteries at the top, is a representative watershed area called the internal border zone. When blood vessels are not affected, blood perfusion from both sides is enough to maintain cerebral blood flow (CBF). However, if both penetrators deteriorate due to generalized SVD, with poor control of risk factors, the watershed area is the first to be impacted by CBF reduction. If this condition persists, damage begins in the tissues most sensitive to CBF. These findings present as ischemic demyelination and associated axonal damage. In severe cases, some neurons and oligodendrocytes may also be lost, even showing incomplete infarction in some areas. In addition to this explanation, leakage of plasma fluid and venous collagenosis due to BBB breakdown have recently been suggested as a mechanism of action, and will be discussed in the later part of this chapter [3].

6.2.2.3 Microbleeds

Cerebral microbleeds are small amounts of hemosiderin deposited in the brain parenchyma, leading to local inhomogeneity around the lesions on MRI, resulting in small lesions of low-signal intensity on GRE or susceptibility-weighted images (SWI) (Fig. 6.4f). The most important point in diagnosing microbleeds is to exclude other lesions or artifacts that may be confused with microbleeds. This is because the GRE or SWI sequences used to diagnose microbleeds visualize all the substances that cause the susceptibility effect. Typically, calcifications, iron deposits, and deoxyhemoglobin inside the blood vessels are substances that cause susceptible effects. Controversy still exists about the size criteria for microbleeds [40]. In general, the minimum diameter is set to 2 mm, but the maximum diameter varies from 5 to 10 mm. However, considering the results from a series of clinical studies, the most appropriate determinant between microbleeds and intraparenchymal bleeding would be 5.7 mm [41]. Using GRE imaging, it is adequate that microbleeds are defined as a circular low-signal intensity lesion within 2–5 mm, but the definition under SWI may be applied differently. The diagnostic criteria illustrated in Table 6.2 are relatively widely accepted [40]. Microbleeds are most frequently found in the deep gray matter—the basal ganglia and thalamus—but are also found in the infratentorial and lobar locations [42–44]. Microbleeds in the deep area are usually caused by the vascular risk

Table 6.2 Recommended criteria for cerebral microbleeds identification

1. Black on T2∗-weighted MRI
2. Round or ovoid (rather than linear)
3. Blooming on T2∗-weighted MRI
4. Devoid of signal hyperintensity on T1- or T2-weighted sequences
5. At least half surrounded by brain parenchyma
6. Distinct from other potential mimics such as iron/calcium deposits, bone, or vessel flow voids
7. Clinical history excluding traumatic diffuse axonal injury

MRI: magnetic resonance imaging. Adapted from Lancet Neurology, Copyright Elsevier [40]

factors of stroke, particularly hypertension, but lobar microbleeds are more frequent in patients with CAA [45]. General pathological findings of microbleeds consist of minute hemosiderin deposition around the lipohyalinotic small arteries and hemosiderin-laden macrophages in the periphery. Therefore, microbleeds describe a small amount of blood leaking through a weak vessel wall, in other words, a subclinical, minute ICH. In patients with CAA, pathological observations showed hemosiderin deposition and inflammatory lesions due to blood leakage from vulnerable vessels with β-amyloid pigmentation [46]. The microbleeds seen on GRE and SWI appear to be exaggerated in size by the blooming effect, so the actual area of hemosiderin deposition is expected to be smaller.

In asymptomatic adults, the prevalence of microbleeds is approximately 3–7% [47, 48]. Old age and hypertension are important risk factors, but the effect of diabetes on microbleeds has been questioned. In the Rotterdam Scan Study, which examined microbleeds in 1062 asymptomatic adults, the prevalence of hypertension was 71.9%, and age was strongly correlated with the presence of microbleeds: 17.8% in 60–69 year-olds, 31.3% in 70–79 year-olds, and 38.3% in patients aged 80 years or older [47]. According to studies with ischemic stroke patients, the incidence of microbleeds among this group is significantly higher than that of normal individuals, ranging from 35 to 71% [48]. There is a clear difference in reporting rates of microbleeds as subtypes of ischemic stroke, characteristics of recruited patients, MRI sequences of microbleeds, and MRI parameters. Microbleeds are more frequent in lacunar infarctions, rather than in cardioembolic or atherothrombotic strokes [49]. The prevalence of microbleeds in ICH is the highest, ranging from 47 to 80% [48]. Further, microbleeds were observed more frequently in Asian ethnic groups than in non-Asian ethnic groups [50]. A higher prevalence of microbleeds in SVD-related strokes, lacunar infarction, and ICH can be easily understood considering the mechanism of development. With regards to this association, my colleagues and I reported that the presence of microbleeds in basal ganglia or lobar areas was strongly related to ICH development in the same regions [44]. Accordingly, the relationship between microbleeds and ICH is stronger than those of any SVD features, such as WMHs or lacunes [40].

Based on the assumption that microbleeds reflect the tendency of the brain tissue to bleed, it has been tested that microbleeds can be used as an indicator of the risk of future hemorrhagic stroke. In Hong Kong, an analysis of 121 patients with acute ischemic stroke showed that patients with baseline microbleeds were more likely to experience hemorrhagic stroke [51]. In addition, the number of microbleeds was proportional to the risk of subsequent hemorrhagic stroke. This suggestion was repeatedly demonstrated in a prospective study of 112 patients with ICH, which found this relationship was more pronounced in patients with WMHs [52]. Overall, a systematic analysis concluded that microbleeds are likely to predict future hemorrhagic stroke [53]. Especially in patients undergoing anticoagulation with atrial fibrillation after recent ischemic stroke or transient ischemic attack, identifying microbleeds may be useful for the prevention of future ICH. According to the CROMIS-2, a prospective large-sized cohort study conducted in the United Kingdom for this purpose, the symptomatic ICH rate in patients with microbleeds was approximately 3.8 times higher than in those without microbleeds (9.8 per 1000 patient-years versus 2.6) with statistical significance [54]. There is no doubt regarding the predictive value of microbleeds on future ICH. We may need a meticulous tuning of strategies for secondary prevention

among ischemic stroke patients with microbleeds. To date, however, no consensus on anticoagulant therapy in patients with microbleeds and atrial fibrillation has been reached. In order to clarify the benefits and losses in these patients, a large-scale clinical trial is urgently needed to identify the risk of microbleeds. Further, new oral anticoagulants (NOAC) are being actively used for the prevention of atrial fibrillation-related stroke. Meanwhile, the effects of microbleeds on NOAC-related bleeding is another topic for further analysis.

6.2.2.4 ePVS

Perivascular space, also called Virchow–Robin space, refers to a space in which the subarachnoid space extends into the brain parenchyma along penetrating arteries branching from the large cerebral arteries (Fig. 6.5). Filled with CSF, it extends along the penetrating arteries at a close distance. In normal adults, it is hardly distinguishable on conventional CT or MRI. However, in aging brains or brains that have been exposed to advanced vascular risk factors such as hypertension, the perivascular spaces are enlarged (hence the term ePVS) and can be clearly visualized on MRI. These lesions are observed in terms of CSF density, mainly on T2-weighted MRI, but are rather indistinguishable on FLAIR MRI or CT. They can be distinguished relatively well in several ways with lacunes: (1) ePVSs are usually smaller with a diameter within 3 mm; (2) ePVSs are distributed more proximally to the brain surface than lacunes, at the base of the basal ganglia, and the juxtasubcortical area near the cortex; (3) they are rarely found as a sole lesion, and a large number of lesions are usually observed at once; (4) there is no perilesional gliotic rim in ePVSs.

There are a few theories about the mechanism of development. Among them, vascular tortuosity-related expansion is a hypothetic mechanism that has long been considered

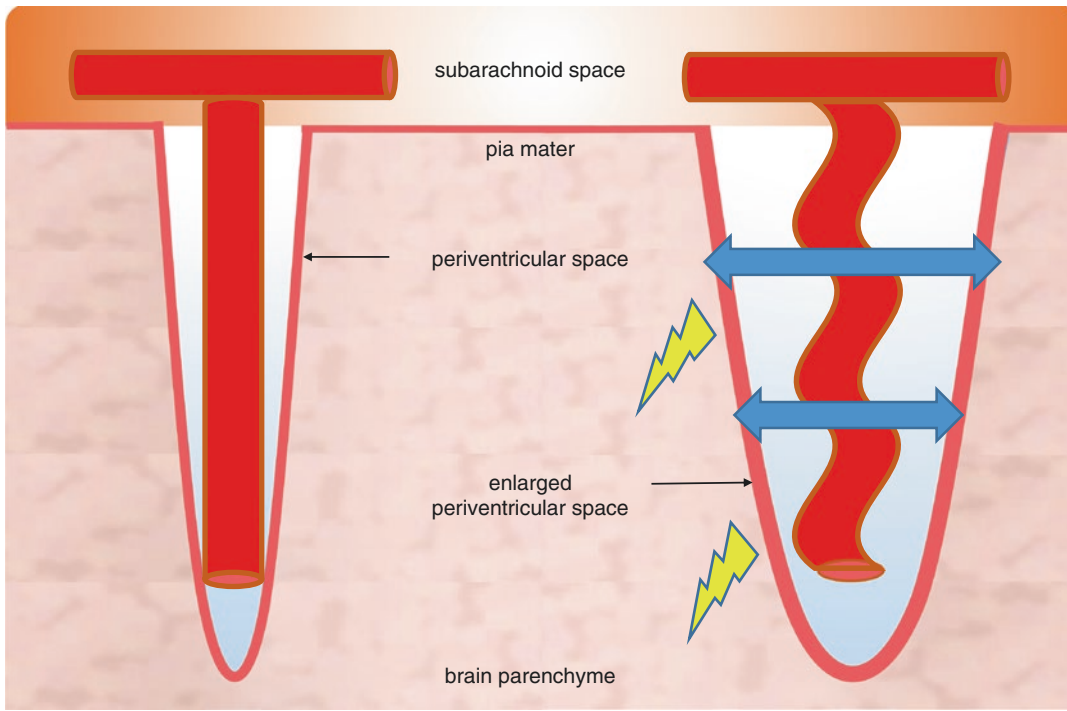

Fig. 6.5 The pathophysiology of enlarged periventricular space. Periventricular spaces are cerebrospinal fluid-filled canals surrounding perforating arteries in the parenchyma of the brain. Their close anatomical structure to arteries brings mechanical expansion of periventricular space by vascular tortuosity, which is a main phenomenon caused by hypertension or aging process

(Fig. 6.5). When penetrating arteries are exposed to hypertension or aging, they can morphologically become tortuous from increased blood pressure. The tortuous arteries progressively push the surrounding brain tissue to the periphery, which gradually widens the perivascular spaces. Since these changes may occur even in the early stages of hypertension, ePVS is frequently found even in the absence of other SVD features, such as WMHs or lacunes. Considering the effects of vascular risk factors on the interface of blood vessels and brain tissue, ePVS seems to be a lesion when blood vessels still tolerate vascular stress. This is because there are no noticeable changes to brain tissue around the ePVS. On the contrary, WMHs, lacunes, and microbleeds seem to be lesions that extend beyond blood vessels, affecting surrounding brain tissue. Accordingly, ePVS may indicate an end-organ damage finding during early to mid-term hypertension, or relatively good stress tolerance in brain tissue, while WMHs, lacunes, and microbleeds may indicate advanced tissue damage beyond the tolerance of the blood–tissue interface. Alternatively, it was suggested that sterile inflammation and exudation of plasma protein are involved in ePVS development, although this hypothesis warrants further evaluation [3].

6.3 Risk Factors

The vascular risk factors that cause SVD are not fully understood. Patients with SVD possess a variety of common atherosclerosis risk factors, such as hypertension, diabetes, hyperlipidemia, and smoking. Moreover, it is difficult to distinguish the risk factors that influence them on an individual level. Based on results from previous clinical studies, it is possible to categorize risk factors into high, moderate, and controversial degrees.

Factors that convey a high risk for SVD include old age and hypertension. As an irreversible risk factor, the association between old age and SVD is clear. Even with hypertension, SVD is rarely identified before age 40, but no matter how healthy, WMHs are generally profuse after age 70. This suggests that aging, namely vascular aging, is closely related to the development of SVD. Aging is associated with all types of SVD and is also implicated in the development of other risk factors. So, distinguishing the effects of aging alone is only statistically possible and practically difficult. A second high risk factor for SVD is hypertension [55]. Hypertension has long been known to be the most potent risk factor for SVD; it is now undoubtedly acknowledged that treatment of hypertension is the most effective means of inhibiting SVD progression [56]. Hypertension is a strong risk factor for all forms of SVD, but long-standing, uncontrolled hypertension conveys greater risk than an acute hypertensive crisis. It is uncertain whether diastolic or systolic blood pressure is more important, with reports that both are relevant or not. A prospective observational study showed that control of hypertension inhibits the progression of WMHs [33]. Among the radiological features of SVD, microbleeds are the type with the strongest effect of hypertension [57]. Although microbleeds in the lobar area are also related to CAA, microbleeds in the deep gray matter or pons are closely associated with hypertension [45]. This was supported by a clinical report which found a dose–response relationship between the burden of hypertension (based on the levels of left ventricular mass index using transthoracic echocardiography) and the number of microbleeds [57].

Meanwhile, smoking and diabetes are moderate risk factors for SVD. The Rotterdam Scan Study, which conducted follow-up MRI in 1077 patients, showed that current smoking was a significant risk factor for WMH progression (OR, 2.63) [58]. However, in a cross-sectional study of 1797 patients from Singapore, Hong Kong, and Korea, only age and hypertension were positively correlated with SVD features—WMHs, lacunes, and microbleeds—but other factors, including smoking, were irrelevant [59]. In addition, the relationship between diabetes and SVD was also inconsistent. A clinical study with an Asian sample showed no effect of diabetes on the likelihood of WMH, lacunes, and microbleeds [59]. In contrast, a study of Caucasian stroke patients showed a clear correlation between diabetes and SVD

features (OR, 2.74) [60]. Smoking is likely to be a risk factor affecting SVD, as well as large-artery atherosclerosis, but diabetes has been regarded as a risk factor only for large-artery atherosclerosis. As for ICH, an important clinical manifestation of SVD, no clear relationship between diabetes and the incidence of ICH has been established. It has also been repeatedly reported that diabetes has a minimal effect on the development of microbleeds. In summary, diabetes is a critical risk factor for the progression of atherosclerosis in large arteries but exerts a limited effect on the development of SVD [61].

Hyperlipidemia has long been misunderstood in association with SVD. A high level of low-density lipoprotein (LDL) cholesterol is the strongest risk factor for large-artery atherosclerosis. It is well known that the use of lipid-lowering agents, such as statins, greatly reduces the risk of coronary artery disease or stroke. Because of its strong association with large-artery atherosclerosis, there has been a prejudice that hyperlipidemia has a significant effect on SVD. However, it is largely unrelated to SVD, and in terms of hemorrhagic SVD manifestations, it was reported to have a protective function that inhibits the development. With regards to WMHs, hyperlipidemia was not associated with the development of the lesions, as indicated by the Rotterdam Scan Study and a clinical study in Asia [58, 59]. Moreover, low, rather than high, serum cholesterol levels are a strong risk factor for microbleeds and ICH [62]. However, these results do not suggest that statins should be prohibited for patients with SVD. Low levels of serum cholesterol in the clinical studies, which were associated with the incidence of microbleeds and ICH, were not generated by the lipid-lowering agents, but other systemic conditions, such as nutrient deficiency and alcohol consumption. Although the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed that high doses of atorvastatin increase the risk of ICH, there is much evidence that statin use does not increase the incidence of ICH in other situations [63]. At the very least, it is important to recognize that there is no association between hyperlipidemia and SVD.

In addition, there are some reports that nutrients such as homocysteine, B12, and folate are associated with the development of SVD. However, this connection is not only sporadic, but also very difficult to clearly distinguish from other risk factors for SVD. Regardless of how advanced statistical methods are, it is unlikely that we will be able to establish a clear relationship.

6.4 Pathophysiology of SVD

As mentioned before, the mechanisms underlying the occurrence of SVD features have already been described. This section will provide a comprehensive description of the known mechanisms of SVD features. With uncontrolled hypertension and aging, microangiopathic changes such as lipohyalinosis are developed in penetrating small arteries and arterioles. These changes cause mechanical disruption, dissection, and thrombosis on the vessel wall. When one vessel is suddenly blocked, lacunar infarction may occur with associated neurological symptoms. If the infarction occurs in the non-active functional area, noticeable neurological symptoms do not occur, but the lesion may later be discovered as a lacune on MRI. If the ischemic intensity is not enough to develop a complete infarction, the lesion may become a WMH lesion or may disappear in the chronic stage. Lacunar infarctions or lacunes are due to hypertension-related microangiopathic changes occurring in penetrating arteries and are common in areas vulnerable to high blood pressure—the basal ganglia, internal capsules, thalamus, corona radiata, and pons. The vessel walls of these penetrating arteries are not thick enough to maintain their integrity with advanced hypertension, and they may rupture and develop a hemorrhage into the brain parenchyma. Small amounts of extravasated blood with a diameter less than 5 mm are usually asymptomatic and can be detected as microbleeds on GRE or SWI sequences. When the extravasated lesions are large enough to develop an abrupt neurological deficit, they may be identified as an acute ICH. The locations of microbleeds and ICH are

quite similar, because the development mechanisms are identical despite the difference in amount of blood. Deep gray matter, such as the basal ganglia and thalamus, are vulnerable to high blood pressure, and are the most common areas for lacunes, microbleeds, and ICH. Looking in detail, we can see that lacunes occur at some distance from a vessel occlusion, whereas microbleeds and ICH occur just at the site of a vascular rupture. Accordingly, microbleeds are found at sites proximal to penetrating arteries branching from parent arteries traveling through subarachnoid space, and lacunar infarctions are more common at distal sites such as the internal capsules and corona radiata. Microbleeds in the lobar area are not uncommon in patients with hypertension but occur more frequently in those with CAA. Even in this case, microbleeds are largely found in juxtacortical areas—sites more proximal to parent branching vessels. Microbleeds in the periventricular area or centrum semiovale are infrequent. Tiny ruptures of leptomeningeal arteries denatured by CAA result in lobar microbleeds. In contrast, when an intraluminal disruption in the same vessels occurs, a small infarction—called a cortical microinfarct—may occur. As microangiopathic changes progress throughout the brain, deep internal areas—called internal border zones—may face problems with blood perfusion. The periventricular area and the centrum semiovale are the representative internal border zones. Chronic hypoperfusion at this site causes incomplete infarction and ischemic demyelination to be observed as WMHs on MRI. Figure 6.6 is a general illustration showing the location and mechanisms of these SVD features [64].

The development of SVD can be explained in most cases by the above overview. Recently, it has been suggested that the development of SVD, particularly WMHs, is due to endothelial failure and subsequent sterile inflammation. Wardlaw

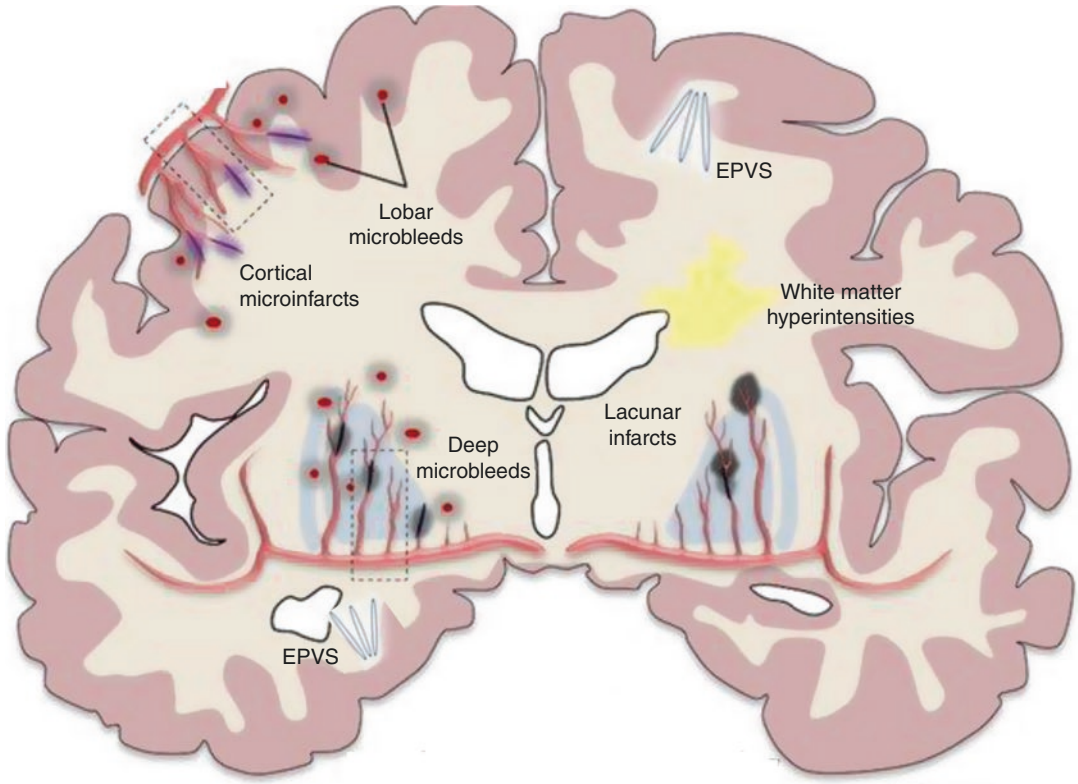

Fig. 6.6 The distribution of cerebral small vessel disease. Adapted with permission from Springer Nature [64]

et al. analyzed the CT and MRI data of nine patients with lacunar infarction, which showed that lacunar infarction could occur as a tubular vessel-like structure around the vessel, rather than at the end of the occluded vessel [65]. The authors distinguished that this appearance might also have been caused by a leak of blood and fluid into the perivascular space around the artery. In other words, it was suggested that leakage of plasma fluid components occurs due to endothelial failure in the early stages of SVD, and the resulting perivascular edema is toxic to brain tissue cells, leading to rarefaction and demyelination. According to this theory, the capillary lacks a smooth muscle layer, resulting in immediate edema and tissue damage when endothelial failure occurs. In arterioles, autoregulatory dysfunction in the thickened vascular walls may lead to ischemia due to the loss of appropriate vasodilation. Here, the reason why endothelial failure occurs in the first place is key to the theory's novelty. They argue that endothelial failure may be caused by (1) problems with BBB integrity due to aging, (2) amyloid deposition on the vessel wall, (3) sterile inflammation, and (4) a diet high in salt. In that case, is this theory necessarily a process unrelated to hypertension? Indeed, vascular stiffness and its associated self-regulatory dysfunction are also responsible for the development of essential hypertension, and conversely, are exacerbated by hypertension. Therefore, the endothelial failure theory should be taken as one of the theories explaining the process of microangiopathy caused by hypertension, which is not a new theory in itself. Perhaps endothelial failures in the microangiopathic vessels are a naturally occurring pathological process.

6.5 Therapeutic Perspectives and Conclusion

Cerebral SVD is a disease whose clinical effects are better known to the brain than other organs. The disease has various clinical manifestations ranging from asymptomatic lesions to highly fatal lesions such as ICH. SVD occurs when adult individuals are chronically exposed to various vascular risk factors such as old age and hypertension. There is no specific treatment targeting SVD. While it is not possible to return to a healthy state once SVD has developed, it is best to minimize progression through strict management of risk factors. Since SVD is a powerful predictor of various brain diseases such as stroke, dementia, parkinsonism, and depression, it is crucial to detect it using brain imaging. SVD can also be a useful surrogate radiologic marker for determining the success of risk control. In this chapter, almost all aspects of SVD—clinicoradiological type, pathology, risk factors, and mechanisms of development have been covered. I hope that this information will be used to facilitate better understanding of cerebral SVD.

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7

Cerebral Amyloid Angiopathy: Emerging Evidence for Novel Pathophysiology and Pathogenesis

Masahito Yamada, Kenji Sakai, Tsuyoshi Hamaguchi, and Moeko Noguchi-Shinohara

Abstract

Cerebral amyloid angiopathy (CAA) is cerebrovascular amyloid deposition being classified into several types according to the amyloid protein involved. Of these, sporadic amyloid β-protein (Aβ)-type CAA is most commonly found in older individuals and in patients with Alzheimer's disease (AD). Cerebral blood vessels affected with CAA are associated with functional and pathological changes (CAA-associated vasculopathies), leading to development of hemorrhagic disorders (lobar intracerebral macrohemorrhage, cortical microhemorrhage, and cortical superficial siderosis/focal convexity subarachnoid hemorrhage), ischemic disorders (white matter disease and cortical microinfarcts), and inflammatory vascular disorders, i.e., CAA-associated inflammation/angiitis; these CAA-related disorders are characterized by unique clinical features and imaging and cerebrospinal fluid abnormalities, contributing to a clinical diagnosis of CAA without brain biopsy. In this review, we particularly focus on topics with emerging evidence for novel pathophysiology and pathogenesis of CAA. They include CAA-related cognitive impairment and neurodegeneration, and CAA-related inflammation and similar disorders associated with Aβ immunotherapies for AD. Furthermore, recent studies indicated that Aβ pathologies, including CAA, would be transmissible in humans as well as experimental settings. Better understanding of mechanisms underlying pathophysiology and pathogenesis of CAA would lead to new strategies for interventions for CAA.

Abbreviations

Aβ	amyloid β-protein
AβPP	β-amyloid precursor protein
ACE	angiotensin-converting enzyme
ACT	α1-antichymotrypsin
ACys	amyloid cystatin C
AD	Alzheimer's disease
AGel	amyloid gelsolin
AL	amyloid immunoglobulin light chain
APOE	apolipoprotein E
APOE	apolipoprotein E gene
APrP	amyloid prion protein
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormalities-vasogenic edema and sulcal effusions
ARIA-H	amyloid-related imaging abnormalities -microhemorrhages and hemosiderin deposits

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ATTR	amyloid transthyretin
BOLD	blood-oxygen-level-dependent
CAA	cerebral amyloid angiopathy
CAA-ri	cerebral amyloid angiopathy-related inflammation
CBF	cerebral blood flow
CJD	Creutzfeldt–Jakob disease
CMB	cerebral microbleed
cSAH	convexity subarachnoid hemorrhage
CSF	cerebrospinal fluid
cSS	cortical superficial siderosis
dCJD	dura mater graft-associated Creutzfeldt–Jakob disease
DMT	disease-modifying therapies
FDG	fluorodeoxyglucose
FLAIR	fluid attenuation inversion recovery
fMRI	functional MRI
hGH	human cadaveric pituitary-derived growth hormone
ICH	intracerebral hemorrhage
iCJD	iatrogenic CJD
LRP-1	low-density lipoprotein-receptor related protein
MB	microbleed
MCI	mild cognitive impairment
PiB	Pittsburgh Compound B
PS1	presenilin 1
p-tau	phosphorylated tau
p-TDP-43	phosphorylated transactive response DNA binding protein 43 kDa
SAH	subarachnoid hemorrhage
sCJD	sporadic Creutzfeldt-Jakob disease
SVD	small vessel disease
TDP-43	transactive response DNA binding protein 43 kDa
TGF-β1	Another CAA-related gene reported by more than one research group transforming growth factor-β1
VaD	vascular dementia
WMH	white matter hyperintensity

7.1 Introduction

Cerebral amyloid angiopathy (CAA) is cerebrovascular amyloid deposition, and is classified into several types according to the amyloid protein involved (Table 7.1). So far, seven amyloid proteins have been reported in CAA including amyloid β-protein (Aβ), cystatin C (ACys), prion protein (APrP), ABri/ADan, transthyretin (ATTR), gelsolin (AGel), and, rarely, immunoglobulin light chain amyloid (AL); among these, sporadic CAA of the Aβ type is most commonly found in older individuals as well as in patients with Alzheimer's disease (AD) (see reviews [1–3]). This chapter reviews sporadic Aβ-type CAA focusing on emerging evidence for novel aspects of pathophysiology and pathogenesis, such as CAA-related neurodegeneration and inflammation, and transmission of Aβ pathology.

7.2 Sporadic Aβ-Type CAA: General Aspects

Sporadic Aβ-type CAA occurs in approximately a half of older individuals showing an increase of the prevalence of CAA with age. Figure 7.1 shows the prevalence of CAA in AD and non-AD subjects. CAA is commonly observed in AD with higher prevalence of 80–90% and higher severity compared with non-AD subjects [2]. In this section, we briefly describe general aspects of sporadic Aβ-type CAA including pathogenesis and pathophysiology, risk factors, CAA-related cerebrovascular disorders, biomarkers, and diagnosis (see review [3]).

7.2.1 Pathology, Pathogenesis, and Pathophysiology

CAA is observed mainly in the leptomeningeal and cortical vessels of the cerebral lobes and cerebellum. The occipital lobe is preferentially affected, whereas CAA is uncommon in the basal ganglia, thalamus, brainstem, and white matter. Mild CAA is almost silent clinically, while, in severe CAA, most of small arteries and arterioles are affected with marked amyloid deposition, associated with degeneration of smooth muscle cells and other vasculopathic changes leading to CAA-related cerebrovascular disorders. Amyloid deposits in capillaries and, occasionally, in arterioles or small arteries appear to infiltrate the surrounding parenchymal tissue, and accompany dystrophic neurites forming plaque-like structures (drüsige Entartung/angiopathie dyshorique). CAA in capillaries has been referred to

Table 7.1 Classification of cerebral amyloid angiopathy (CAA)

Amyloid protein	Clinical phenotype
1. Amyloid β-protein (Aβ)	1. Sporadic; associated with: (a) Aging (b) Sporadic Alzheimer's disease (AD) (c) Other conditions, including vascular malformations, irradiation
	2. Hereditary or genetic; associated with: (a) Mutations in the amyloid β-protein precursor (AβPP) gene, including hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D) E693Q, E693K (Italian), E693G (Arctic), A692Q (Flemish), E694N (Iowa), L705V (Piedmont), A713T (Italian), and AβPP gene duplication. (b) Mutations of presenilin genes (c) Down syndrome
2. Cystatin C (ACys)	HCHWA-Icelandic type (HCHWA-I) associated with a mutation (68Leu → Gln) of the cystatin C gene
3. Prion protein (PrP) (APrP)	Prion disease associated with mutations of the PRNP gene (Y145Stop, Y163Stop, Y226Stop)
4. ABri/ADan	Familial British or Danish dementia (FBD/FDD) associated with mutations of the BRI gene
5. Transthyretin (ATTR)	Meningocerebrovascular involvement of familial transthyretin (TTR) amyloidoses (familial oculoleptomeningeal amyloidosis, familial amyloid polyneuropathy) associated with mutations of the TTR gene
6. Gelsolin (AGel)	Meningocerebrovascular involvement of gelsolin-related amyloidosis (familial amyloidosis, Finnish type) associated with mutations of the gelsolin gene
7. Immunoglobulin light chain amyloid (AL)	CAA with leukoencephalopathy due to brain-restricted monoclonal plasma cell proliferation

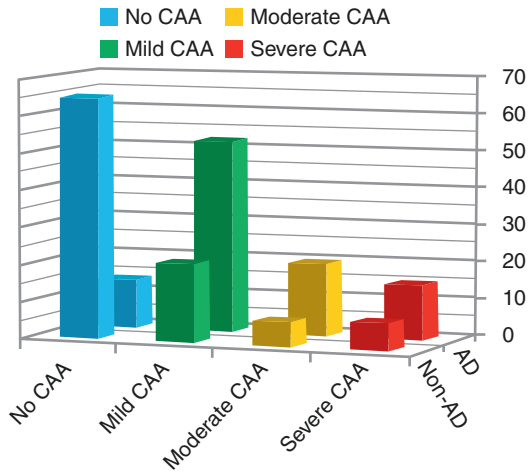

Fig. 7.1 The distribution of the severity of cerebral amyloid angiopathy (CAA) in elderly individuals (n = 201; age, 85.9 ± 8.0 years) with and without Alzheimer's disease (AD), from our autopsy series including AD (n = 82; age, 86.1 ± 7.9 years) and non-AD cases (n = 119; age, 85.7 ± 8.0 years). (Cited from the reference [2])

as "capillary CAA (CAA-Type 1)," to distinguish it from non-capillary CAA (CAA-Type 2). CAA-associated vasculopathies include duplication ("double-barrel" lumen), obliterative intimal changes, hyaline degeneration, microaneurysmal dilatation, and fibrinoid necrosis.

How does Aβ deposit in walls of cerebral blood vessels? Aβ cleaved from the β-amyloid precursor protein (AβPP) by β-secretase and β-secretase has heterogeneity of the C-terminal; the length of Aβ deposited in senile plaques is mainly 42–43 residues ($Aβ_{42}$), while that of cerebrovascular Aβ (CAA) is mainly 39–40 residues ($Aβ_{40}$) (Fig. 7.2). Aβ in CAA is considered to derive from the brain; after releasing from neurons, $Aβ_{42}$ easily aggregates and deposits in the brain parenchyma as senile plaques; whereas, $Aβ_{40}$ does not aggregate so easily as $Aβ_{42}$, and is transported, through periarterial interstitial fluid drainage pathways, for clearance. In this process, $Aβ_{40}$ aggregates on vascular basement membranes [1].

The pathophysiology of Aβ-type CAA is shown in Fig. 7.3. CAA-associated vasculopathies lead to development of hemorrhagic lesions [lobar intracerebral (macro)hemorrhage (ICH), cortical microhemorrhage or microbleed (MB), and cortical superficial siderosis (cSS)/focal convexity subarachnoid hemorrhage (cSAH)], ischemic lesions [cortical infarction and isch-

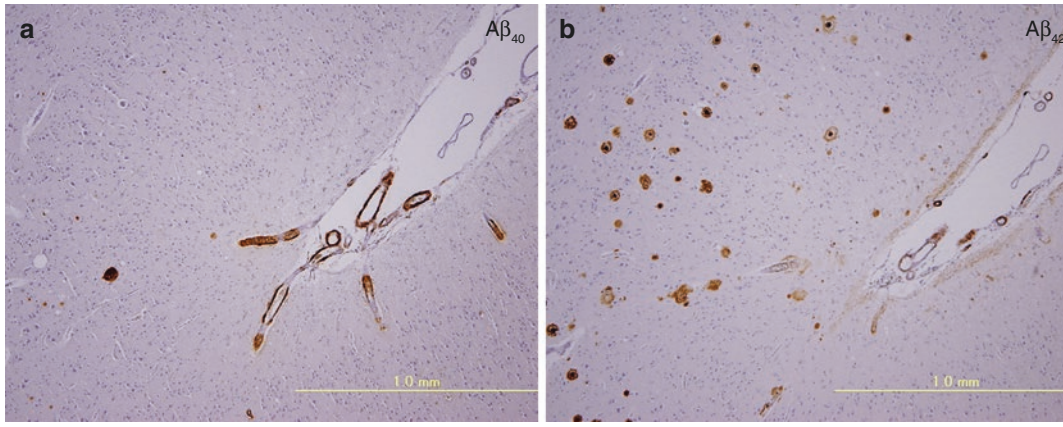

Fig. 7.2 Serial sections of the cerebral cortex immunostained with antibodies to $A\beta_{40}$ (**a**) and $A\beta_{42}$ (**b**). A major component of cerebrovascular amyloid is $A\beta_{40}$, while, that of parenchymal amyloid (plaques) is $A\beta_{42}$

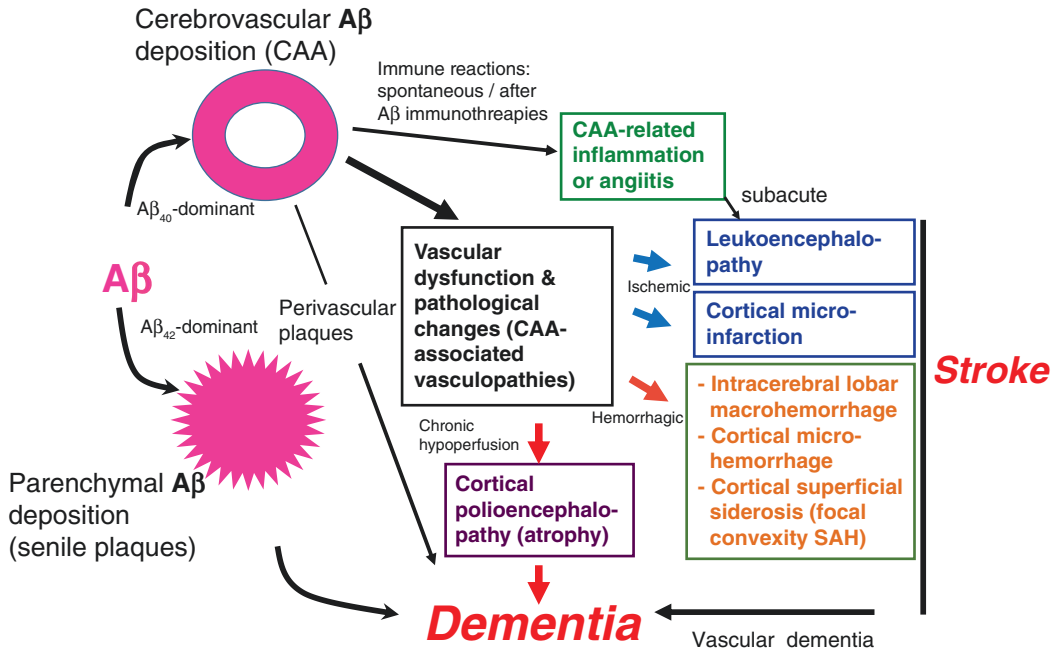

Fig. 7.3 Pathophysiology of cerebral amyloid angiopathy (CAA) and CAA-related disorders. Aβ shows parenchymal (senile plaques) or vascular deposition (CAA), depending on dominance of $A\beta_{42}$ or $A\beta_{40}$, respectively. CAA is related to stroke and dementia. (Modified from the reference [3])

emic changes of the white matter (leukoencephalopathy)], cortical polioencephalopathy (atrophy), and subacute leukoencephalopathy caused by CAA-related inflammation/angiitis. CAA-related disorders as well as coexisting AD pathology contribute to cognitive impairment or dementia. Thus, CAA is related to dementia, stroke, encephalopathies, and dementia.

7.2.2 Risk Factors

Besides aging and AD, some genetic and nongenetic risk factors of CAA and CAA-related disorders have been reported.

The apolipoprotein E (APOE) gene (*APOE*) has been reported to be a risk factor for sporadic CAA as well as AD; the ε4 allele for CAA itself,

and the ε2 allele for CAA-related ICH. The *APOE* ε2/ε4 genotype was associated with early recurrence of lobar ICH in patients who survived a lobar ICH. The *APOE* ε4 allele is risk for capillary CAA (CAA-Type 1), CAA-related inflammation, [4] cerebral MBs (CMBs), and CAA in head injury cases, and *APOE* ε2 for cSS. Other genetic factors include polymorphisms in the genes of transforming growth factor (TGF)-β1, presenilin 1 (PS1), α1-antichymotrypsin (ACT), neprilysin, low-density lipoprotein-receptor related protein (LRP-1), angiotensin-converting enzyme (ACE), and CR1.

Some factors increase risk for CAA-related hemorrhages, including hypertension, and thrombolytic, anticoagulation, and antiplatelet therapies [5]. CAA could be a risk factor for ICH with thrombolytic therapies for acute myocardial infarction, pulmonary embolism, or ischemic stroke, and for ICH with warfarin therapies. Thrombolytic or anticoagulation therapies in patients with MBs are potential risk factor for ICH. The *APOE* ε2 and ε4 alleles were reported as strong risk factors for lobar warfarin-related ICH; this association was considered to be mediated by CAA. The use of antiplatelet drugs, such as aspirin, is associated with the presence of MBs, and with strictly lobar MBs suggestive of CAA. A review for antithrombotic (antiplatelet or anticoagulant) therapy for patients with ischemic stroke/transient ischemic attack and cerebral MBs suggested that less than five CMBs should not affect antithrombotic decisions, although with more than five MBs the risks of future ICH and ischemic stroke are finely balanced, and antithrombotics might cause the net harm [5].

7.2.3 CAA-Related Cerebrovascular Disorders

7.2.3.1 Hemorrhagic Disorders

CAA-associated vasculopathies in the cortical and meningeal vessels of cerebral and cerebellar cortices accompany symptomatic lobar ICH, lobar CMBs, and cSS/focal cSAH.

Lobar Intracerebral Hemorrhages/Cortical Microbleeds CAA-related lobar ICH was noted in 12–20% of total ICH cases with a recent increase of its incidence. CAA-related lobar ICH is characterized by multiple and recurrent occurrence and clinical manifestations including motor paresis, disturbance of consciousness, abnormalities in higher brain functions, such as aphasia, visual loss, with headache which is probably related to secondary subarachnoid hemorrhage (SAH), at the acute stage, and dementia and seizures during chronic stages.

With sensitive MR imaging techniques, such as gradient-echo T2∗ imaging and susceptibility-weighted imaging, MBs were found in 47.4% of patients with pathologically confirmed CAA cases [6]. CAA-related MBs are frequently lobar in distribution. Studies with amyloid positron emission tomography (PET) using ^{11}C-Pittsburgh Compound B (PiB) reported close spatial and temporal relationships between lobar MBs and amyloid deposits.

A recent meta-analysis of prospective cohorts following ICH indicated that the annual recurrent ICH risk was higher in CAA-related ICH vs CAA-unrelated ICH [7]. Patients with lobar MBs are at considerable risk of future symptomatic lobar ICH. In the meta-analysis for patients with CAA-related ICH, higher numbers of multiple baseline MBs were associated with higher risk of ICH recurrence during follow-up; however, single MB was not associated with recurrent ICH [7].

Cortical Superficial Siderosis/Focal Convexity Subarachnoid Hemorrhages CAA is a frequent cause of cSS/focal cSAH, a subtype of non-aneurysmal SAH, in patients over the age of 60 and in those with AD [8]. cSS is found in 60.5% of pathologically confirmed CAA cases [6]. Although cSS is associated with lobar MBs, cSS tends to occur in individuals with relatively fewer cortical MBs, suggesting differences in vasculopathic changes between CAA-related MBs and cSS. cSS/cSAH is associated with an increased future risk of bleeding, lobar ICH, or cSAH [9]. Importantly, cSS and cSAH have been reported to present with transient focal neurological episodes (TFNEs), mainly spreading sensory symptoms; TFNEs are a clinical marker of cSS and may be caused by cSS through cortical spreading depression or focal seizure [9]. Antiplatelet or anticoagulant therapies based on the misdiagnosis of CAA-related TFNEs as transient ischemic attacks may induce CAA-related ICH.

7.2.3.2 Ischemic Disorders

CAA-related cerebral hypoperfusion or occlusive small-vessel disease may cause progressive white matter lesions and cortical microinfarcts.

White Matter Disease Patients with CAA-related ICH exhibit occipital dominant white matter hyperintensities (WMHs) on MRI, compatible with predilection of CAA pathology for posterior brain regions. A posterior distribution of WMH on MRI is associated with the presence of CAA pathology, which could be a possible marker of CAA. Amyloid burden in non-demented CAA subjects correlated with WMH volumes.

Cortical Microinfarcts Acute or subacute subclinical ischemic infarcts are common in CAA-related ICH. As a result of the difficulty in detection, CAA as a cause of cortical microinfarcts is underrecognized (see the section of biomarkers).

7.2.4 Biomarkers and Diagnosis

7.2.4.1 Biomarkers

Common Imaging Markers Blood-sensitive MRI techniques, such as gradient-echo T2∗ imaging and susceptibility-weighted imaging, are useful for detection of MBs and cSS. In addition, enlarged perivascular spaces in the centrum semiovale are associated with clinically diagnosed CAA with ICHs, MBs, or cSS, and with pathologically confirmed CAA, suggesting that they could be an MRI marker for CAA [10]. For ischemic lesions, acute or subacute cortical or subcortical infarctions can be recognized in CAA on diffusion-weighted images; however, old cortical microinfarcts are often difficult to detect, probably requiring high-resolution MRI. A high-resolution MRI-histopathological study indicated that MBs on MRI are specific for microhemorrhages in CAA, and that, in contrast, the vast majority of microinfarcts currently remain under the detection limits of clinical in vivo MRI [11].

Functional Imaging Impaired cerbrovascular reactivity in response to visual stimulation was reported in studies with transcranial Doppler ultrasound or functional MRI (fMRI) measuring changes in blood-oxygen-level-dependent (BOLD) signal and regional cerebral blood flow (CBF) using pseudo-continuous arterial spin labeling [12]. Impaired vascular function was detected even in presymptomatic subjects with hereditary CAA of Dutch type [12].

Amyloid PET Amyloid imaging with a PET ligand, ^{11}C-PiB, revealed an increase of PiB binding that often shows greater occipital uptake in CAA-related ICH and is also associated with cortical MBs. Recent studies indicated that ^{18}F-florbetapir, another PET tracer, labeled vascular amyloid in patients with CAA-related ICH, providing a sensitivity of 100% and a specificity of 89% to discriminate CAA-related ICH from hypertensive ICH [13]. The tracers label both parenchymal and vascular amyloid deposits, and amyloid positivity is frequently found in healthy elderly individuals with preclinical AD and patients with clinical AD. Therefore, amyloid PET has low specificity for CAA; however, a negative PiB scan rules out CAA with excellent sensitivity [7].

Biochemical Markers Cerebrospinal fluid (CSF) markers are useful. CSF levels of $A\beta_{40}$ as well as $A\beta_{42}$ show a significant decrease in patients with probable CAA. Decreased CSF levels of $A\beta_{40}$ and $A\beta_{42}$ occur before onset of hereditary CAA of Dutch type in mutation carriers [14]. The findings would reflect trapping of $A\beta_{40}$ and $A\beta_{42}$ in the cerebrovasculature in early steps of CAA pathogenesis. Patients with isolated cSS also showed lower CSF $A\beta_{42}$ and $A\beta_{40}$ levels. CSF levels of total tau and phosphorylated tau are higher in patients with probable CAA than in controls, but lower than in AD. The presence of anti-Aβ autoantibodies in CSF is a marker of CAA-related inflammation (see below) [15].

7.2.4.2 Diagnosis

The Boston criteria were used for the diagnosis of CAA-related ICH (Table 7.2), and high diagnostic accuracy was reported with a small pathologic series [16]. As cSS has been established as a biomarker of CAA, cSS was incorporated into the classic Boston criteria (the modified Boston criteria) (Table 7.2), in which the sensitivity increased from 89.5 to 94.7%, and the specificity was 81.2%

Table 7.2 Classic[a] [16] and modified Boston criteria [6] for diagnosis of CAA-related hemorrhage

1. Definite CAA Full postmortem examination demonstrating: • Lobar, cortical, or corticosubcortical hemorrhage • Severe CAA with vasculopathy[b] • Absence of other diagnostic lesions
2. Probable CAA with supporting pathology Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating: • Lobar, cortical, or corticosubcortical hemorrhage • Some degree of CAA in the specimen • Absence of other diagnostic lesions
3. Probable CAA Clinical data and MRI or CT demonstrating: • Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed) [or §single lobar, cortical, or corticosubcortical hemorrhage, and focal[c] or disseminated[d] superficial siderosis] • Age ≥55 years • Absence of other causes of hemorrhage [or §superficial siderosis][e]
4. Possible CAA Clinical data and MRI or CT demonstrating: • Single lobar, cortical, or corticosubcortical hemorrhage[or §focal[a] or disseminated[b] superficial siderosis] • Age ≥55 years • Absence of other causes of hemorrhage [or §superficial siderosis][e]

The modified criteria are indicated by §

[a]Criteria established by the Boston Cerebral Amyloid Angiopathy Group: Steven M. Greenberg, MD, PhD, Daniel S. Kanter, MD, Carlos S. Kase, MD, and Michael S. Pessin, MD

[b]As defined in: Vonsattel JP, Myers RH, Hedley-Whyte ET, Ropper AH, Bird ED, Richardson EP Jr. Cerebral amyloid angiopathy without and with cerebral hemorrhages: a comparative histological study. *Ann Neurol* 1991;30: 637–649 [52]

[c]Siderosis restricted to 3 or fewer sulci

[d]Siderosis affecting at least 4 sulci

[e]Other causes of intracerebral hemorrhage: excessive warfarin (international normalization ratio, INR > 3.0); antecedent head trauma or ischemic stroke; central nervous system tumor, vascular malformation, or vasculitis; and blood dyscrasia or coagulopathy. INR > 3.0 or other nonspecific laboratory abnormalities permitted for diagnosis of possible CAA

for both the classic and modified criteria [6]. In near future, amyloid imaging and CSF markers (see above) should be included to improve diagnostic accuracy without brain biopsy.

7.3 CAA-Related Cognitive Impairment and Neurodegeneration

7.3.1 Dementia Incidence in Non-demented Patients with CAA

Dementia is found in a subgroup of patients with CAA-related ICH at the onset of the initial ICH. In a prospective cohort study, lobar ICH was associated with higher risk of new-onset dementia after spontaneous ICH compared with non-lobar ICH, and disseminated superficial siderosis, cortical atrophy score, a higher number of CMBs, and old age were risk factors of new-onset dementia, which suggest that underlying CAA was a contributing factor [17]. In patients with a CAA-related syndrome including ICH, cognitive symptoms without dementia, CAA-related inflammation, or transient focal neurological symptoms, mild cognitive impairment (MCI) was very prevalent showing lower executive function and processing speed, which was similar to that in vascular cognitive impairment [18]. Cumulated dementia incidence in patients without ICH was estimated to be 14% at 1 year and 73% at 5 years; age, presence of MCI status, medial temporal atrophy, and small vessel disease (SVD) score were independent predictors for dementia conversion in these patients [19]. In a general population of older people, the presence of CMBs located in deep or mixed CMBs, but not lobar CMBs, were associated with a greater cognitive decline of verval memory, processing speed, and executive

function [20]. Similarly, deep or mixed CMBs, but not purely lobar CMBs, were associated with risk of incident dementia [21]. These results suggest that hypertensive vasculopathy and interaction of hypertensive vasculopathy and CAA, rather than pure CAA-related MBs, may have a definite role in the pathogenesis of cognitive deterioration or dementia incidence.

7.3.2 CAA in Patients with Alzheimer's Disease or Cognitive Impairment

In patients with AD or cognitive impairment, CAA-related lesions are frequently observed. Cerebral MBs were noted in 16.7–32% of AD patients with lobar predominance, which is higher than in the general population (5–6%), when examined by gradient-echo T2∗ MRI, and in 78% of patients with AD dementia or MCI on ultra-high field strength 7T MRI.

In patients with AD or cognitive impairment, the prevalence of cSS is higher than in the general population. In a recent study, cSS was found in 40 of 1504 memory clinic patients (2.7%) with prevalence of 13% for vascular dementia and 5% for AD, including focal cSS in 33 cases and disseminated cSS in 7 cases; the presence of cSS was associated with lobar CMBs, high-degree centrum semiovale perivasuclar spaces, severe white matter hyperintensities, and a higher prevalence of *APOE* ε4/ ε4 genotype compared with those without [22]. MRI-visible perivascular spaces in the centrum semiovale was reported to be independently associated with AD [23]. Thus, cSS as well as CMBs in patients with AD or cognitive impairment indicate the presence of CAA suggesting future risk of CAA-related ICH and CAA-related contributions to cognitive decline.

Besides these MRI markers of CAA, CSF biomarkers were investigated for CAA-related CMBs in AD patients. Our group reported that CAA-related lobar CMBs in AD patients were associated with significantly lower CSF levels of $A\beta_{40}$ and $A\beta_{42}$ compared with those without CMBs, reflecting the deposition of both $A\beta_{40}$ and $A\beta_{42}$ in the cerebrovasculature [24]. CSF $A\beta_{40}$ levels could be a marker of complication of CAA in AD.

For amyloid imaging, current PET ligands such as PiB and florbetapir cannot discriminate vascular from parenchymal deposition or Aβ from other amyloid proteins. It was suggested that early-phase ^{11}C-PiB occipital/posterior cingulate SUVR ratio in CAA patients are significantly lower as compared to AD [25]; however, it is difficult to differentiate AD with CAA from AD without CAA. We need amyloid imaging specific for vascular Aβ deposition for the diagnosis of Aβ-type CAA in AD patients.

7.3.3 Pathological Studies of Dementia and Cognitive Impairment in CAA

Dementia was noted in 74% of individuals with severe CAA at autopsy, including AD, vascular dementia (VaD), mixed dementia of AD and VaD, and vascular variant of AD characterized by severe plaque-like Aβ angiopathy [26]. A prospective cohort study of aging with neuropsychological tests and pathological investigations indicated that moderate-to-very severe CAA is associated with impaired performance in specific cognitive domains, most notably perceptual speed, which is separate from the effect of AD pathology [27]. Further studies with two longitudinal clinical-pathological studies of aging reported that CAA was an independent contributor to AD dementia, over and above AD pathology and other common age-related neuropathologies such as infarcts and Lewy bodies, and CAA was associated with faster rates of decline in global cognition, perceptual speed, episodic memory, and semantic memory, suggesting that CAA pathology independently and importantly contributes to late-life cognitive outcomes [28]. The association of CAA with a lower level of cognition is relatively stable over time in late-life cognitive decline [29]. It is suggested that CAA is a relatively distinct pathological process associated with adverse cognitive outcomes in old age which is independent of AD pathology and other common age-related neuropathologies such as infarcts and Lewy bodies; other mechanisms may be important to link CAA with late-life cognitive outcomes [28].

7.3.4 CAA-Related Neurodegeneration

CAA-related pathomechanisms other than CAA-related cerebrovascular disorders (hemorrhagic and ischemic lesions) may include CAA-related neurodegeneration. Recent studies suggested CAA-related cortical polionencephalopathy, in addition to leukoencephalopathy (Fig. 7.3).

Our group investigated relationships between CAA-related MBs with cognitive function, gray matter volume, and glucose metabolism in patients with AD using MRI and ^{18}F-FDG PET [30]. The AD patients with CAA-related MBs showed gray matter atrophy in the temporal lobe and cerebellum, and glucose hypometabolism in the temporal lobe, and differences in cognitive profile compared with those without MBs (Fig. 7.4) [30]. Relatively severe leukoaraiosis shown in AD with CAA-related MBs suggested underlying widespread ischemia due to CAA [30]. Preferential involvement (atrophy/hypometabolism) of the temporal lobe in spite of occipital predominance of MBs suggests that the temporal lobe may be susceptible to CAA-induced effects in AD [30].

CAA-related cortical atrophy independent of AD pathology was demonstrated on MRI in patients with hereditary CAA of Dutch type characterized by minimal AD pathology and in patients with sporadic CAA and healthy and AD controls [31]. They also found associations between cortical thickness and vascular dysfunction, measured by BOLD time-to-peak, in patients with hereditary or sporadic CAA; and CAA-related structural lesions, such as lobar MBs or white matter hyperintensity, had no effect on cortical thickness [31]. Incidental cortical MBs in cognitively normal older people are associated with widespread reductions in resting-state CBF assessed by arterial spin labeling of MRI, suggesting the possibility that CAA could result in chronic cerebral hypoperfusion leading to cognitive decline [32]. In addition, reduction of struc-

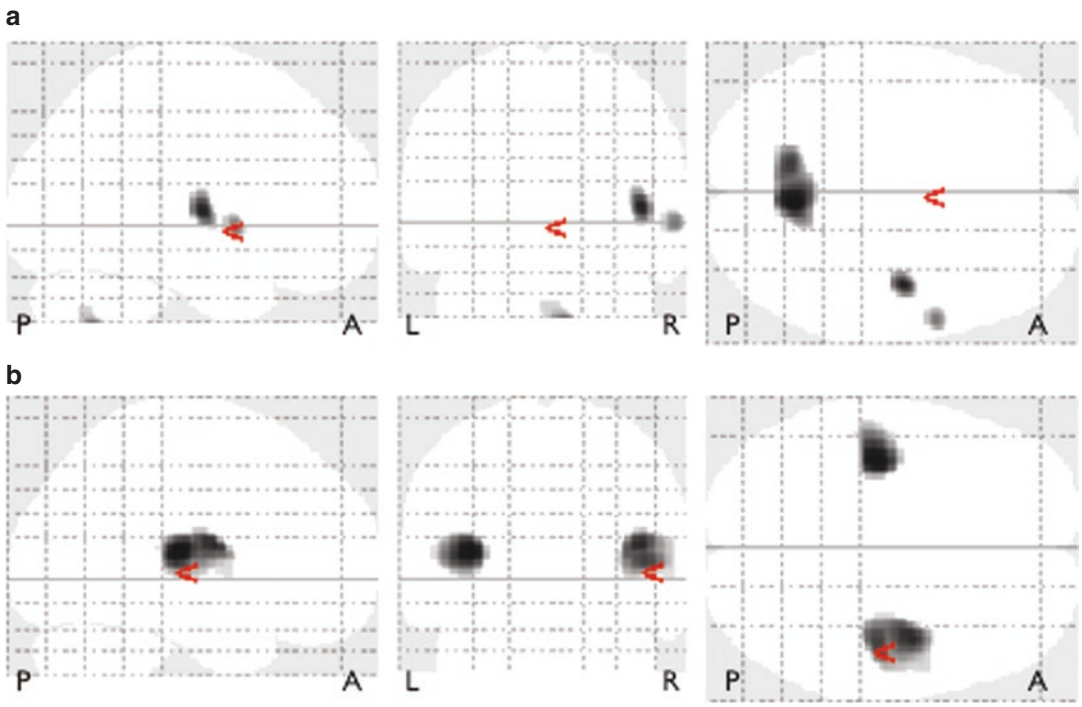

Fig. 7.4 Significantly low gray-matter volume areas (**a**) and significantly reduced ^{18}F-FDG uptake areas (**b**) in the AD patients with CAA-related microbleeds compared with the AD patients without microbleeds. The patients with CAA-related MBs showed gray-matter atrophy in the temporal lobe and cerebellum (**a**), and glucose hypometabolism in the temporal lobe (**b**), compared with those without MBs. See the reference [30] for details. (Height threshold <0.001, uncorrected for multiple comparisons; extent threshold was set to 100 voxels)

tural brain network efficiency, reconstructed from diffusion tensor imaging, was reported in CAA, which might mediate the relationship between advanced CAA and neurologic dysfunction [33].

7.4 CAA-Related Inflammation and Aβ Immunotherapies for AD and CAA

7.4.1 CAA-Related Inflammation

CAA-related inflammation (CAA-ri) or angiitis is characterized by subacute leukoencephalopathy that is treatable with immunosuppressive therapies [4, 34]. The clinical features include subacute cognitive impairment or behavioral change, focal neurological sign, and seizure, and MRI findings show asymmetric T2 or fluid attenuation inversion recovery (FLAIR) hyperintense white matter lesions, in addition to preexisting CAA-related MBs [4]. Based on clinical and MRI features, diagnostic criteria for CAA-ri was proposed [35]; recently, the modified criteria for CAA-ri have been validated with pathologically confirmed inflammatory or noninflammatory CAA cases, giving a good sensitivity and excellent specificity for the probable criteria [36]. The modified criteria include the followings: (1) clinical symptoms, such as headaches or decrease in consciousness, could occur over longer time frames (i.e., chronic, as well as acute or subacute); (2) WMH patterns would be asymmetric and extend to the immediately subcortical white matter (to meet the more stringent criteria for probable CAA-ri) or simply extend to the immediately subcortical white matter (possible CAA-ri); and (3) the appearance of superficial siderosis would be counted as one bleeding manifestation for CAA [36].

Importantly, CAA-ri is associated with an increase in anti-Aβ antibodies in cerebrospinal fluid (CSF) [15]. Patients with CAA-ri showed cortical amyloid deposition with lower retention in swollen areas as well as an increase of anti-Aβ autoantibodies. Elevated CSF levels of anti-Aβ antibodies as well as positive findings of amyloid PET further specify the diagnosis of CAA-ri, requiring further modification of the criteria for CAA-ri.

It should be noted that cerebrovascular amyloid deposition commonly accompanies immune reactions even in the absence of obvious inflammation [34]. CAA would be associated with an immune mechanism in various degrees for Aβ clearance from the vessel walls. In this sense, "CAA-ri spectrum" would range from very slight inflammation with no or scarce clinical or radiological findings to severe inflammation with clinical and radiological findings typical of CAA-ri/angiitis. Further studies are necessary to explore mildly symptomatic or asymptomatic cases of CAA-ri.

7.4.2 Aβ Immunotherapies for AD and CAA

Clinical as well as experimental studies of Aβ immunotherapies for AD or AD models have reported microvascular abnormalities probably related to CAA. Patients treated with Aβ42 immunization for AD (AN1792, Elan) showed a significantly higher frequency of CAA, cortical microhemorrhages, and microvascular lesions than unimmunized AD controls, suggesting that Aβ immunization resulted in solubilization of Aβ42 in plaques, which migrates out of the brain parenchyma via perivascular interstitial fluid drainage pathways, causing an increase in CAA and CAA-related hemorrhages [37]. While, the longest living had a virtually complete absence of both plaques and CAA [37]. In addition, an AD patient in phase 2a of AN1792 presented with a CAA-related ICH. Meningoencephalitis occurred in 6% of patients treated in the AN1792 trial, and perivascular infiltration of lymphocytes was observed around vessels with CAA.

In a phase 2 trial of bapineuzumab, a humanized monoclonal anti-Aβ antibody, amyloid-related imaging abnormalities (ARIA) were reported: vasogenic edema and sulcal effusions (ARIA-E) in 17%, and microhemorrhages and hemosiderin deposits (ARIA-H) in 47% of the patients with ARIA-E [38]. The findings of ARIA were also reported in other clinical trials of Aβ immunotherapies, including phase 3 trials of bapineuzumab and treatment with gantenerumab. In a phase 1b trial of aducanumab for prodromal or mild AD, ARIA was found

in 47% of patients treated with 10 mg/kg aducanumab including symptomatic and asymptomatic cases; ARIA included ARIA-E in 41%, ARIA-H in 6%, and both ARIA-E and ARIA-H in 8% [39]. ARIA-E was dose-dependent and more common in *APOE* ε4 carriers [39], as reported in clinical trials with other anti-Aβ antibodies. APOE has a critical role in the removal of plaques and transport of Aβ to the cerebral vasculature induced by Aβ immunotherapy [40]. Thus, Aβ-targeting therapies may result in vascular permeability changes, inflammation, and disruption of CAA-affected vessels. It was recommended by the Alzheimer's Association Research Roundtable Workgroup that the cutoff value of four MBs should be used for exclusion at baseline in trials of amyloid-modifying therapies for AD.

Importantly, vasogenic edema was noted in 2 of 2762 patients with AD at the baseline of the clinical trial as "spontaneous ARIA"; the MRI findings were compatible with those of CAA-ri although they were asymptomatic [41]. CAA-ri is associated with the presence of anti-Aβ autoantibodies in CSF as discussed above [15]. Thus, CAA-ri/angiitis share common pathophysiology with ARIA induced by Aβ immunotherapies. Further studies are required to elucidate immunological mechanisms underlying CAA-ri/angiitis and Aβ immunotherapy-induced ARIA, which would lead to prediction, prevention, and treatment of these disorders.

Currently, no disease-modifying therapies (DMT) are available for CAA. Anti-amyloid therapies for CAA are under development. For Aβ immunotherapies for CAA, ARIA-like CAA-related events should be carefully avoided. Ponezumab is a humanized monoclonal antibody that binds specifically to the carboxyl terminus of $A\beta_{40}$ and showed beneficial effects on reducing CAA and improving vascular reactivity in an animal model [42]. An acceptable safety profile, including ARIA-like events, has been reported for ponezumab in clinical trials for AD. Ponezumab (PF-04360365) was applied to CAA as a phase 2, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability, pharmacokinetics, and efficacy in adult patients with probable CAA-related hemorrhages (NCT01821118); ponezumab was safe and well-tolerated, but the treatment effect of ponezumab on CAA was opposite to the hypothesized direction [43].

7.5 Transmission of Aβ Pathology and CAA

Many experimental studies have established prion-like transmission of Aβ and other proteins related to neurodegenerative diseases such as tau and α-synuclein; induction of cerebral Aβ deposition in APP transgenic mice has been reported by inoculation with intracerebral injection of brain homogenates from AD patients or AD animal models, through the Aβ-contaminated steel wires, by peripheral (intraperitoneal) inoculation with Aβ-rich brain extracts, and by intracerebral injection of synthetic Aβ peptide (see review [44]). Furthermore, Aβ-type CAA and plaques were induced in primates (marmosets) intracerebrally injected with brain homogenates containing Aβ after very long incubation period.

Human-to-human transmission of Creutzfeldt–Jakob disease (CJD) has occurred through medical procedures resulting in iatrogenic CJD (iCJD). Two major causes of iCJD are (1) peripheral (intramuscular) injection of human cadaveric pituitary-derived growth hormone (hGH) to treat growth hormone deficiency, and (2) grafting of human cadaveric dura mater for neurosurgical procedures. Since 1985, 226 cases of CJD in hGH recipients (until June 2012) have been reported in several countries with the largest numbers of cases occurring in France and the United Kingdom. Dura mater graft-associated iCJD (dCJD) has been found in similar number of cases (n = 228, until June 2012), of which about two-thirds have been reported from Japan (n = 153, until February 2017).

Aβ accumulation in the central nervous system has been reported in both hGH-iCJD and dCJD. Jaunmuktane and his colleagues evaluated eight autopsied patients with hGH-CJD aged 36–51 years, and found that four of them had moderate to severe Aβ pathology in the gray matter and blood vessels (CAA) [45], showing significantly higher severity of CAA and cortical Aβ deposition in hGH-CJD compared with age-matched control patients with prion diseases;

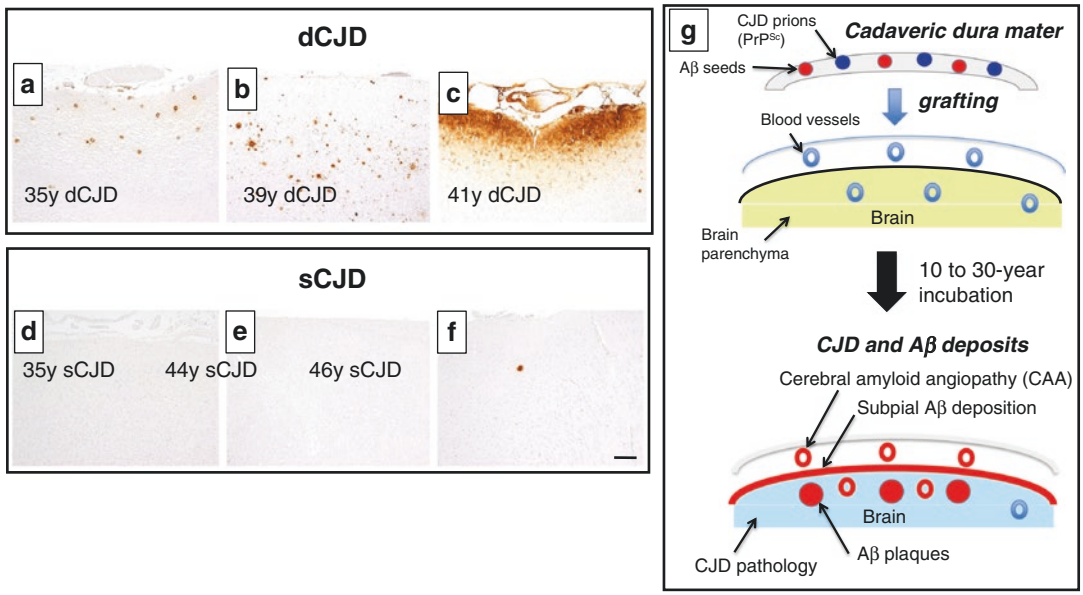

Fig. 7.5 (**a**–**f**) Deposition of Aβ in the brain from patients with dura mater graft-associated CJD (dCJD) (**a**–**c**) and sporadic CJD (**d**–**f**). Immunostaining for Aβ suing anti-Aβ antibody (4G8, monoclonal) in the cerebral cortices of representative cases aged younger than 50 years at autopsy. Parenchymal, subpial, and vascular Aβ deposition is observed in younger dCJD cases (**a**–**c**), while Aβ deposition is scarce in younger sCJD cases (**d**–**f**). Quantitative comparison between dCJD and sCJD with statistical analyses are shown in the reference [47]. Bar = 200 μm. (**g**) A scheme for transmission of Aβ seeds as well as CJD prions via grafting of cadaveric dura mater. Dura mater contaminated with both CJD prions and Aβ seeds was grafted on the brain surface. After 10–30-year incubation, CJD developed with Aβ deposits. Aβ deposition affected more superficial portions of the brain, such as subpial Aβ deposition and meningeal CAA, suggesting direct propagation from the contaminated dura mater

they also reported Aβ deposition in pituitary from patients with high Aβ load in the brain [45]. Furthermore, Ritchie et al. reported Aβ accumulation in 5/12 hGH recipients who died from causes other than CJD, as well as in 18/33 hGH-iCJD patients, indicating that Aβ in the pituitary gland had a seeding effect in the brain of about 50% of all hGH recipients, regardless of whether CJD had developed [46]. Aβ seeding can occur without abnormal prion protein.

Regarding dura mater graft-associated cases, we investigated deposition of Aβ, phosphorylated tau (p-tau), phosphorylated α-synuclein, and phosphorylated transactive response DNA-binding protein of 43 kDa (TDP-43) (p-TDP-43) in 16 Japanese patients with dCJD compared with 21 age-matched patients with sporadic CJD (sCJD) [47]. Subpial Aβ deposition and meningeal CAA in the patients with dCJD were significantly more severe than those in sCJD, and that subpial Aβ deposition and meningeal CAA showed significant positive correlations with incubation period between dura mater graft and death, although there was no significant correlation between the severity of subpial Aβ deposition or meningeal CAA and the age at death or the duration of CJD (Fig. 7.5a–f). The results are consistent with those of our experimental study with intracerebral injection of Aβ seeds to APP transgenic mice at different age, in which the incubation period (the presence of Aβ seeds), but not the age of the host per se, is critical to the initiation and spread of Aβ aggregation in the brain [48]. In addition, there were no differences in p-tau, p-α-synuclein, or p-TDP-43 between dCJD and sCJD cases. Another study with dCJD cases from Europe reported similar results. Importantly, 13% of 84 dura mater samples (age: 79–89 years) from community-based study had Aβ deposition in the form of CAA or amorphous aggregates, indicating that dura mater is a potential source of Aβ seeds [49].

These data suggest that Aβ pathology, including CAA, could be transmitted from humans to humans

via medical procedures, such as dura mater grafting (Fig. 7.5g) and hGH injection. Importantly, recent reports have described early-onset, non-genetic cases of CAA-related ICH with histories of neurosurgeries in their childhood, suggesting the possibility of transmission of Aβ seeds from contaminated dura mater grafts or surgical instruments leading to clinical onset of CAA-related ICH (see review [50]). Interestingly, intraperitoneal inoculation of Aβ-containing brain extracts to APP transgenic mice resulted in predominantly cerebrovascular amyloid deposition [51]; the peripheral route of Aβ seeding may induce the CAA phenotype, probably related to the transport of Aβ aggregates from the periphery to the brain. Further investigations are necessary to evaluate such events of Aβ seeding and, also, cross-seeding between Aβ and other protein aggregates, as risk for development of CAA as well as AD.

7.6 Future Perspectives

Recent studies have opened novel aspects of CAA in the pathogenesis, pathophysiology, biomarkers, diagnosis, and development of DMT, requiring further studies to understand and overcome CAA. Etiologies of sporadic Aβ-type CAA would be multifactorial, including genetic and nongenetic factors. Age- and AD-related pathomechanisms underlying sporadic Aβ-type CAA need to be further investigated, including disturbance of clearance through periarterial interstitial fluid drainage pathway, possible transmission of CAA-related Aβ seeds, and so on. While, CAA types with single etiologies such as hereditary CAA of Dutch type caused by a point mutation in the APP gene, would be directly linked to pathomechanistic studies and development of DMT for CAA.

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8 Cerebral Autosomal Dominant Arteriopathy with Subcortical Ischemic Strokes and Leukoencephalopathy (CADASIL)

Yerim Kim

Abstract

Of these inherited small vessel diseases, cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy (CADASIL) is the most frequent single-gene disorder caused by the mutations in the Notch3 gene located on chromosome 19p13. This Notch3 gene has 33 exons, but almost CADASIL mutations are clustered in exons 2–24. More than 95% of these mutations are missense mutations and most of which involve gain or loss of cysteine residue. However, despite the debates, novel mutation of R75P, not involving a cysteine residue, was reported in Asian populations, thus broadening the spectrum of CADASIL. The main symptoms include subcortical ischemic events, migraine, progressive cognitive decline, seizure, and psychiatric features. Typical diagnostic criteria of neuroimaging show severe white-matter hyperintensities usually involving anterior part of the temporal lobe and external capsules.

In contrast, previous studies suggested differences in the clinical and genetic spectrum of CADASIL between Asians and Caucasian populations. While exon 4 was the major Notch3 mutation sites in Caucasian population, exon 11 was the most common in Asian population. Although it is unclear that genetic differences might affect the phenotypes in ethnicities, Asian population shows less migraine or seizure, but more intracerebral hemorrhage. Furthermore, especially in patients with R75P mutations, the sensitivity of MRI detecting anterior temporal pole abnormalities was lower.

The terminology of small vessel disease refers to the pathological process that occurs in the small vessels of brain, including small arteries, arterioles, small veins, and capillaries. However, the definition of small vessel disease is not uniform and is used to refer only to the arterial vessels of the brain [1]. There are different etiologies of small vessel diseases and one of the etiological classifications was proposed previously (Table 8.1) [1].

Of these inherited or genetic types, cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy (CADASIL) is the most frequent single-gene disorder of small cerebral arteries caused by the mutations in the Notch3 gene located on chromosome 19p13.

Although its overall prevalence is unknown, a small study from Scotland, UK, announced a prevalence of 4.15 cases per 100,000 [2].

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Table 8.1 Etiologic classification of small vessel diseases of brain [1]

Types	
Arteriolosclerosis	Fibrinoid necrosis, Lipohyalinosis, Microatheroma Microaneurysms, Segmental arterial disorganization
Sporadic and hereditary cerebral amyloid angiopathy	
Inherited or genetic small vessel diseases distinct from cerebral amyloid angiopathy	Cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy, cerebral autosomal recessive arteriopathy with subcortical ischemic strokes and leukoencephalopathy, hereditary multi-infarct dementia of the Swedish type, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes, Fabry's disease, hereditary cerebroretinal vasculopathy, hereditary, endotheliopathy with retinopathy, nephropathy and stroke, small vessel diseases caused by *COL4A1* mutations
Inflammatory and immunologically mediated small vessel diseases	Wegener's granulomatosis, Churg–Strauss syndrome, microscopic polyangiitis, Henoch–Schonlein purpura, cryoglobulinaemic vasculitis, cutaneous leukocytoclastic angiitis, primary angiitis of the central nervous system, Sneddon's syndrome, nervous system vasculitis secondary to infections, nervous system vasculitis associated with connective tissue disorders such as systemic lupus erythematosus, Sjögren's syndrome, rheumatoid vasculitis, scleroderma, and dermatomyositis
Venous collagenosis	
Other small vessel diseases	Post-radiation angiopathy and non-amyloid microvessel degeneration in Alzheimer's disease

However, because many cases would not have been revealed, the actual prevalence of CADASIL could be much higher.

8.1 Molecular Genetic Analysis

Notch3 gene located in chromosome 19p13 encodes a single pass transmembrane receptor with an extracellular domain containing 34 tandem epidermal growth factor repeats (EGFR) (Fig. 8.1a). This Notch3 gene has 33 exons, but almost CADASIL mutations are clustered in exons 2–24. More than 95% of these mutations are missense mutations and over 150 mutations have been reported, most of which involve gain or loss of cysteine residue [3] (Fig. 8.1b).

However, novel mutation of R75P, not involving a cysteine residue, was reported in Asian populations, thus broadening the spectrum of CADASIL [4–6]. At present, there is still debate over whether the R75P mutation also causes CADASIL or not pathogenic polymorphism. Of note, although no evidence is available, previous report evaluating 27 Korean mutation carriers and family members suggest that this is a true mutation for following reasons: index patients had typical clinical and neuroimaging features and some of them showed granular osmophilic granules (GOM) on skin biopsy. Furthermore, family members of patients with R75P mutation often had Notch3 mutations, typical symptoms, and MRI abnormalities, whereas the subjects without R75P mutation, none had typical CADASIL symptoms [4].

Although the clinical phenomenon of CADASIL varies, the clinical suspicion is based on the following main conditions: (1) onset at a young age (fifth to sixth decades); (2) absence of conventional stroke risk factors; (3) frequent lacunar infarctions with progressive white matter changes; (4) typical clinical symptoms such as migraine with aura, subcortical ischemic events, seizure, and cognitive impairment; (5) autosomal dominant inheritance [7]. The flowchart of CADASIL diagnosis is presented in Fig. 8.2.

8.2 Clinical Presentation

The range at onset of clinical symptoms is broad. The main symptoms include subcortical ischemic events, migraine, progressive cognitive decline, seizure, and psychiatric features. The temporal profile of main clinical presentations is presented in Fig. 8.3.

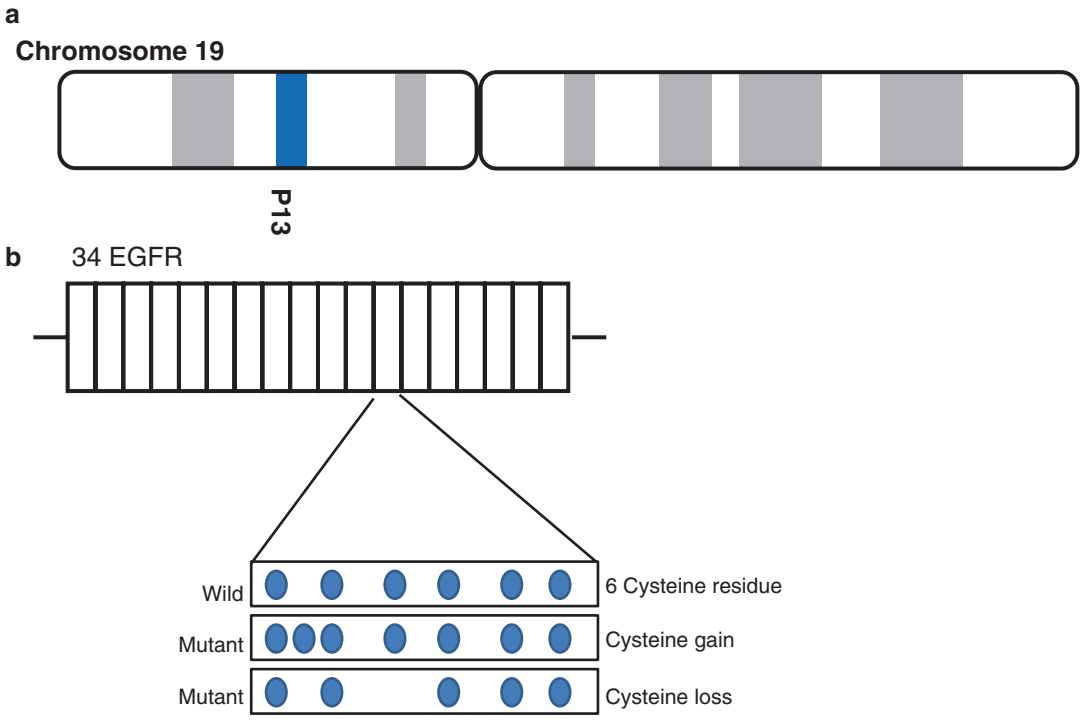

Fig. 8.1 Schematic drawing of Notch3 mutation. (**a**) genetic locus of Notch3 mutation on chromosome 19. (**b**) The epidermal growth factor like repeat (EGFR) and cysteine gain or loss [8]

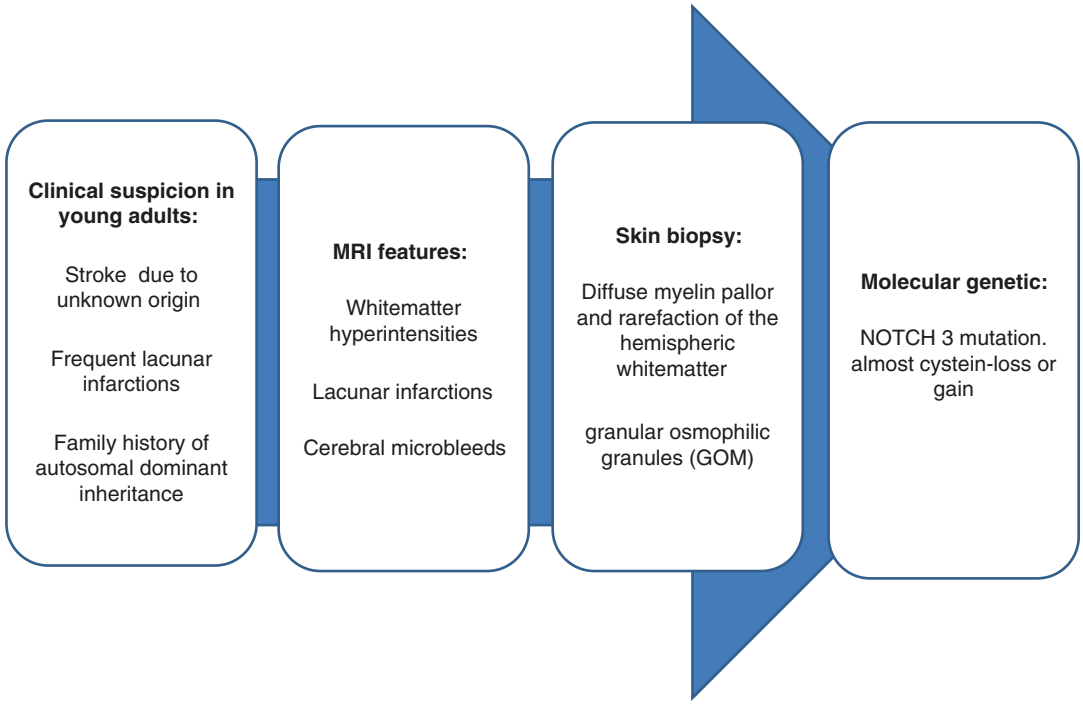

Fig. 8.2 Diagnostic keys for CADASIL

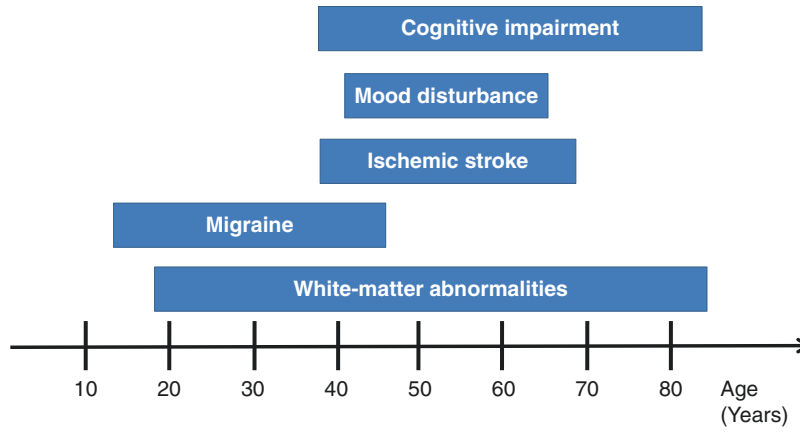

Fig. 8.3 Temporal profiles of the main clinical manifestations of CADASIL

8.2.1 Subcortical Ischemic Stroke

Ischemic strokes and transient ischemic attacks are the most frequent in CADASIL, occurring in approximately 85% of symptomatic subjects. These occur at mean age 45–50 years. Ischemic episodes are almost subcortical and typically present as a lacunar syndrome. In patients with severe subcortical ischemic strokes, diagnosis of CADASIL should be more considered, if there is no conventional risk factor. However, because some risk factors such as hypertension, dyslipidemia, and smoking are often accompanied, it is unclear whether this is associated with coincidental or CADASIL pathology [9, 10].

8.2.2 Intracerebral Hemorrhagic Stroke

CADASIL has been shown typically ischemic form, while intracerebral hemorrhage (ICH) has been rarely reported. Previous single center study in Korean population demonstrated that 25% of 20 consecutively enrolled patients with CADASIL had ICH [5]. It is unclear whether ICH in CADASIL patients developed as a process of diseases associated with specific gene. However, cerebral microbleeds (MBs) have been found in 31–69% of patients with CADASIL [11, 12]. Those might be found in various regions, but frequently found in cortico-subcortical junction, thalamus, and brainstem [5, 11, 13]. Although the exact mechanisms of ICH in CADASIL patients are unknown currently, MBs and antithrombotics might be related to the increased risk of ICH [5, 14].

8.2.3 Migraine

Migraine is often the first feature, generally around 30 years (range from 6 to 48 years). It is reported in approximately 55–75% of Whites, while it is less frequent in Asians [4]. In a recent study in 378 CADASIL patients, a total of 54.5% of subjects had migraine and over four-fifth of these had migraine with aura [15]. By contrast, migraine without aura has the similar frequency in subjects with general population and CADASIL [3].

The exact patho-mechanism leading to increased migraine with aura is not clearly elucidated. One possible explanation is that Notch3 mutations increase susceptibility to spreading depression in cerebral cortex [16]. Another explanation is also possible that this is related to the brainstem region in CADASIL patients.

8.2.4 Cognitive Impairment

Cognitive impairment is the second major symptom of CADASIL. The earliest sign is reduced

processing speed and executive dysfunction, with relative preservation of episodic memory [17, 18]. Executive dysfunction is presented with a mean age of onset of 42 years. Memory impairment was reported later in the disease processing. Cognitive impairment more worsens with aging, and recurrent strokes [17, 18]. It is noteworthy that although cognitive decline is progressive, severe aphasia, agnosia, or apraxia is rarely reported [18].

8.2.5 Other Clinical Manifestations

Seizure has been described in 5–10% of CADASIL patients. It is usually presented with first symptom in a patient without known CADASIL and mainly related to the presence of an ischemic stroke [3, 11, 19].

Mood disturbances are reported in approximately 20% and are generally manifested as severe depressive mood. Because these episodes occur with manic episodes before typical MRI findings, physicians could mistake this for bipolar disease [19].

8.3 Neuroimaging

MRI findings in CADASIL patients shows age- and stage of disease-dependent features. Typical diagnostic criteria of neuroimaging show three types as follows: [1] severe white-matter hyperintensities usually involving anterior part of the temporal lobe and external capsules (Fig. 8.4a, b), [2] lacunar infarctions in centrum semiovale, thalamus, basal ganglia, and brainstem, [3] cerebral microbleeds [20]. Except for some cases, MRI changes may precede the initiation of other clinical symptoms by 10–15 years [3]. Many studies have demonstrated that typical anterior temporal and external capsule involvement could be diagnostic imaging markers for CADASIL [21]. According to a previous report, anterior temporal pole changes had high sensitivity and specificity (approximately 90% for each) and had a higher specificity than external capsular region (approximately 50%) [22, 23]. However, in Asian populations, anterior temporal hyperintensities have been shown less commonly involvement [4, 24].

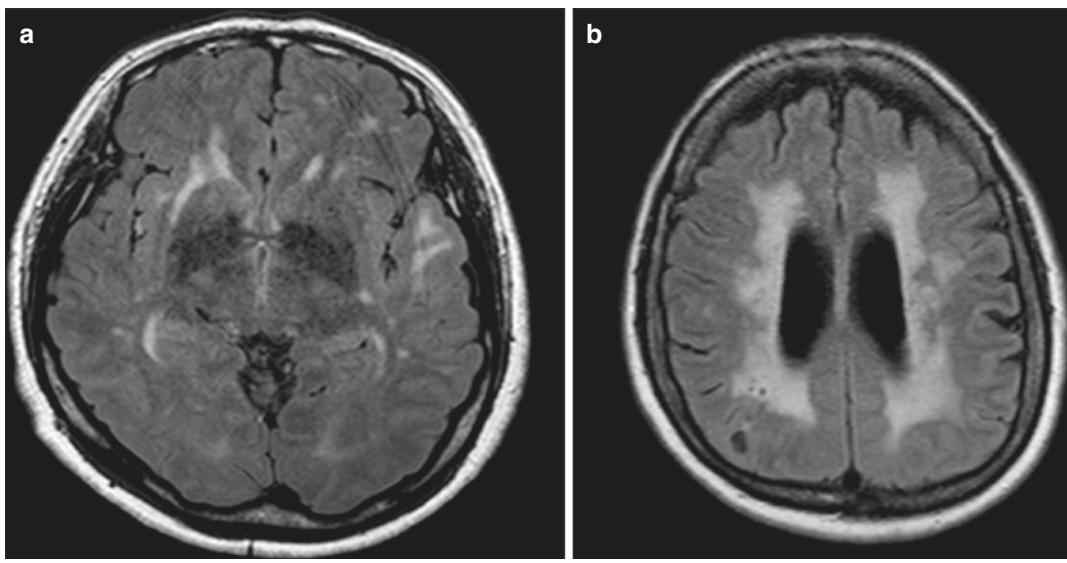

Fig. 8.4 Typical magnetic resonance imaging in CADASIL. (**a**) Hyperintensities in anterior temporal pole and external capsule. (**b**) Severe periventricular white-matter change and microbleeds

8.4 Characteristic Differences Between Caucasians and Asians

Previous studies suggested differences in the clinical and genetic spectrum of CADASIL between Asians and Caucasian populations. In Caucasian population with CADASIL, exon 4 was the major Notch3 mutation sites. Notch3 mutations were clustered in exons 2–6 [21]. While exon 3 is the second most common mutation site in British and French groups, exon 11 is the most frequently involved in Dutch population [21, 25, 26]. However, in Asian population, the most common Notch3 mutation was in exon 11, followed by exon 18, 4, and 3 [5, 24].

The "founder effect" is a special genetic drift, occurring when a small group was split off from the original population and established a new one, thus lost the genetic variation. These phenomenon have been reported in some inland or island areas, e.g., R544C in Koreans [5], R133C in Finland [27], and R607C in Italians [28] (Fig. 8.5).

8.5 Cystein Sparing CADASIL Mutations

Whether cystein sparing variants can cause CADASIL is still debated. However, R75P was described in many Asian families [4–6]. Despite a lot of controversies, based on earlier descried assumption [4], R75P could be considered the best explained cystein sparing Notch3 mutation to date.

Furthermore, recent study identified that another novel cystein sparing Notch3 mutation (D80G) in 4 German families [29]. These data can be considered to provide novel insights on the potential significance of cystein sparing Notch3 mutation.

Although it is unclear that genetic differences might affect the phenotypes in ethnicities, Asian population shows less frequent migraine or seizure. While approximately 40–50% of patients had migraine in Caucasians, only 5–10% of subjects in Asians had migraine [4, 21, 24]. ICH was relatively common in East Asians [24, 30].

Fig. 8.5 Several CADASIL founder mutations [8]

Table 8.2 Available treatment in CADASIL

Symptoms	Treatment
Migraine	Antiepileptic drugs (sodium valproate) Beta blockers Acetazolamide Conventional analgesics
Ischemic attacks	Antiplatelet drugs Treatment for vascular risk factors
Cognitive impairment	Acetylcholinesterase inhibitor

Especially in patients with R75P mutations, the sensitivity of MRI detecting anterior temporal pole abnormalities was lower than in sites where mutations occurred frequently in Caucasians [4, 24]. These results suggest that anterior temporal involvement cannot be a marker for diagnosis of CADASIL, at least in Asians.

8.6 Treatment

At present, there is no effective treatment for CADASIL. Therefore, the goal of treatment is to control clinical symptoms. In Table 8.2, available treatments for clinical presentations were summarized [3, 23].

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Part IV

Clinical Science: Cardioembolism

9 Pathophysiology of Cardioembolism

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Abstract

Cardioembolism is caused by occlusion of the cerebral artery due to a blood clot created by structural and functional abnormalities of the heart. As the world's population ages, the prevalence of cardiovascular disease is on the rise, as is the rate of cardioembolism. Thrombus formation has two mechanisms: first, fibrinogen mediates activated platelets, which causes platelet aggregation and produces white thrombi; and second, clotting factors in the plasma in which the fibrin clot is finally generated through the contact activation and tissue factor pathways, and red thrombi are formed by interlocking red blood cells. The thrombi formed by cardioembolism are red, produced by plasma coagulation, and structurally unstable. Therefore, red thrombi are prone to degradation, and clinical symptoms of ischemic stroke due to cardioembolism tends to fluctuate. Intracardiac thrombi are most common in the appendages of the left atrium and apex of the left ventricle. Atrial fibrillation, the most common cause of cardioembolism, has a higher incidence in men than in women. However, the proportion of elderly women is higher than that of men, so the absolute prevalence of atrial fibrillation is higher for women. In women, atrial fibrillation increases after menopause. Covert atrial fibrillation has been discussed as a leading cause of embolic stroke of undetermined source. Covert atrial fibrillation is more likely to be detected in a longer measurement period. Therefore, devices for long-term electrocardiography measurements are under development. Although related studies are underway, to date, non-vitamin K antagonist oral anticoagulants do not have an advantage over aspirin for preventing stroke recurrence in patients with embolic stroke of undetermined source.

9.1 Introduction

Cardioembolism (CE) accounts for about 20–30% of all ischemic strokes [1], and its proportion is gradually increasing as the population ages. CE tends to have higher neurological severity in the early stages of stroke compared to stroke caused by other mechanisms. Recovery and prognosis are also poor and recurrence rates are higher than other mechanisms [2]. However, if CE is diagnosed with appropriate tests and treated with anticoagulants, stroke can be effectively prevented. This chapter introduces CE, which is growing in importance in the field of stroke. The first part of the chapter describes the molecular and pathophysiological mechanisms

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and features of CE, while the second part addresses specific considerations. This chapter is derived in part from the previously published Stroke Revisited series, Volume 1, "Diagnosis and Treatment of Ischemic Stroke." In addition to the previously described contents, the author has provided additional contents that may be helpful.

9.2 Mechanism of Thrombus Formation in CE

Stroke is the second most common cause of death worldwide. Among them, CE accounts for about 20–30% of all stroke patients, and the proportion is increasing over time [1]. Since CE is caused by clotting of the blood vessels generated by various heart diseases, the mechanism may be complicated. However, within that complexity, there is a basic mechanism of thrombus formation that we will summarize here (Fig. 9.1).

9.2.1 Platelet Aggregation

Thrombocytosis is associated with platelets can be classified into two types according to the involved component. First, we describe the process by which platelets participate. Collagen and tissue factors are located below normal vascular endothelial cells. When collagen and tissue factors under the endothelial cells are exposed to the bloodstream due to atherosclerosis, inflammation, and injury, platelet aggregation begins. Collagen exposed to the blood adheres to platelets through two major anchors: Platelet glycoprotein Ib-V-IX and collagen von Willebrand Factor (vWF) bind to each other (anchor 1), while platelet glycoprotein VI interacts with collagen directly (anchor 2). Through this process, collagen and platelets bind tightly. In particular, glycoprotein VI plays an important role in platelet activation and granulation during early thrombus generation. GpIIb/IIIa, located on the membranes of activated platelets, is modified by disulfide

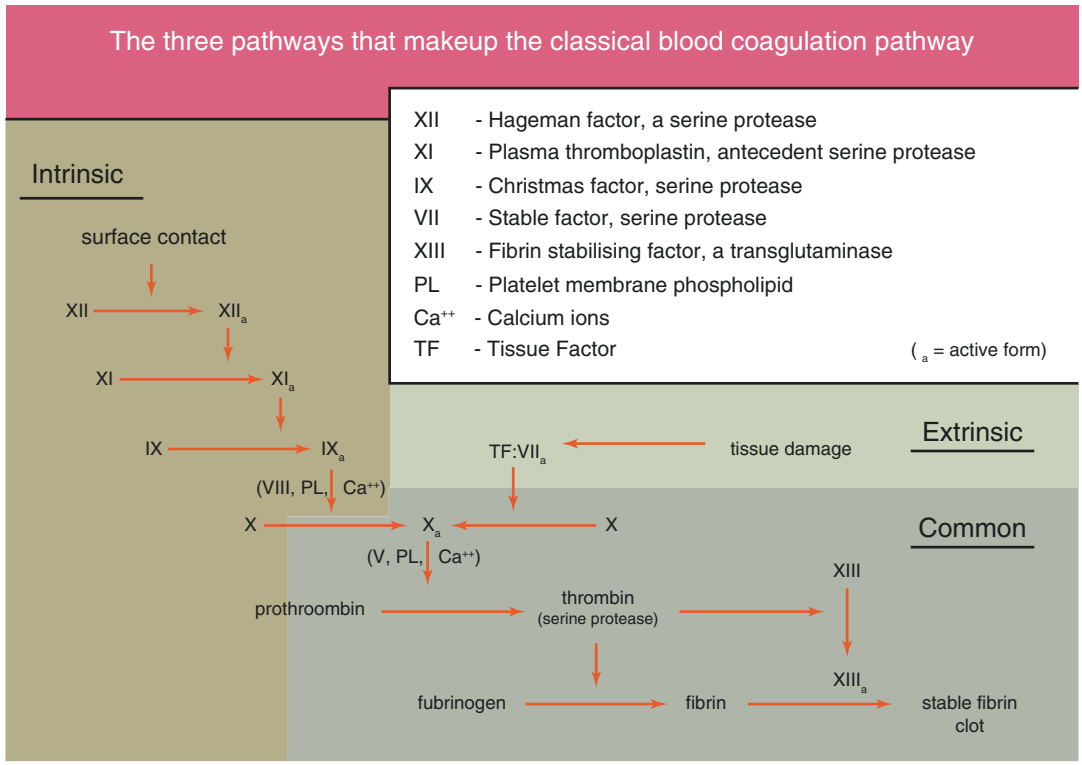

Fig. 9.1 Cascade of blood coagulation

isomerase. This increases the affinity for fibrinogen and vWF, allowing platelets to aggregate. On the other hand, the activated granules secrete alpha granules and dense granules to the outside. In particular, dense granules contain adenosine diphosphate (ADP) and calcium ions. ADP is further attached to P2Y1 or P2Y12 receptors on platelets to further promote platelet activation.

The next consideration is tissue factors, which exist in two main forms and are inactivated in the blood vessel wall but activated in the endothelial cells. Inactive tissue factors in the vessel wall are activated by protein disulfide isomerase. Tissue factors activated by isomerase complex with factor VIIa in the blood, which activates factor IX. Thereafter, various coagulation factor cascade and thrombin are activated. Thrombin plays an important role in fibrin production of the plasma coagulation mechanism described later and breaks down the activated receptor 4 of platelets, thereby activating platelets. Activated platelets secrete ADP, serotonin, and thromboxane A2 to activate other platelets. This series of processes leads to fibrinogen-mediated platelet aggregation. In blood vessels that are narrowed or occluded by arteriosclerosis or damaged, platelets are mainly involved in blood clot formation. Platelet-rich clots produce white thrombi that reflect platelet color.

9.2.2 Coagulation Cascade

The next mechanism to be examined is the plasma coagulation process involving various coagulation factors in the plasma. Here the contact activation and tissue factor pathways are activated, and these two processes converge to factor X via the coagulation factor cascade. After thrombin and fibrin activation, a stable thrombus is formed.

9.2.2.1 Contact Activation Pathway (Intrinsic Pathway)

Initiation of the contact activation pathway begins when high-molecular-weight kininogen and prekallikrein meet factor XII. As they become complexes, prekallikrein is converted to kallikrein, which converts factor XII to factor XIIa. Activated factor XIIa in turn activates factor XI and factor IX. Factor IX activates Factor X as Factor Xa with the help of a complex consisting of Factor VIII, platelet membrane phospholipid, and calcium ions. In this process, Factor XII is the starting point of the contact activation pathway; if it is deficient, the activated partial thromboplastin time becomes prolonged.

9.2.2.2 Tissue Factor Pathway (Extrinsic Pathway)

Tissue factor pathways are important for rapidly generating thrombin through feedback. Tissue factors are involved in the initiation of the pathway and distributed in fibroblasts, pericytes of the epicardium, and smooth muscle cells of blood vessels. The pathway begins when disulfide isomerase secreted from activated endothelial cells or platelets breaks down disulfide bonds of tissue factors. Tissue factors without disulfide bonds are activated and then complexed with factor VII. This complex converts Factor X to Factor Xa. Through this cascade of processes, the tissue factor pathway converges to Factor Xa along with the contact activation pathway described above.

From this point forward, the hemostatic process leads to a common pathway. Activated Factor Xa complexes with Factor V, phospholipids, and calcium ions to convert prothrombin to thrombin. Thrombin then converts the fibrinogen into fibrin, which becomes entangled to form a stable fibrin clot. Thrombin, on the other hand, acts directly on fibrinogen and activates Factor XIII, which also has a bypass pathway that promotes fibrin clot production. Thrombin can independently stimulate Factors V and VIII, causing rapid thrombin production.

9.2.3 Other Factors Involved in Blood Coagulation

The cofactors and modulators involved in the coagulation process participate in a series of processes from the beginning to the end of the coagulation process and play an important role in

maintaining overall homeostasis. The first cofactor to mention is calcium and phospholipids, the cell membrane components of platelets. The two cofactors participate in the formation of complexes involving Factors VIII and IX as well as in the complexes of Factors V and X and form thrombin. Vitamin K's role is also essential. Vitamin K acts as a coenzyme of hepatic gamma-glutamyl carboxylase and helps gamma-glutamyl carboxylase attach carboxyl groups to Factors II, VII, IX, and X and proteins C, S, and Z, which participate in the progression and termination of the coagulation process. Vitamin K acts as a coenzyme and oxidizes; vitamin K epoxide reductase is the enzyme that reverses it. Warfarin, which is widely used for its anticoagulant effect, exhibits this effect by inhibiting vitamin K epoxide reductase.

Let us examine the cofactors. Protein C acts as an anticoagulant and is activated by the thrombin and thrombomodulin complexes. Activated protein C degrades factors V and VIII with the help of protein S and phospholipids. Therefore, patients who are naturally deficient in protein C or S are more likely to develop blood clots. Antithrombin acts as a serine protease inhibitor to inhibit thrombin as well as factors IX, X, XI, and XII. Tissue factor pathway inhibitors inhibit tissue factors and interfere with the coagulation mechanisms mediated by tissue factors. Plasmin regulates the coagulation process by breaking down fibrin into a fibrin degradation product. Plasmin is made from plasminogen, which is catalyzed by tissue plasminogen activator (tPA). Artificially synthesized recombinant tPA is useful for thrombolysis in patients with acute ischemic stroke. And finally, prostacyclin inhibits granule secretion associated with platelet activity.

9.2.4 Blood Coagulation and CE

Several cardiovascular diseases can cause CE, but the underlying cause is stagnant blood flow caused by heart disease [3]. When blood flow is slowed by cardiovascular disease, a core of red blood cells is temporarily formed in the heart. Once the erythrocyte core is created, various coagulation factors are involved to activate the blood coagulation process. This process causes fibrin to bind to red blood cells, which rarely involves platelets, producing a red blood cell-rich "fibrin meshwork (red thrombi)" [4]. As such, intracardiac thrombi are produced by coagulation cascades rather than platelet aggregation. However, as described earlier, coagulation factors, including tissue factors, are also involved in the process of inducing platelet aggregation. Although not as effective as anticoagulants, this means that antiplatelet agents may also have some ability to prevent CE.

Another consideration in CE is the fact that the distribution of coagulation factors in the stroke of stroke patients due to atrial fibrillation (AF) is abnormal. Related studies reported increased fibrin turnover in patients with acute or chronic AF [5, 6]. Patients with AF have prothrombotic index abnormalities, and some prothrombotic indexes have been identified only in AF or paroxysmal AF [7, 8]. However, past studies were sporadic, and the rationale for supporting such studies remain insufficient. The authors reviewed the relevant reports and summarized the mechanism by which coagulation factor distribution differs from normal in AF patients. First, long-term AF causes endocardial damage and structural remodeling. Structural changes in the endocardium cause dysfunction of the various coagulation factors that work in association with it, which promotes blood clot production [2]. As mentioned earlier, cardiac dysfunction, such as AF, interferes with normal blood flow, which leads to abnormal distribution of coagulation factors such as D-dimer, thereby promoting thrombus formation. Blood clotting factor abnormalities in cardiovascular disease, including AF, are an essential topic for elucidating the key mechanisms of CE, which should be clarified through ongoing research.

9.3 Features of CE

CE differs from stroke due to atherosclerotic thrombosis, with the most severe neurologic deficits at the time of stroke and often a dra-

matic improvement in symptoms. This property is closely related to the thrombus component produced in the heart. Intracardiac thrombi are red thrombi containing few platelets. In contrast, the thrombi produced by atherosclerotic vessels are platelet-rich and white. Unlike white thrombi, red thrombi are unstable and easily decomposed because few platelets play a role in structural stabilization. That is, even if the intracardiac thrombus occludes the cerebral artery, the blood vessels are often reopened due to high blood pressure and proximal blood flow. At this time, if the blood vessels are quickly reopened before ischemic tissue damage is caused by the thrombus, the patient's symptoms may be rapidly improved. However, if a vessel is opened after a period of time after the tissue is damaged, hemorrhage or hemorrhagic transformation may occur in the damaged tissue, which may worsen the patient's symptoms. Therefore, it is reasonable to suspect CE if the patient's symptoms improve sharply after a stroke or if hemorrhagic or hemorrhagic transformation is identified by brain computed tomography (brain CT) or magnetic resonance imaging (MRI).

Intracardiac blood clots tend to affect specific areas (atria and ventricles) depending on their location. First, in the atrium, it is likely to occur in the left atrial appendage, a tissue attached to the atrium with a narrow entrance and a long internal structure. This structure slows the internal circulating blood flow, increasing the chance of thrombus formation [9]. In the ventricles, thrombus is often produced in the apex of the left ventricle. In particular, left ventricular (LV) aneurysm or acute myocardial infarction are associated with further blood flow impediments, increasing the chance of blood clots. The risk of thrombosis is highest at the time of acute myocardial infarction and then gradually decreases.

AF, an important cause of CE, differs between the sexes. In a study of North American and European populations, males showed a 1.5–2 times higher incidence of AF than females; the incidence increases with age in both sexes. Prevalence was also reported to be higher in males than females [10]. Nevertheless, women have a longer life expectancy than men, so the absolute figure is higher for them. This trend is evident in North America and Europe but not in Asia (0.78% for males and 0.76% for females) [11]. The prevalence of AF has increased more than in the past. According to the Minnesota study, the incidence of AF has increased in both men and women since the 1980s at rates that were similar in men and women [12]. Although there is a difference according to the study, the actual frequency of CE was higher in women. This is because the prevalence of AF in women after menopause is higher than that in men. The effects of AF on stroke incidence also vary by sex. If a woman has AF, the risk of stroke is higher than that for men [13].

9.4 Noteworthy CE Points

CE is caused by clogging of the cerebral artery due to structural and functional abnormalities of the heart. CE has various causes that are classified into high risk and medium to low risk according to the degree of contribution. High risks include AF, mechanical prosthetic valve, left atrial thrombus, left ventricular thrombus, and dilated cardiomyopathy. Medium to low risks include patent foramen ovale, atrial septal aneurysm, mitral valve prolapse, and congestive heart failure. Although CE usually comes to mind only AF, as mentioned above, AF is one of its several causes.

The ESUS (embolic stroke of undetermined source) is a new concept proposed in 2014 that refers to non-lacunar strokes among cryptogenic strokes where the specific cause of stroke is unknown [14]. As the term suggests, the cause is unknown but suggests an embolic source. ESUS accounts for about 17% of all ischemic strokes [15], but the cause is unknown and there has been disagreement among researchers regarding its diagnosis and treatment. Recently, covert AF, one of the causes of CE, has attracted attention as the underlying cause of ESUS. Covert AF is a condition in which AF occurs shortly, but it

was not confirmed by cardiac rhythm examination, but in reality, AF occurs intermittently. Past studies reported that intermittent AF occurs at the same level of thromboembolic complications as sustained AF [16]. This suggests that the presence of AF is more important than duration. If a patient has covert AF but the doctor has not diagnosed it, the patient may not be adequately treated, which may increase the likelihood of stroke recurrence. On the other hand, if covert AF is found, appropriate treatment may effectively prevent secondary stroke. However, 24-h Holter monitoring, which is commonly used to monitor heart rhythm in stroke patients, has difficulty identifying covert AF. Instead, a study of 149 patients with ischemic stroke or TIA reported a higher probability of finding covert AF as the test duration increased. Electrocardiography at admission (2.7%), echocardiography (4.1%) within 5 days, 24-h Holter monitoring (5%), and recorder (5.7%) for 7 days [17]. Studies such as the CRYSTAL AF and EMBRACE have also shown that long-term electrocardiographic monitoring is useful for covert AF detection. Recently, a device for monitoring the heart rate by attaching it to a mobile phone or a smart watch has been developed, and an implantable loop recorder that can be monitored for several years by implanting the device in the body has also been developed (Figs. 9.2 and 9.3).

As the importance of covert AF emerges and related research continues, the American Heart Association guideline recommends prolonged rhythm monitoring for up to 30 days. A recent large-scale study compared the secondary prevention effect of NOAC and aspirin in patients with ischemic stroke classified as ESUS [18, 19].

Fig. 9.2 REVEAL XT and Reveal LINQ, Medtronics' implantable loop recorder

Fig. 9.3 KardiaMobile EKG Monitor from AliveCor, capable of measuring heart rhythm in conjunction with a smartphone

Two studies of dabigatran and rivaroxaban showed no advantage over aspirin, and apixaban studies are ongoing. We should wait for one more study, but we can estimate that ESUS is temporarily overcoagulated by other causes than AF, including covert AF, and that NOAC may not effectively suppress it.

9.5 Conclusions

CE has a poor prognosis compared to stroke due to other mechanisms, and the prevalence of CE is increasing due to the global aging trend. The social interest in CE is ever higher. There are also more opportunities for neurologists to confront CE patients. In recent years, the CE treatment paradigm has also shifted rapidly from warfarin to NOAC. To keep pace with these increased social concerns and rapid changes in care practices, it is time for neurologists to pay more attention to CE and consider it carefully to ensure proper diagnosis and treatment.

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10 Atrial Fibrillation and Other Cardiac Dysfunctions Related with Stroke

Woo-Keun Seo

Abstract

Cardioembolic stroke is caused by embolus originating from the heart or aorta. Of all cardioembolic stroke cases, about a quarter are ischemic stroke cases. The clinical features and neuroimaging findings of cardioembolic stroke make differences from other stroke subtypes due to the peculiarity of pathogenesis. Among the causes of cardioembolic stroke, atrial fibrillation is the most frequent and important disease. Stroke patients with atrial fibrillation have severe neurological symptoms and should be managed differently from patients with other types of ischemic stroke. The importance of atrial fibrillation-related stroke has recently been highlighted as the use of newer oral anticoagulants has been introduced. In this chapter, recent trends of diagnosis and treatment for stroke patients with atrial fibrillation, as well as other cardiac dysfunctions related to stroke, will be discussed.

10.1 Introduction

Stroke is a set of clinical syndromes characterized by acute or rapidly progressive focal neurological symptoms originating from diseases of cerebral vessels. Cerebral vascular diseases that cause stroke include atherosclerosis, small vessel occlusion, and cardioembolism. Strokes from different the etiologies have different clinical features, risk factors, and outcomes. In addition, therapeutic strategies also differ according to etiologic mechanism. In that context, cardioembolic stroke has peculiar features from other types of stroke.

Cardioembolic stroke is an ischemic stroke subtype characterized by cortical infarction, sudden onset and rapid regression of symptoms, and simultaneous multiple territorial infarctions [1]. It is responsible for approximately 20% of ischemic stroke cases [2]. The proper diagnosis of cardioembolic etiology in acute stroke patients has become a pressing issue after the introduction of newer oral anticoagulants (NOACs) and with the advancement of reperfusion therapy using endovascular thrombectomy. Unlike other stroke subtypes, the potential source of cardioembolism (PSCE), which is originated from the outside of the brain, is the cause of cerebral arterial occlusion. Among the PSCE, atrial fibrillation (AF) is the most frequent type, and its importance is increasing with the aging of the population [3]. AF accounts for >70% of cardioembolic stroke cases [4], and AF patients with prior stroke or TIA carry even higher stroke

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risks [2]. Although NOACs are rapidly replacing vitamin K antagonists and reduce the risk of stroke, the risk of stroke in patients with AF is still considerably high.

However, the diagnosis of cardioembolic stroke is still a matter of concern. Approximately one-fourth of those with ischemic stroke is a stroke of an undetermined cause despite thorough investigations, including laboratory tests, brain imaging (cerebral computed tomography [CT]/magnetic resonance imaging [MRI]), MR/CT angiography, and cardiac workup [5]. Considering that the primary etiology of cryptogenic stroke is thromboembolism [6], "embolic strokes of undetermined sources (ESUS)" is a more clinically compatible and suitable definition that imparts a significance to the presence of potential embolic sources [7]. Moreover, AF is considered the major cause of stroke in ESUS. It is important to detect undiagnosed (or paroxysmal) AF in patients with ESUS because patients with AF are recommended to receive oral anticoagulant (OAC) treatment, whereas most patients with other stroke types are usually treated with antiplatelet agents.

Therefore, in this chapter, the clinical importance of AF in stroke prevention will be discussed with an emphasis on the detection of AF in stroke patients. In addition, several other cardiac diseases associated with the incidence of stroke will be discussed.

10.2 Diagnosis and Treatment of Stroke Patients with AF

10.2.1 Stepwise Diagnostic Approach to Detect AF in Stroke Patients

10.2.1.1 Initial Step: History Taking

A stepwise diagnostic approach for cardioembolic stroke was presented in Fig. 10.1. In stroke patients, an essential step is to check for the presence of AF from the early period after the onset of stroke to provide proper management. However, the detailed process for the detection of AF differs according to the clinical situation and pathway in each hospital. In acute stroke patients who are candidates for reperfusion therapy, baseline electrocardiography (ECG) assessment is being recommended [8]. However, the more important step to obtain information about the presence of AF is history taking.

In acute stroke patients who are candidates for reperfusion therapy using intravenous tissue plasminogen activator (t-PA), previous OAC use is an exclusion criterion. Before the era of NOACs, the OAC effect of vitamin K antagonists was estimated with prothrombin time measurement. However, unfortunately, no reliable and clinically applicable measures have been established for the anticoagulant activity of NOACs, until now. Furthermore, about half of patients with AF among those with ischemic stroke have paroxysmal AF, which can be omitted from detection on baseline ECG in the emergency department. Therefore, detailed history taking is crucial to avoid the use of t-PA in orally anticoagulated patients.

10.2.1.2 Second Step: Suspecting Stroke with AF

As AF is the most important cause of cardioembolic stroke, AF-related stroke shares clinical features and findings on brain imaging with cardioembolic stroke. According to the TOAST (Trial of Org 10,172 in Acute Stroke Treatment) classification, diagnosis of cardioembolic stroke is based on cortical or cerebellar dysfunction with the exclusion of lacunar syndrome, lesions >1.5 cm in size, absence of cerebral arterial stenosis, and presence of a cardiac source of emboli [9]. In detail, cerebral dysfunction in cardioembolic stroke includes sudden onset to the maximal neurological deficit or rapid progression of symptoms; frequently accompanying cerebral cortical symptoms such as visual-field defects, aphasia or neglect, and rapidly improving neurological deficits related to early spontaneous recanalization in some instances; and altered consciousness [1]. Wallenberg's syndrome, cerebellar infarct, and top-of-basilar syndrome are the common clinical features in cardioembolic stroke involving the posterior circulation [1, 10, 11]. Moreover, when the lacunar syndrome is

present, the possibility of cardioembolic origin is low. Besides, seizure or headache at stroke onset, which were suggested as unique features of cardioembolic stroke, are not specific to cardioembolic stroke [1].

More sophisticated approaches to suspect stroke with AF have been made using statistical models. Seo et al. reported that they predicted the presence of AF among acute stroke patients by using a model composed of clinical, neuroimaging, and biomarker variables [12]. The model included age, left atrial size, free fatty acid level, triglyceride level, susceptibility vessel sign, hemorrhagic transformation, and cortical involvement as variables and showed a C-statistic value of 0.908. A similar approach was made to distinguish etiologic mechanisms among patients with ESUS [13]. In this model, clinical and neuroimaging findings were used for the prediction of etiology. Stroke caused by paroxysmal AF had a higher National Institutes of Health Stroke Scale (NIHSS) score at baseline and larger lesion volume.

10.2.1.3 Third Step: Baseline ECG, Telemonitoring, 24-h Holter Monitoring, and Long-Term Monitoring

AF is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with a resulting deterioration of atrial mechanical function [14]. ECG diagnosis of AF is based on the disappearance of consistent P waves, which are replaced by rapid oscillations or fibrillation waves. The diagnosis of AF is based on the findings from the documented 12-lead ECG, telemetric, or implantable long-term recordings. Current guidelines recommend ECG monitoring for at least 24 h after a stroke [15]. However, the need for the extended periods of monitoring is controversial. In a meta-analysis that assessed the stepwise approach to detect AF in stroke patients, 23.7% of the patients had AF at the final step [16]. In this study, four sequential steps were suggested to improve the detection of AF in stroke patients as follows: baseline ECG, in-hospital ECG monitoring, first ambulatory Holter monitoring, and additional long-term monitoring. Each step improved the detection rate of AF. The first step was admission ECG, which revealed post-stroke AF in 7.7% of the patients. In-hospital ECG tests such as serial ECG, continuous inpatients cardiac telemetry, and in-hospital Holter monitoring can increase the detection rate by 4.2%. If ambulatory Holter monitoring is added to the test, 7.5% of new AF cases can be detected. Finally, additional long-term cardiac monitoring, including outpatient telemetry, external loop recording, and implantable loop recording can detect an additional 4.3% of AF patients. This stepwise approach can improve the detection rate for hidden AF in patients with paroxysmal AF.

As described in the earlier section, a considerable proportion of stroke patients have no confirmatory etiology and are often classified as having a cryptogenic stroke or stroke of undetermined etiology with a negative evaluation result. Recently, ESUS is replacing cryptogenic stroke [17]. In patients with ESUS, the main etiologic disease is speculated to be paroxysmal AF. The most promising method for detecting paroxysmal AF is long-term ECG monitoring using an implantable loop recorder. Its superiority in detecting AF in cryptogenic stroke was validated in the Cryptogenic Stroke and Underlying AF trial [18]. In this randomized controlled trial, 441 stroke patients without AF on 24-h ECG monitoring were divided into an implantable cardiac monitoring group and a conventional evaluation group. The implantable cardiac monitoring group showed a 6.4-fold improvement in AF detection rate as compared with the conventional evaluation group. However, the overall detection rate by 12 months was only 12.4%, which is unexpectedly low. Several case series about long-term ECG monitoring using implantable cardiac monitoring devices showed a similar yield [19].

10.2.2 Neuroimage and Blood Biomarkers of AF-Related Stroke

10.2.2.1 Imaging Biomarkers

Brain images also provide important clues for the diagnosis of cardioembolic stroke. Various imaging modalities are used to assess the etiology of stroke. The most well-known feature of

brain images in cardioembolic stroke is bihemispheric involvement or simultaneous multiple infarcts in multiple territories [1]. In fact, many researchers tried to distinguish embolic stroke from stroke of other causes. However, a simple topographic distribution of infarction was insufficient to differentiate cardioembolic stroke from stroke associated with atherosclerotic occlusion [20]. However, the recent advances in brain imaging technology, such as diffusion-weighted imaging (DWI) are useful to differentiate stroke etiologies. Kang et al. analyzed topographic patterns on DWI in acute stroke patients and reported that a single cortico-subcortical lesion and multiple lesions in multiple territories suggested cardioembolic stroke [21]. However, even with DWI, differentiation between AF-related embolic stroke from the stroke of other embolic sources is not reliable [22].

Noninvasive imaging modalities for evaluating intracranial cerebral arteries improved our understanding of stroke etiology. Early recanalization strongly suggests a cardioembolic stroke.

Another well-known imaging feature of cardioembolic stroke is hemorrhagic transformation [1]. Over 70% of cardioembolic stroke patients experienced hemorrhagic transformation, whereas only 20–40% of all stroke patients did [1]. CT is the first classic modality to identify hemorrhagic transformation. The severity and extent of hemorrhagic transformation in acute stroke are closely related to the clinical outcome and treatment plan for antithrombotics (especially in the case of OAC use). Therefore, quantitative measurement of the severity of hemorrhagic transformation is greatly important, and several grading systems have been developed and used [23]. Gradient echo (GRE) imaging is a new modality that can provide better sensitivity for the detection of hemorrhagic transformation than CT.

Cardioembolic stroke occurs when an arterial embolus originating from the heart or aorta occludes the cerebral artery. Sometimes, the embolus stuck in the cerebral artery can be visualized on brain imaging. The classic "hyperdense middle cerebral artery (MCA) sign" is well known to suggest emboli in the MCA. Red thrombi mainly composed of red blood cells (or hemoglobin) have a higher Hounsfield unit count and appeared as a brighter MCA than the contralateral MCA on cross-sectional non-contrast-enhanced CT imaging [24]. The clinical significance of this sign is that red clots are readily recanalized by thrombolytic agents [25]. GRE imaging is useful for the detection of thrombus as a characteristic dark black signal within the arterial lumen with a blooming artifact [26]. This sign, so-called "susceptibility vessel sign," has a characteristic larger diameter than the contralateral vessel diameter and a tram-like two-layered vessel sign [27]. Figure 10.2 demonstrates the image findings of acute cardioembolic stroke.

In addition, many researchers are investigating the application of artificial intelligence or deep learning technique using clinical and imaging data to predict stroke occurrence, diagnose etiology, and predict outcomes [28]. For example, an artificial intelligence-based approach had been made to distinguish clots of AF and non-AF causes on the basis of dark signals on GRE imaging in acute stroke patients.

10.2.2.2 Blood Biomarkers of Cardioembolic Stroke and AF-Related Stroke

Blood biomarkers are also important targets for investigation in this field. However, most surrogate markers for cardioembolic stroke were nonspecific for cardioembolic or AF-associated stroke [29]. In contrast, biomarkers of AF have specific targets, such as altered hemodynamics, atrial dilatation, myocyte damage, atrial fibrosis, electrical remodeling, prothrombotic state, or impaired cardiac function [30].

The most popular biomarker specific to cardioembolic stroke or AF-associated stroke is brain natriuretic peptide (BNP), an antifibrotic cardiac hormone. BNP derives from the cleavage of inactive NT-proBNP (N-terminal of proBNP) from pro-BNP. Many studies have reported that BNP or NT-proBNP level is predictive of cardioembolic stroke or AF-associated stroke. A recent pooled meta-analysis revealed that the measurement of BNP or NT-proBNP level improved the

accuracy of the diagnosis of cardioembolic stroke or AF-associated stroke [31]. The NT-proBNP level is also predictive of stroke in patients with AF [32]. High-sensitivity troponin, also a marker for myocyte damage, is associated with the cardioembolic stroke subtype or ESUS [33].

GDF-15, a member of the TFG-β cytokine family, is released from macrophages or cardiac myocytes as a stress-inducible cytokine. Plasma levels of GDF-15 is related to increased risk of major bleeding, cardiovascular mortality, and stroke or systemic embolic events in patients with AF [34]. GDF-15 incorporated in a model (ABC score) with age and clinical history, is also validated to predict stroke and other cardiovascular events [35]. The ABC score outperformed the CHA2DS2-VASc score in predicting thromboembolic events and the HAS-BLED score for bleeding complications [34, 36].

Recently, a growing body of evidence shows that FFA is an important biomarker of cardioembolic stroke subtype and outcome in embolic stroke patients [4, 37–39]. The FFA level measured in plasma or cerebrospinal fluid was predictive of the cardioembolic stroke subtype [4, 38]. Moreover, elevated FFA level is a predictive biomarker of recurrent stroke in cardioembolic or AF-associated stroke [37, 39]. All these findings imply that FFA could have a close relationship with cardioembolic stroke.

Currently, several pathogenetic relationships between FFA and cardioembolic stroke have been suggested. Free fatty acids (FFAs), in addition to their role as energy fuel and an important metabolite of lipid metabolism [40], have other important biological activities such as the regulation of platelet activation and thrombosis [41]. The causal relationship between elevated FFA level and thrombogenesis was proved in earlier animal studies [42, 43], and the factors responsible for the thrombogenic effect of FFA appear to be multiple, including oxidative stress, increased inflammation, decreased nitric oxide level with reduced vasodilatation, and platelet activation associated with the arachidonic acid pathway [41]. Another explanation for the association between cardioembolic stroke and FFA level is the arrhythmogenic effect of FFA, which could be supported by the results of the Cardiovascular Health Study [44]. In this population-based cohort study with long-term follow-up, elevated plasma FFA levels at baseline were predictive of future AF development in a dose-dependent manner. Clinical studies have also shown that AF mediates between FFA level and embolic stroke [4, 39]. Finally, elevated FFA levels might be associated with atrial cardiomyopathy. FFAs, through the mitochondrial fatty acid β-oxidation, are the most efficient and predominant substrates for energy production in the normal adult human heart [45]. However, pathological conditions exhibit a "metabolic shift," where the rate of the oxidative metabolism of fatty acids is decreased in favor of increased uptake and metabolism of glucose. Therefore, elevated FFA levels may reflect dysregulated mitochondrial β-oxidation and dysfunctional myocardial disease [45].

10.2.3 Risk Assessment and Treatment of AF-Associated Stroke

10.2.3.1 Risk Assessment

The mainstay of treatment for stroke patients with AF is focused on anticoagulant use. For stroke patients with AF, treatment with long-term anticoagulation is recommended to prevent thromboembolic events. The current guidelines recommend antithrombotic treatment for AF patients according to their risk of thromboembolism, especially embolic stroke. The risk of thromboembolism or stroke can be easily estimated using risk-estimating schemes such as the $CHADS_2$, CHA_2DS_2-VASc, and ATRIA scores. The $CHADS_2$ score includes congestive heart failure, hypertension, age of ≥75 years, diabetes mellitus, prior stroke, and transient ischemic attack (2 points), with a maximum score of 6 points. The CHA_2DS_2-VASc score includes congestive heart failure, hypertension, age of ≥75 years (2 points), diabetes mellitus, previous stroke or transient ischemic attack (2 points), vascular disease, age of 65–74 years, and sex (female), with a maximum score of 9 points. The ATRIA score with the previous stroke includes age of <65 years (8 points), age

65–84 years (7 points), age of ≥85 years (9 points), sex (female), congestive heart failure, hypertension, diabetes mellitus, proteinuria, estimated glomerular filtration rate of <45 mL/(min·1.73 m^2), or end-stage renal disease requiring renal replacement therapy, with a maximum score of 15 points. However, unfortunately, the performances of these risk scoring systems are unsatisfactory with low C-statistic values in recent meta-analyses [46, 47]. In stroke patients with AF, the performances of these scoring systems were not systematically evaluated because all AF patients with a stroke history are considered a high-risk population. Therefore, all stroke patients with AF should be treated with long-term oral anticoagulation. However, these risk-estimating schemes are used as important variables that characterize subjects in clinical studies for AF patients. To compare the results between groups or studies, risk-estimating schemes such as the $CHADS_2$ or CHA_2DS_2-VASc scores are the most useful and reliable explanatory variables that can characterize subjects. However, the performances of these scoring systems are even lower in stroke patients with AF than in non-stroke patients. Therefore, newer risk estimators for stroke patients are needed.

The risk of bleeding in AF patients is assessed using the HAS-BLED score, which is composed of hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), and advanced age (>65 years, frailty). The use of the $HEMORR_2HAGES$ (hepatic or renal disease, ethanol abuse, malignancy, older age [≥75 years], reduced platelet count or function, rebleeding risk, hypertension, anemia, genetic factors, excessive fall risk, and stroke) score, which was suggested previously, is not usually recommended because of its complexity. Instead, the ORBIT and ABC scores are newly suggested as alternatives [48]. The current guidelines recommend the more convenient and practical HAS-BLED score for the assessment of bleeding risk. The predictive value of this score in stroke patients has also been validated.

10.2.3.2 Antithrombotic Treatment for Stroke Patients with Atrial Fibrillation

Vitamin K Antagonist Versus NOACs

Currently, vitamin K antagonists and four NOACs are available for long-term prevention of stroke or embolization in patients with AF. The four NOACs include one direct thrombin inhibitor (dabigatran) and direct factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban). The efficacy and validity of each NOAC in comparison with those of vitamin K antagonists were validated in pivotal clinical trials [49–52]. Subgroup analyses for each trial also verified the efficacy and safety of each NOAC in stroke populations [53–55]. A meta-analysis based on the standard-dose treatment of NOACs in comparison with vitamin K antagonists evaluated the efficacy and safety of each drug in >70,000 patients. As a result, NOACs significantly reduced the risk of stroke by 19% as compared with vitamin K antagonists, and the difference was mainly driven by the reduced risk of hemorrhagic stroke (relative risk, 0.49). Although the risk of gastrointestinal bleeding increased by 1.25-fold with marginal significance, mortality decreased by 10%, and the risk of intracranial hemorrhage decreased by 50% [56]. Furthermore, patients treated with NOACs feel comfortable because of the improved food or drug interaction property and the fact that no regular blood testing is required for INR measurement. This convenience in taking the drug improved drug compliance. Real-world data also showed similar results from those of clinical trials. On the basis of the results of these clinical trials, for stroke patients with AF, the current guidelines favor the use of NOACs over vitamin K antagonists [48]. However, several unsolved issues remain regarding the use of OACs in stroke patients with AF.

Each NOAC class has its own characteristics, and the selection of the appropriate drugs should be individualized according to the patient's condition.

Timing of OAC Therapy Initiation

The timing of initiating OAC therapy is one of the practical issues. Hemorrhagic transformation and intracranial hemorrhage complicated by acute stroke are important causes of neurological deterioration in acute stroke patients. Especially cardioembolic stroke due to AF tends to change into the hemorrhagic stroke, and the occluded cerebral artery in cardioembolic stroke easily recanalizes without reperfusion therapy. Therefore, identification of the optimal timing of OAC therapy initiation is an important issue. The TRIPLE-AXEL trial compared the early use of rivaroxaban and warfarin in mild AF-related stroke and showed comparable efficacy and safety [57]. However, a limitation of this study was that the patients enrolled only had a substantially minor stroke. A recent guideline suggested a practical recommendation in that the start of (N)OAC can be determined according to stroke severity (NIHSS score) and additional factors. This recommendation could be the best way to individualize the timing for initiating OAC therapy according to the patient's condition based on the clinical decision of the physician.

In addition, hemorrhagic stroke patients with AF is another clinical vignette. Several observational studies have reported that OAC uses 4–8 weeks after the onset of hemorrhagic stroke is acceptable considering the composite risks of ischemic and hemorrhagic stroke [58].

Optimal Dose or Intensity of Anticoagulants

When a vitamin K antagonist is used for the prevention of thromboembolic events in AF patients, the dose of the drug or intensity of the treatment can be estimated by measuring prothrombin time (with INR). In AF patients, the recommended optimal INR was between 2.0 and 3.0 [48]. On the other hand, the anticoagulant effect of NOACs is challenging to measure. The recommended doses of NOACs on packaging labels were decided based on early-phase clinical trials performed in small numbers of subjects. Thus, the validity of the dose should be reconfirmed. Recently, several real-world data about this issue have been reported. However, the results were inconsistent and needed to be validated, especially in Asian populations.

A significant proportion of stroke patients with AF have comorbid arterial thrombotic diseases and frequently need to be treated with interventions such as percutaneous coronary intervention or carotid artery stenting. In these cases, the decision for the simultaneous use of OACs and antiplatelets is complex. The patients underwent percutaneous coronary intervention and triple antithrombotic therapy for one month, followed by dual therapy (OAC plus aspirin or clopidogrel) for 1 year. However, no controlled studies have been conducted, and no guidelines have been established about stroke patients with atherosclerotic disease or patients who had undergone cerebral artery intervention. Many neurologists or neurosurgeons apply the guideline for PCI in stroke patients after the cerebral vascular intervention, but separate studies are needed.

10.2.3.3 Non-OAC Treatment for Stroke with AF

Some patients with AF irrespective of a previous stroke are contraindicated for long-term OAC use, although NOAC use has become popular. These patients include those with cerebral amyloid angiopathy, those with esophageal varix, or those who need specific drugs that interact with (N)OACs. In these cases, exclusion of cardiac atrial appendage can be one of the options for the prevention of thromboembolic events. Surgical occlusion or exclusion of the left atrial appendage may be considered for stroke prevention in patients with AF if long-term OAC use is contraindicated. Two clinical trials were conducted to compare the efficacy of percutaneous closure of the left atrial appendage with that of vitamin K antagonist therapy and showed non-inferiority of the former, implying that left atrial occlusion could be an alternative to vitamin K antagonists. The relative efficacy and safety of left atrial appendage occlusion in comparison with those of NOAC therapy are well studied and should be investigated with controlled clinical trials.

In terms of non-OAC treatment, rhythm or rate control for AF is usually indicated for symptom improvement in patients with AF, but its efficacy has

not been validated for stroke patients with AF, especially for the prevention of thromboembolic events.

10.3 Patent Foramen Ovale and Other Stroke-Related Cardiac Diseases

Various cardiac or aortic diseases can produce embolus, resulting in cardioembolic stroke. Because the moment when emboli block the cerebral arteries is difficult to determine, etiologic conditions, which are presumed to cause cardioembolic stroke are called PSCE. Several lists of cardiac or cardio-aortic sources of embolisms exist, with subtle differences among the lists. However, recent myocardial infarction, mitral valve disease, severe congestive heart failure, infective endocarditis, intracardiac mass, and nonbacterial thrombotic endocarditis are commonly considered sources of cardioembolic stroke. On the other hand, the thrombogenic properties of patent foramen ovale (PFO), mitral annular calcification, and aortic arch atheroma are controversial. Thus, these conditions are considered sources of embolism when no cardiac source is apparent in patients with a suspected embolic stroke.

Among these conditions, PFO is a common condition even in the general population and has been associated with non-stroke neurological diseases such as migraine. A long-lasting controversy surrounds the usefulness of PFO closure in stroke patients. Recently, three clinical trials that compared percutaneous closure of PFO with the conventional treatment showed the beneficial effect of PFO closure in terms of reducing the risk of recurrent stroke among cryptogenic stroke patients [59–61]. In light of these results, a recent guideline recommends percutaneous PFO closure for cryptogenic stroke patients aged 18–65 years [62]. Further investigations are needed to specify the target population who would significantly benefit from the treatment and reassess the concern about the new AF development (Figs. 10.1 and 10.2).

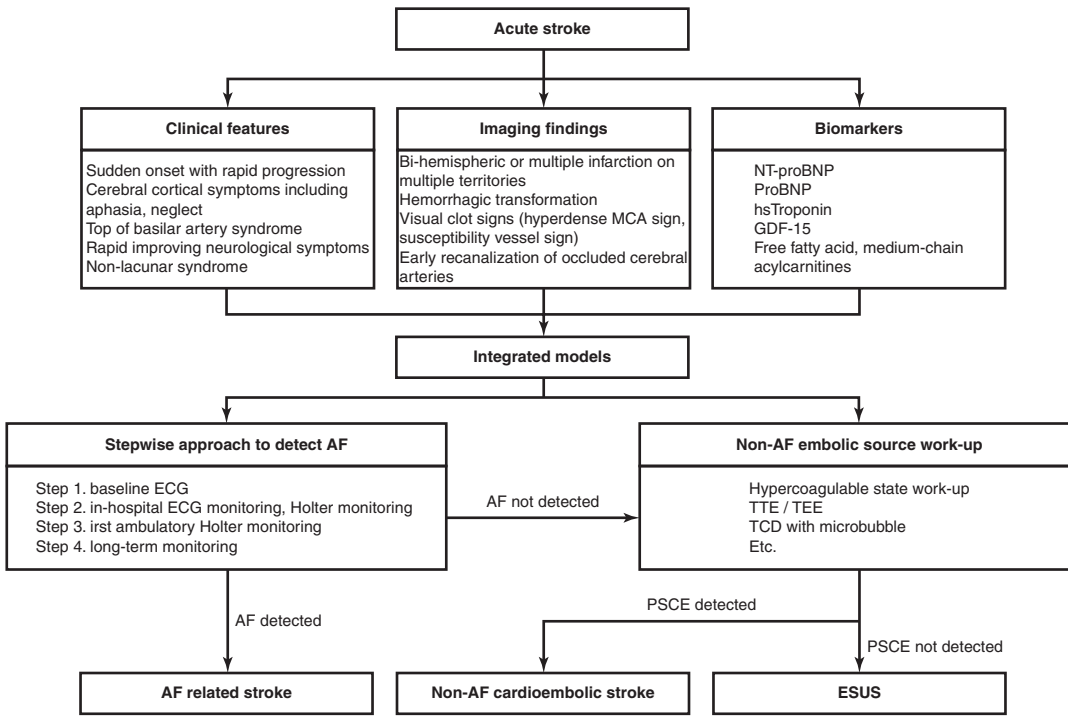

Fig. 10.1 The flow of diagnosis in patients with embolic stroke

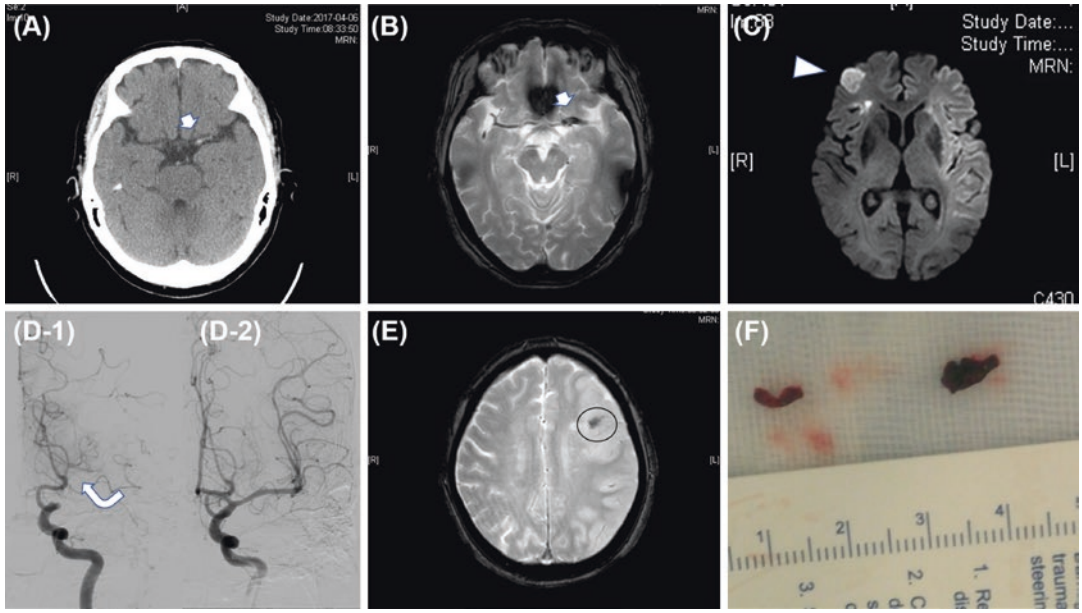

Fig. 10.2 Illustrated case of cardioembolic stroke. A 66-year-old female with a history of atrial fibrillation presented sudden aphasia and right hemiparesis. (**a**) Non-contrast brain CT at the emergency department revealed a hyperdense MCA sign (white arrow). (**b**) At the same lesion, enlarged dart signal intensity with blooming artifact on the GRE image is shown (susceptibility vessel sign). (**c**) The diffusion-weighted image of the patient revealed multiple acute infarctions with different stages involving both cerebral hemispheres. (**d**) Transfemoral catheter angiography before (D-1) and after (D-2). The left middle cerebral artery was recanalized after the endovascular thrombectomy procedure was performed. (**e**) On the GRE image obtained just after the thrombectomy procedure, the small cortical hemorrhagic transformation was found. (**f**) The thrombus extracted from the occluded cerebral artery by endovascular thrombectomy

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Part V

Clinical Science: Pathophysiology of Specific Causes

Cerebral Vessel Wall Diseases

11

Keun-Hwa Jung

Abstract

The cerebral arterial wall is composed of three layers, the tunica intima, tunica media, and adventitia, which are common structures in human systemic arteries. As the composition and cellular origin of each component differ according to the vessel locations, such as intracranial, extracranial, anterior, and posterior, the response and vulnerability to injury vary for each arterial site. Cerebral vessel wall diseases are characterized by the partial or complete involvement of vascular wall components by an inciting factor. Typical manifestations include transient ischemic attack, cerebral infarction, or intracranial bleeding by luminal narrowing, thrombus formation, or rupture. The main pathophysiological sequence of cerebral vessel wall diseases includes endothelial dysfunction, smooth muscle cell proliferation or degeneration, extracellular matrix degeneration, inflammation, and rheological stress. This chapter deals with three typical cerebral vessel wall diseases including moyamoya disease, arterial dissection, and vasculitis. The cerebral vessel wall diseases may require early differential diagnosis because they are associated with different therapeutic options. However, the early diagnosis may be difficult because these diseases often share clinical manifestations and angiographic features. Recently, the advent of vessel wall imaging techniques and the increasing availability of pathological studies prompt us to better differentiate the diseases and identify the pathomechanism of each disease. This chapter reviews the advances in the histopathological and clinical data of cerebral vessel wall diseases with the aim of unraveling their pathophysiology.

11.1 Introduction

The peculiar anatomy of cerebral arteries and a variety of pathophysiological signals contribute to the development of various cerebrovascular diseases, providing a unique classification of cerebral vessel wall disease. Common nonatherosclerotic, cerebral large-vessel wall diseases include moyamoya disease, arterial dissection, and cerebral vasculitis. The current stroke classification system defines these disease entities as uncommon causes of stroke. In particular, these cerebral vessel wall diseases are considered an important differential diagnosis in young age-onset stroke.

Detection of cerebral vessel wall disease is largely based on vascular imaging modalities such as transcranial Doppler (TCD), computed

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tomography angiography, magnetic resonance angiography (MRA), and digital subtraction angiography (DSA). However, these conventional imaging techniques have often missed the presence of wall disease, because they merely monitor blood flow within the vascular lumen. Increased flow velocity on TCD might indicate the presence of good collateral vessels as well as stenosis. While CTA, MRA, and DSA sensitively detect the luminal narrowing, flow velocity or luminal narrowing is dependent on the volumetric change of the total artery, total wall, concentric wall, and eccentric wall [1]. The cerebral arteries undergo positive and negative remodeling during the disease course, the characteristics of which may be different according to each disease entity. Classical luminal imaging is critically limited by poor delineation of the wall status that is not helpful in the diagnosis of cerebral vessel wall diseases or in understanding their pathophysiology (Fig. 11.1). Currently, with the advent of black blood imaging techniques and higher magnetic field strengths, high-resolution vessel wall images have become feasible in clinical practice. Indeed, imaging the vessel wall of cerebral arteries may improve our ability to detect unrecognized cerebral vessel wall disease.

Diagnostic evaluation typically focuses on clinical features and radiological findings. However, there is significant overlap in the angiographic

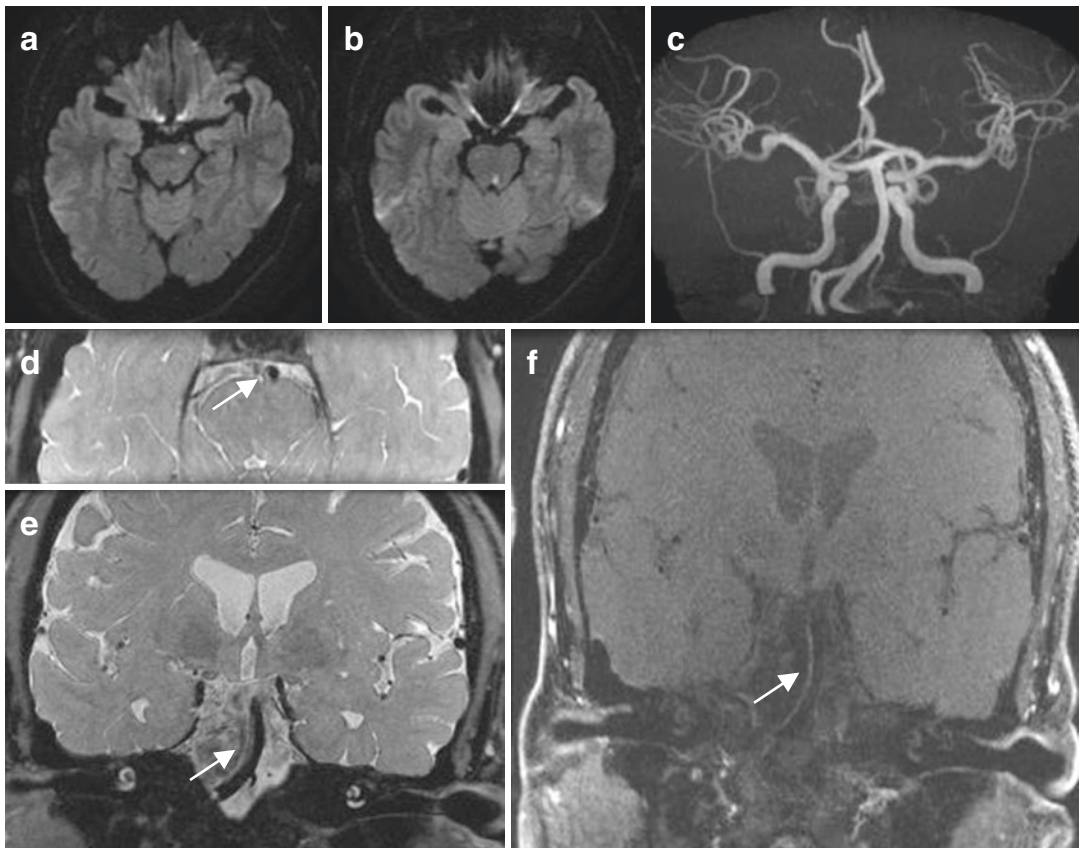

Fig. 11.1 Limitation of luminal imaging for evaluating the cerebral vessel wall disease. A 62-year-old man visited us because of sudden dizziness and diplopia. Brain DWI-MRI (**a**, **b**) showed two tiny infarcts involving the left anterior pons and the left pontine tegmentum. Time-of-flight (TOF) MRA (**c**) showed no luminal narrowing in the basilar artery. However, high-resolution MRI (**d**–**f**) displayed the eccentric enhancing atherosclerotic plaque (white arrows), which was identified by axial (**d**) and coronal view (**e**) of proton density images, and contrast-enhanced T1-weighted images (**f**)

patterns of cerebral vessel wall diseases. Moreover, moyamoya disease, cerebral artery dissection, and cerebral vasculitis share clinical, pathological, and genetic traits. The frequency of each disease is higher in patients with another vessel wall disease than in the general population. The pathophysiologies of moyamoya disease, cerebral artery dissection, and cerebral vasculitis are largely unclear as of yet. The majority of knowledge regarding their pathophysiology is derived from histological data based on biopsy or autopsy and, in part, from non-invasive radiological findings. This review will address the anatomy, embryology, and pathology of cerebral arteries, with the primary focus on the common cerebrovascular diseases occurring in the arterial wall.

11.2 Anatomy of the Cerebral Vessel Wall

Anatomical integrity is crucial to maintain the functional homeostasis of cerebral vessel walls and its perturbations eventually lead to the development and progression of cerebral vessel wall disease. Moyamoya disease, cerebral artery dissection, and cerebral vasculitis commonly involve anatomical and functional changes in the vessel wall. Knowledge of the pathophysiological characteristics of each disease should stem from a detailed recognition of the structural anatomy and embryological origin of cerebral arteries, and its differences from other systemic arteries.

11.2.1 Common Arterial Structure

The cerebral arterial wall consists of three layers, the tunica intima, tunica media, and tunica adventitia [2], which are also characteristic of other systemic arteries (Fig. 11.2). The tunica intima refers to the luminal side of arteries lined with endothelial cells. The internal elastic lamina is situated as a partition between the tunica intima and tunica media. Endothelial cells produce elastin and maintain the integrity of the internal elastic lamina by interacting with smooth muscle cells in the tunica media. The tunica intima is essential in maintaining the homeostasis of blood and adjacent vascular cells, whereas it contributes little to the structural support of vessels.

The tunica media is composed of two main components, smooth muscle cells, and elastin. Smooth muscle cells are located in a direction circumferential to the lumen, whereas elastin fibers run in a parallel direction to the longitudinal axis of the artery and perpendicular to the smooth muscle layer [3]. The density of smooth

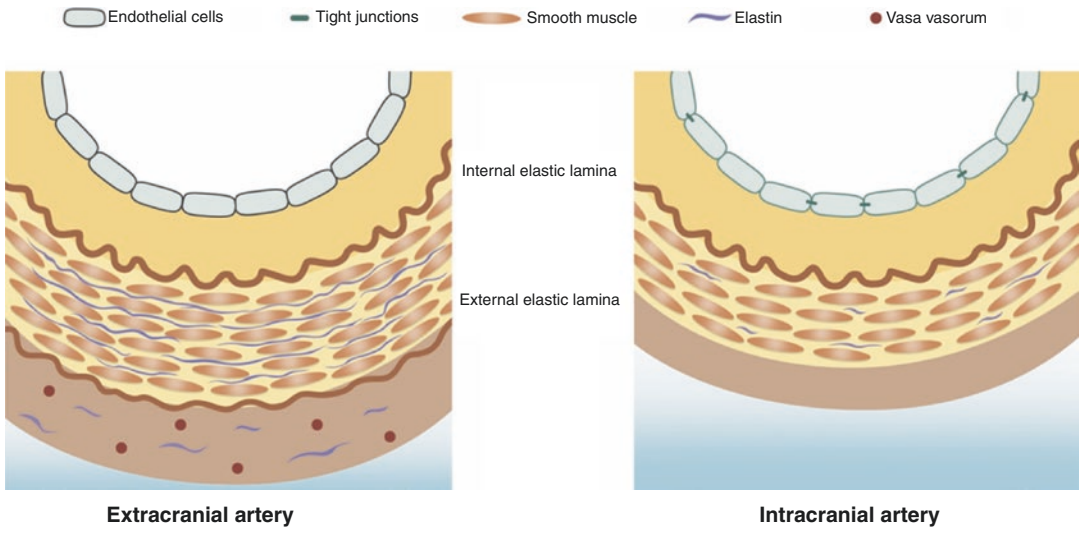

Fig. 11.2 Structural difference of extracranial and intracranial artery wall

muscle cells within the tunica media diminishes from the proximal to the distal vascular tree. Smooth muscle cells in the tunica media play two critical roles in maintaining the integrity of the vascular wall. One is a contractile function, which is important in regulating blood flow in small and medium-sized arteries. The other is a regulatory function on extracellular matrix production, which is crucial for enduring the blood pressure in large arteries. The structural network of extracellular matrix produced by smooth muscle cells typically confers a mechanical strength for vascular health. The two principal components of the extracellular matrix are the elastin and collagen generated by smooth muscle cells in the media layer. There are other cellular and matrix elements supporting the tunica media including fibroblasts, proteoglycans, and fibrillin. Elastin is assembled into a three-dimensional, stratal network that assists in resolving the pressure stress. There are collagen bundles between the lamellar layers of elastin, which shift their arrangement according to blood pressure changes. The proper organization of elastin and collagen is achieved by lysyl oxidases that facilitate lysine-derived cross-linking in elastin and collagen. Along with the structural support, the extracellular matrix is also imperative for maintaining the functional integrity of the artery as a reservoir for growth factors or transcriptional factors. The matrix molecules act as instructive signals that regulate vascular cellular function. In the tunica media, proliferative rates of smooth muscle cells and elastic fibers are low, and the turnover of collagen fibers occurs more rapidly than that of other elements. The layers of elastin are laid down during the early developmental period and have a half-life of about 40 years [4]. Therefore, the original elastin structure organized in the developmental stage is important for vascular health over a lifetime and is not easily rescued once injured.

The adventitia is the outermost layer of the vessel, which is demarcated from the tunica media by the external elastic lamina. It is composed of fibroblasts and collagen-rich extracellular matrix produced by myofibroblast cells. The relatively high level of collagen in the adventitia is advantageous in preventing rupture resulting from abrupt pressure increase. This layer is also supported by the vasa vasorum and innervated by nerve endings. The intradural segments of intracranial arteries have no vasa vasorum and receive essential nutrients directly from the blood or cerebrospinal fluid.

11.2.2 Characteristics of the Intracranial Arteries

There are two different types of arteries in the systemic vasculature, i.e., muscular and elastic arteries. The two types of arteries differ primarily in terms of the composition of the tunica media. While the elastic arteries are composed of elastic fibers, the muscular arteries are composed of smooth muscle cells. Among the extracranial arteries, the common carotid artery is an elastic artery, and the internal carotid artery is a muscular artery. The intracranial arteries are muscular arteries, but they have anatomically unique structures that are distinct from other muscular arteries of a similar caliber. The extradural and intradural portions of the internal carotid artery have different anatomical structures. The adventitia is thicker in the extradural segment than in the intradural segment. While the intradural segment has a firm internal elastic lamina, the external elastic lamina disappears from the intradural segment of the internal carotid artery, the cavernous portion of the internal carotid artery. Marked attenuation of elastic fibers and the absence of an external elastic lamina are also noted in the vertebral arteries entering the cranium. The fact that the intracranial artery has a minimal number of elastic fibers in the media with no external elastic lamina suggests that the intracranial artery is more vulnerable to rupture than the other muscular arteries. The adventitial layer of the intracranial arteries is typically thin compared to that of other systemic arteries. They have no vasa vasorum and are in direct contact with cerebrospinal fluid, such that the adventitia of the intracranial artery is referred to as the rete vasorum.

The intracranial artery accommodates a disease process via compensatory remodeling.

Remodeling can vary in direction and degree depending on the nature of the injury and the vessel inflicted. Positive outward remodeling of the cerebral artery preserves upwards of 60% of the lumen. Posterior circulation is more capable of positive remodeling compared with the anterior circulation [5]. In contrast, inward remodeling, so-called negative remodeling, can occur in certain vessel wall pathologies such as moyamoya disease with constriction of the vessel area and induction of stenosis.

11.2.3 Embryological Origins of Cerebral Smooth Muscle Cells

Endothelial cells are originated from mesodermal precursors that generate angiogenic cells, whereas vascular smooth muscle cells are derived from either different origins of progenitor cells according to the vessel location or different segments of the same vessel [6]. The different types of vascular smooth muscle cells play different roles in maintaining the structural integrity of mature vessels. Two distinct populations give birth to the smooth muscle cells of the large elastic vessels such as the aorta and cerebral arteries. The first is the somatic and splanchnic mesoderm constituting the dorsal aorta. Smooth muscle cells of mesodermal origin primarily provide mechanical strength by exerting a contractile function. The second population is the neural crest cells, which differentiate to smooth muscle cells in the aortic valvular cusps, ascending and arch of the aorta, the ductus arteriosus, the brachiocephalic and subclavian arteries, and the carotid and intracranial arteries. A major function of the vascular smooth muscle cells of neural crest origin is to synthesize and organize the elastin and collagen, such that the walls of the elastic arteries show impaired formation of the elastic lamellae when the neural crest cells are not appropriately positioned.

The muscular arteries in the large part of head and neck are also derived from neural crest cells. The neural crest is a unique structure in the early embryogenesis of vertebrates with a high degree of migration and differentiation throughout the body. The neural crest cells detach from the neural folds, migrate into the anterior and ventral head, and encounter mesoderm-derived endothelial precursors. The neural crest cells and endothelial precursors are expanded and merged into a vascular tree of head, neck, and heart outflow tracts [7]. In contrast, the dorsal and posterior parts of the head and neck are mainly supplied by the vessels of mesodermal origin. The two vascular trees of neural crest and mesodermal origin are connected and re-diverge at the level of the circle of Willis.

Although the lineage-specific smooth muscle cell populations share phenotypic properties, there are critical differences in the responses to factors that contribute to the development of cerebral vessel wall disease. In the context of the shared origin of the cerebral wall, the patients with bicuspid aortic valve are also vulnerable to dilatation, aneurysm formation, and rupture of the ascending aorta, as well as dissection of the aorta and the cervical and intracranial arteries [8]. Bicuspid aortic valve has been detected in the genetic connective tissue diseases such as Marfan syndrome and Ehlers–Danlos syndrome. The concurrent development of theses arterial abnormalities is primarily associated with a common embryonic origin of inflicted vessels and tissues [9].

11.3 Common Pathway for Cerebral Vessel Wall Disease

The solid structure of the cerebral vessel wall is changed into a disorganized pattern in response to injury signals relevant to the disease process. Histopathological studies over the past decades have identified several unifying components leading to structural fragility in the arterial wall. The main histopathological alterations include endothelial dysfunction, functional and structural degeneration of smooth muscle cells, extracellular matrix degradation, inflammation, and hemodynamic factors (Fig. 11.3). There are close pathogenetic interactions between each of the components.

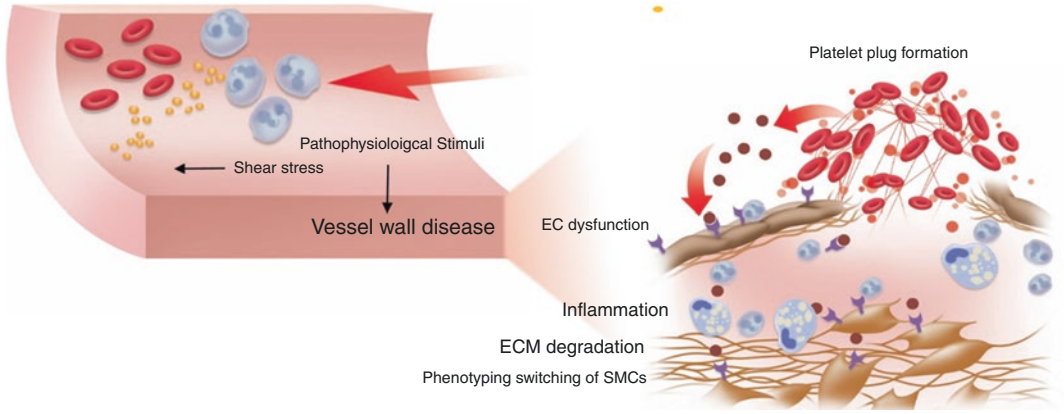

Fig. 11.3 Common pathophysiological pathway incurring cerebral vessel wall disease. EC, endothelial cell; ECM, extracellular matrix; SMC, smooth muscle cell

11.3.1 Endothelial Dysfunction

Endothelium is characterized by the continuous cellular lining of the systemic vasculature and is widely distributed in the human body. It plays the most vital role in maintaining the homeostasis of organs and supporting their healthy functionality. Healthy endothelial lining is a good container for blood. The luminal surface secretes vasculoprotective molecules and prevents the intrinsic coagulation cascade or platelet adhesion, thereby inhibiting leukocyte infiltration, smooth muscle proliferation, and thrombus formation [10]. Moreover, endothelial cells act as biomechanical transducers for mechanical forces into biological signals. Endothelial cells show morphological and functional changes in response to hemodynamic changes. The morphological changes of endothelial cells give adaptation to flow alterations and protect the vessel wall, whereas stress may activate the injury signals including inflammatory cascades. Finally, in response to growth factors, pro-inflammatory cytokines, or endotoxins, they play a regulatory role in the balance of pro- and anti-inflammatory actions within the arterial wall. Thus, dysfunction of the endothelium generally leads to thrombus formation, smooth muscle cell proliferation, extracellular matrix degeneration, and vessel wall inflammation.

Endothelial cell damage or dysfunction is a universal pathological feature seen in various cerebral vessel wall diseases. Pathological changes of the endothelium are noted in the initial stage of disease. Endothelial cell dysfunction initiates a complex pathophysiological sequence due to loss of the selective barrier function. It accelerates the adhesion of blood monocytes into the intima, where they differentiate into macrophages, and activates the inflammatory process. Growth factors and cytokines are also stimulated by activated endothelial cells, and these mediators in turn stimulate the nearby smooth muscle cells. In response to various pathophysiological signals, dysfunctional endothelial cells further increase specific local pathological processes within the arterial wall. Endothelial cell dysfunction is a reversible process, and treatment targeting endothelial dysfunction may be effective to prevent the subsequent damage in the vessel wall.

11.3.2 Phenotypic Switching of Smooth Muscle Cells

The smooth muscle cells maintain the structural integrity of the vessel wall. Vascular smooth muscle cells normally occupy 70% of the media, and this composition is altered under conditions of cerebral vessel wall disease. In response to injury signals, vascular smooth muscle cells undergo phenotypic modulation in a way to produce a pro-inflammatory signal, and some proliferate and induce vascular narrowing. In normal cerebral arteries, smooth muscle cells express a wide array

of smooth muscle cell markers including myosin heavy chain, 22-kDa SMC lineage-restricted protein, ACTA2, and smoothelin. However, in disease states, smooth muscle cells lack these markers and instead acquire the markers and properties of macrophages. The cells undergoing phenotypic switching secrete various extracellular matrix proteins and cytokines, acquire increased proliferative and migratory properties, and promote inflammatory signals [11]. The proinflammatory phenotypes are followed by the promatrix remodeling process. The signals driving the switching of smooth muscle cells to macrophage-like cells vary according to the nature of the vessel wall disease. Under a certain injury signal, the smooth muscle cells migrate into the intima and proliferate, resulting in the presence of a large number of intimal smooth muscle cells, which is called intimal hyperplasia.

While vascular smooth muscle cells with phenotypic switching eventually go into apoptosis, smooth muscle cell degeneration may be a primary and early event in some vessel wall diseases. Smooth muscle cell apoptosis accelerates the features of medial degeneration including decreased density of smooth muscle cells, elastin fragmentation, and increased glycosaminoglycans [12]. It also critically affects the integrity of the vascular wall and makes the vessel prone to rupture. Smooth muscle cell degeneration is induced by macrophages through death ligand and death receptor interactions [13]. Dying cells release IL-1 and subsequently activate the inflammatory cascade.

11.3.3 Extracellular Matrix Degradation

Arterial tensile strength depends on the integrity of the smooth muscle cells and extracellular matrix of the tunica media. However, loss of smooth muscle cells is not associated with a significant reduction in the static mechanical properties of the arteries, suggesting that the mechanical properties of the large arteries are primarily attributable to the elastin and collagen components. The vessel walls have a high degree of the cross-linking of elastin and collagen and rarely undergo a wear and tear process throughout life. Elastin production begins in midgestation, and there is minimal synthesis throughout the life. The longevity of elastin is estimated to be the human life span. Hence, if the vessels undergo extracellular matrix degradation, the disease course may be irreversible.

Extracellular matrix components show a different distribution according to the specific location of the vasculature. Various types of defects of the elements comprising the extracellular matrix have been reported in patients with connective tissue disease, which has also been commonly associated with concomitant cerebral vessel wall disease. Collagen types I and III are the vascular components that impart strength to the vessel wall. Osteogenesis imperfecta has complications of bone fragility in association with mutations in collagen type I, and collagen type III is defective in vascular Ehlers–Danlos IV syndrome. Fibrillin-1 is essential for the firm organization of the extracellular matrix, including the maintenance of elastic fibers. Marfan syndrome has mutations of the fibrillin-1 gene on chromosome 15, and it is characterized by cardiac, skeletal, and ocular abnormalities [14].

Changes in the extracellular matrix components occur as a consequence of vascular remodeling. Matrix metalloproteinases (MMPs) and their inhibitors (tissue inhibitors of metalloproteinases [TIMPs]) are involved in the process of vascular remodeling. MMPs are produced by smooth muscle cells and leukocytes, and they digest the extracellular matrix, causing further injury via the production of other proteinases. Overexpression of various proteases, particularly MMP2, has been identified in the plasma of patients with cerebral vessel wall disease [15]. Altered regulation of MMPs and TIMPs actively contributes to vascular remodeling and the progression of cerebral vessel wall disease.

11.3.4 Inflammation

Various patterns of the inflammatory response have been identified as triggers and accelerators

to cerebral vessel wall disease. Within the arterial wall, various components of the innate and adaptive immune response operate in an orchestrated manner. As a common pathway of inflammatory reaction, monocytes/macrophages infiltrate into the vessel wall and play a key role in vascular remodeling via the release of MMP [16]. Endothelial dysfunction is associated with the impaired barrier function between the bloodstream and the tunica media, which provokes the infiltration of inflammatory cells and downstream inflammatory cascades. Monocyte chemoattractant protein 1 (MCP1) and NF-kB are pivotal in recruiting monocytes into the vessel wall, initiating the inflammatory reaction, and leading to the phenotypic modulation of smooth muscle cells. Phenotypically switched smooth muscle cells further evoke pro-inflammatory responses, by producing various cytokines and chemokines to mediate macrophage and T cell function. Conversely, smooth muscle cells and extracellular matrix also display anti-inflammatory properties. The balance between the two opposing signals determines the characteristics of medial pathology. Alongside macrophages, T cells and mast cells also actively participate in the inflammatory reaction of vascular diseases. Cytokines, soluble short-acting proteins, have also been studied as pathogenetic contributors of various cerebral wall diseases. Cytokines are produced by monocytes, macrophages, and T cells, and they function as key mediators of the immune response. IL1β, IL6, and tumor necrosis factor-α (TNFα) have been principally involved in the pathogenesis of various vessel wall diseases. Therapeutic approaches targeting the inflammatory pathway may be effective in some cerebral vessel wall diseases.

Inflammation accompanies the proliferation of the adventitial vasa vasorum with extension of the neovessels into the media. The endothelial cells near the lumen are partly fed by the luminal fluid, and nutrition beyond this zone is supplied by the vasa vasorum. Therefore, if the vascular cells in the tunica media activate in response to injury signals, there is a robust increase in the density of the vasa vasorum, extending into tunica media. Therefore, in diseases with active inflammation, vessel density increases threefold over that of stable lesions. Recent advancements in the field of neuroimaging have enabled the imaging of inflammation and neovascularization in the arterial wall. As a site of immunoprivilege, the avascular media may be spared by some disease conditions such as immune-mediated disorders, whereas leukocyte infiltration in the tunica media and media degeneration may be significant in other conditions such as vasculitis.

11.3.5 Hemodynamic Change on the Wall

It is natural that the vascular lesions are distributed randomly throughout the arterial tree, because the whole vasculature is exposed to similar insults. However, the involved sites of disease are far from random; rather, they include areas with specific arterial geometries. This phenomenon supports the hypothesis that unique hemodynamic patterns in particular areas may be important in the development of cerebral vessel wall disease. A pulsatile blood flow through the vasculature provokes various mechanical stimuli. Laminar flow within the vessel maintains the normal function of vascular components and prevents vascular disease [17]. When the luminal area of vessel and blood flow is not disturbed, a hemodynamic force leads endothelial cells to downregulate inflammatory cytokines and growth factors. Within a normal range, this force prevents atherogenesis, thrombosis, adhesion of inflammatory cells, smooth muscle migration and proliferation, and extracellular matrix degeneration. However, disturbed laminar flow or turbulent flow can occur during the disease course, especially in areas with complex geometry. Initially, hemodynamic changes in the vessel wall direct the regulatory mechanism in favor of maintaining the normal range of force. Endothelial cells are actively trying to adapt to changes of hemodynamic stress by various compensatory mechanisms. However, sustained alteration of the hemodynamic force associated with endothelial maladaptation may initiate the cerebral vessel wall disease, and accelerate the disease progression. Unregulated hemo-

dynamic force causes endothelial cells and smooth muscle cells to upregulate the levels and activities of MMP-2 and MMP-9 and to degrade the extracellular matrix, which results in vascular remodeling [18].

The major mechanical forces on the endothelial cells are cyclic stretch, pulsatile pressure, and wall shear stress. Of these mechanical forces, wall shear stress has been proposed as a trigger for disease initiation and progression. Wall shear stress is calculated by the shear rate multiplied by the fluid viscosity. The shear rate is a velocity gradient in the axial plane of the vessel, which depends on the luminal diameter and flow velocity [19]. Decreasing vessel diameter inversely increases the shear rate and subsequently wall shear stress. Variations in arterial wall geometry can influence the distribution and magnitude of wall shear stress, which is a strong determinant in maintaining vascular health and contributing to site-specific disease distribution. Wall shear stress regulates endothelial function, and the presence of mechanoreceptors on the endothelium is thought to change flow signals into biological signals. Shear stress stimulates gene expression, activation of channel and receptor, and the cytoskeletal alignment. Endothelial cells activate different pathological pathways in the course of cerebral vessel wall disease depending on the type and magnitude of shear stress. While stable levels of shear stress promote genes related to the vasculo-protective phenotype, sustained high or low levels of shear stress have been implicated in cerebral vessel wall disease. Biological responses to high wall shear stress include increased endothelial cell damage, endothelial cell turnover, extracellular matrix degradation, medial thinning, and smooth muscle cell apoptosis formation. Meanwhile, low wall shear stress induces pro-inflammatory changes of endothelial cells that are leaky and sticky, impairs nitrous oxide-dependent dilation, and increases inflammatory cell infiltration, thrombus formation, and smooth muscle cell proliferation and migration. The evaluation of wall shear stress as a contributor to cerebral vessel wall disease may help to identify individuals at risk of disease progression and to predict long-term outcomes.

11.4 Pathophysiology of Cerebral Vessel Wall Diseases

It is very hard to define the pathophysiology of moyamoya disease, cerebral artery dissection, and cerebral vasculitis owing to the nonspecific nature of the radiological findings and the lack of convincing histopathological data. Further complicating our knowledge are the unpredictable phenotypes that each disease can exhibit during different time periods of the disease. Nevertheless, significant progress has been made for elucidating the critical pathways that initiate and progress the disease (Table 11.1). Recent information on the pathophysiologies of moyamoya disease, cerebral artery dissection, and cerebral vasculitis, as well as unsolved issues awaiting future research are addressed here.

Table 11.1 Pathological features for common cerebral vessel wall diseases

	Moyamoya disease	Cervical artery dissection	Primary CNS vasculitis
Smooth muscle cells	Migration into intima, proliferation and concentric thickening, transformation from contractile to synthetic type	Cell apoptosis, medial degeneration	Phenotypic switching from contractile to inflammatory type
Extracellular matrix	Alteration of collagen to elastic ratio, matrix degradation	Inherited deformity of collage and elastin cross-link	Matrix degradation
Inflammation	Elevated levels of MMPs, VCAM-1, ICAM-1, E-selectin	Elevated levels of MMPs	Increased macrophages, lymphocytes, proteases, cytokines
Internal elastic lamina	Fragmentation and wavy appearance	Breakdown and degradation	Degradation

11.4.1 Moyamoya Disease

Moyamoya disease is primarily a disease of the medial layer of the arterial wall that is characterized by the progressive steno-occlusion of the distal internal carotid artery and proximal vessels of the circle of Willis. The occlusive changes of the major basal arteries are accompanied by the formation of dilated, fragile arterioles at the base of brain, designated as moyamoya vessels. The latter phenotype is recognized as primary aberrant neo-vascularization or a compensatory process due to the reduced cerebral blood flow. Moyamoya disease manifests as transient ischemic attack, cerebral infarction, or intracranial bleeding with separate age peaks for children and adults and a female predominance. Transient ischemic attack and cerebral infarction result from hemodynamic compromise or artery-to-artery embolism from the thrombosed neovessels, whereas intracranial bleeding occurs owing to rupture of the fragile moyamoya vessels or associated aneurysms. Moyamoya disease is most prevalent in Asian countries or those of Asian ancestry, and founder mutations have been discovered in Asians [20]. Given the distinct genetic architecture of Asian and European ancestry, various subtypes of moyamoya disease may exist [21]. Moyamoya disease is diagnosed by clinical and imaging criteria: idiopathic stenosis or occlusion of both distal internal carotid arteries, followed by characteristic hypertrophy and proliferation of the small lenticulostriate arteries (Fig. 11.4). The current diagnostic guidelines that were revised by the Research Committee of MMD of the Japanese Ministry of Health, Labor, and Welfare in 2015 include patients with both bilateral and unilateral disease. However, it remains unclear whether unilateral moyamoya disease is an early form of bilateral disease or a unique disease entity. Differently from moyamoya disease, moyamoya syndrome indicates a moyamoya disease-like condition secondary to atherosclerosis, vasculitis, dissection, sickle cell disease, and inherited coagulopathy. The natural course of moyamoya disease is not well known and the progression of arterial stenosis has variable courses. The five-year risk of recurrent

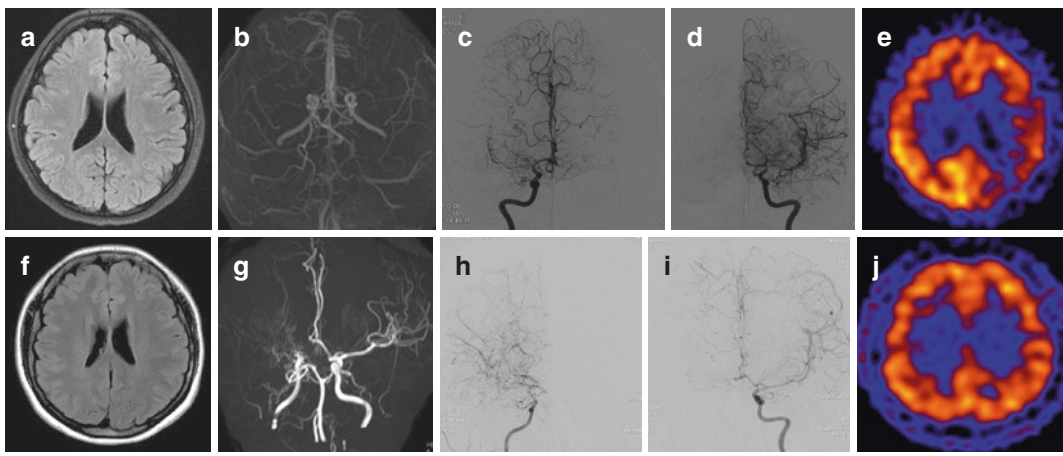

Fig. 11.4 Phenotype of moyamoya disease. Moyamoya disease manifests as various clinical and radiological phenotypes. Upper panel (**a**–**e**) indicates bilateral moyamoya disease. A 37-year-old woman complained of recurrent transient aphasia and right-sided weakness. FLAIR image (**a**) showed no abnormal lesions, but MRA (**b**) showed near occlusions of the bilateral MCAs. Conventional angiography (**c**, **d**) revealed complete occlusions of the bilateral MCA with distal reconstitution via basal collaterals. Brain SPECT (**e**) showed a significant reduction of blood flow in the left frontoparietal area. Lower panel (**f**–**j**) indicates a unilateral moyamoya disease. A-32-year-old woman presented with recurrent headache and dizziness. FLAIR image (**f**) showed no abnormal lesions, but MRA (**g**) showed near occlusion of right MCA. Conventional angiography (**h**, **i**) revealed occlusion of the right ACA and MCA with distal reconstitution via basal collaterals, and mild stenosis of the left proximal MCA and ACA. Brain SPECT (**j**) showed a slightly decreased blood flow in both frontal areas

ipsilateral stroke is 65% in the medically treated symptomatic cases and 82% in patients with bilateral symptoms of ischemia [22].

Histological findings of moyamoya disease include reduced outer diameters of the involved arteries, unregulated proliferation of smooth muscle cells and fibroblasts and migration into the intima, breakdown of the internal elastic lamina, intima thickening, and media thinning. Moyamoya vessels show fibrin deposits in the wall, fragmentation of elastic lamina, attenuated media, and microaneurysm, which are all prone to rupture. Various cerebrovascular diseases can display similar angiographic findings with conventional imaging techniques. Recently, high-resolution vessel wall MRI has provided some information for the differentiation of moyamoya disease from other arteriopathies. This imaging can more clearly visualize luminal stenosis associated with concentric negative remodeling. The most common vessel wall MRI findings for moyamoya disease are non-enhancing, negative-remodeling lesions without T2 heterogeneity [23]. Based on our study, moyamoya disease could be differentiated from atherosclerosis in that moyamoya disease shows more homogenous wall thickening with faint contrast enhancement, with more prevalent spring-like vascular structures around the stenotic area [24]. In another study, decreased wall area and remodeling index and concentric enhancement in the arteries at the circle of Willis were noted in moyamoya disease, whereas focal eccentric enhancement was noted in atherosclerotic lesions [25]. Diffuse concentric enhancement might indicate the hyperproliferation of smooth muscle cells and extracellular degradation by increasing levels of matrix metalloproteinase. The difference in the enhancement pattern between studies is likely due to the different ethnic populations at varying stages of the disease.

Despite diagnostic advancements, an etiologic answer cannot yet be given to patients with moyamoya disease. The symmetrical involvement feature of the disease suggests this arteriopathy may be genetically or developmentally determined. However, cerebral manifestations along without evidence of systemic involvement suggests a complicated genetic etiology. Approximately 10% of patients with moyamoya disease have a familial occurrence. Moyamoya disease is often inherited and several genetic mutations have been discovered. ACTA2 mutation has been suggested as the key mediator of vascular occlusion in familial moyamoya disease [26]. More recently, the ring finger 213 (RNF213) gene has also been suggested as a susceptible gene for moyamoya disease but with a low penetrance rate. Various RNF213 genetic variants have been robustly detected in Japanese moyamoya diseases [27] and in Caucasian and Chinese populations [28]. Polymorphisms in the MMP-3 gene and the TIMP-2 promoter gene have also been associated with familial moyamoya disease.

Alternatively, exposure to environmental factors in a critical period, such as maternal infection or inflammation, in genetically susceptible patients may trigger the vascular changes of moyamoya disease. Some epidemiological observations have indicated that infection during the early postnatal period may lead to the development of moyamoya disease, although no specific infective pathogens have been identified [29]. Immune-related factors have been involved in the anatomical changes of the vascular wall. Immunohistochemical studies of intracranial vessels from moyamoya patients display the aberrant expression of immunoglobulin G, alpha-smooth muscle actin (αSMA), and S100A4 protein in the vessel wall [30]. The proteins of αSMA and S100A4 are robustly detected in the thickened intima. IgG binds to the internal elastic lamina, deposits, and disrupts the internal elastic lamina. It is plausible that the damaged internal elastic lamina allows the S100A4-positive smooth muscle cells to migrate into the intima, proliferate, and result in luminal narrowing. This observation compels us to consider the influence of fetal environmental factors on the risk of moyamoya disease in the future. Maternally derived immunologic factors may affect the vessel wall integrity of the fetus. Given the female dominance and a higher association with maternal moyamoya disease, there seems to be a fetal environmental exposure resulting in an increased

risk of moyamoya disease rather than a heritable factor, although mitochondrial or X-linked inheritance remains a theoretical possibility. On the other hand, there exists a link between moyamoya disease and autoimmune disease, including Graves's disease, diabetes mellitus, and systemic lupus erythematosus, supporting the contribution of an autoimmune component of moyamoya disease.

There are several lines of mediators implicated in the pathophysiology of moyamoya disease. Growth factors have been implicated as a pathogenetic contributor to smooth muscle cell migration and intima thickening. Various growth factors including basic fibroblast growth factor, cellular retinoic-acid-binding protein I (CRABP-1), and hepatocyte growth factor are robustly detected in the cerebrospinal fluid of patients with moyamoya disease [31]. Overexpression of MMP-9 and the reduced expression of MMP-3, TIMP-1, and TIMP-2 in moyamoya disease are thought to be involved in the concentric remodeling process. However, these growth factors might also mediate the formation of moyamoya vessels during the disease course. Cytokines including vascular-cell adhesion molecule type 1, intercellular adhesion molecule type 1, and E-selectin enhance the vasculo-proliferative process. Circulating endothelial progenitor cells have been involved in the disease course and progression. Indeed, endothelial progenitor cell function is impaired and their levels are increased or decreased according to the different stages of moyamoya disease [32]. In addition, smooth muscle progenitor cells derived from the blood of patients with moyamoya disease were characterized by unique features that differed from those of healthy subjects, such as irregularly arranged and thickened tubules and altered gene expression [33].

The predilection for particular regions of the intracranial vasculature of moyamoya disease may be primarily explained by hemodynamic stress on the vessel. The vessels are more vulnerable to hemodynamic stress at the site of vascular branching, where the flow is substantially fast and branches are in an acute angle. Moreover, moyamoya disease dynamically changes the geometrical parameters of the diseased vasculature. Elevated wall shear stress at the non-occluded lesions is associated with moyamoya disease progression and an increased risk of vascular events [34]. In addition, the dynamic changes of arteriogenesis can cause a local increase in wall shear stress, which may be associated with aneurysm formation and rupture. In contrast, the magnitude of wall shear stress at the near-occluded lesions is considerably lower, making the vessels more susceptible to occlusion. Under the low level of shear stress during concentric negative remodeling, endothelial cells increase the genes related to cell growth and thrombosis. A detailed evaluation of shear stress may assist in predicting the progression of moyamoya disease.

11.4.2 Cerebral Artery Dissection

The extracranial segments of the cerebral arteries are more susceptible to dissection than the intracranial segments because they are more frequently exposed to injury by bony structures such as the vertebrae and styloid processes in association with the high mobility and the wide directional changes of the vessels [35]. As previously mentioned, the intracranial arteries have no external elastic lamina and have an attenuated tunica media where the elastic fibers are only one-third as thick as the extracranial artery, and the majority of elastic fibers are located in an internal elastic lamina. Since there is so little tissue buffering the changes in mechanical strength, intracranial arterial dissections show a higher rate of subarachnoid hemorrhage than do extracranial dissections, constituting about 50–60% of all reported series of intracranial artery dissection. Collectively, the dissections of the intracranial artery and cervical artery have different mechanisms, symptoms, and outcomes. In terms of intracranial artery dissection, the risk factors and the predisposing conditions are also unknown. There are only small case series of intracranial artery dissection in association with trauma and rare genetic disorders. Further studies of intracranial artery dissection are required to provide a firm link between wall fragility and

hemodynamics and dissection. In this section, we focus on dissection at the cervical level, which is of greater clinical impact.

Cervical artery dissection is defined as the splitting of the carotid and vertebral artery wall. It is rare, accounting for about 2% of all ischemic strokes, though it constitutes 20% of incidences of ischemic stroke in young adults [36]. The internal carotid artery is 3–5 times more affected than the vertebral artery. Cervical artery dissection occurs equally by sex, but females show more frequent involvement of the vertebral artery and multiple vessels. About 85% of cases of cervical artery dissections manifest as transient ischemic attack or stroke, whereas the minor manifestations include headache, neck pain, cranial nerve palsy, and Horner's syndrome [37]. The ischemic events essentially result from thromboembolic or hemodynamic mechanisms, and severe stenosis or occlusions are more likely to be associated with ischemic events than are cases without steno-occlusion. Aneurysmal dilatation is associated with cervical artery dissection in about one-third of cases, and cervical artery dissection is occasionally associated with subarachnoid hemorrhage when the dissection extends to the intradural segment of the vessel. Although neck trauma or strenuous exertion can cause cervical artery dissection, the majority of cervical artery dissection occurs spontaneously. Occasionally, cervical artery dissection presents with minor trauma histories associated with hyperextension, rotation, or lateroversion of the neck. Various clinical situations that increase shear stress, such as hypertension, systemic inflammation, and peripartum cardiomyopathy can also increase the risk of cervical artery dissection. The dissection of the internal carotid artery occurs most frequently 2–3 cm from the bifurcation and rarely extends over the petrous bone. Vertebral artery dissection typically occurs at the V2/V3 junction where the arteries emerge from the axis vertebra and suddenly curve to enter the cranium. Vertebral artery dissection can also involve the V1 portion of the vertebral artery, since the vertebral artery is highly mobile until reaching the intervertebral foramen at C5 or C6. The dissection in the V4 portion of vertebral artery may extend to the intracranial segment. Neck pain, history of chiropractic procedure, and bilateral involvement are more common in patients with vertebral artery dissection than in those with carotid artery dissection [37].

CT angiography, TOF-MRA, and MRA with gadolinium infusion are considered sensitive techniques for the diagnosis and follow-up of cervical artery dissection. The main angiographic patterns of dissection include stenosis, occlusion, and aneurysmal dilatation (Fig. 11.5). Conventional angiography is the gold standard in imaging for cervical artery dissection, but it is only considered when endovascular intervention is anticipated owing to its invasiveness. MRA and conventional angiography are greatly limited in that they reveal only indirect signs such as a tapered vessel or aneurysms. Recent advances have been made by the use of high-resolution MRI that enables the high-quality imaging of large vascular walls. Vessel wall imaging may yield the pathognomonic findings of arterial dissection, such as an intramural hematoma or a double lumen in the damaged artery. The clinical course of cervical artery dissection is highly variable, which complicates the physician's process of selecting a therapeutic strategy. Overall, patients have a 0.3% rate of symptomatic dissection recurrences per year after the first cervical artery dissection event [38]. Patients with connective tissue disease or family history would account for the majority of the recurrences. Most steno-occlusive lesions re-canalize within weeks or months; however, some may persist in 10–20% of patients, and recanalization of cervical artery dissection is mainly achieved within the first 6 months after dissection. Apart from neurological deficits incurred by incident stroke, the long-term prognosis of cervical artery dissection is fairly good. Large, multicenter studies including the CADISS trial (Cervical Artery Dissection in Stroke Study) and the CADISP study (Cervical Artery Dissection and Ischemic Stroke Patients) showed a stroke recurrence rate of 2–3% at 3 months, with all recurrences occurring within the 2 weeks after onset [39–41]. The natural history of dissection depends on the initial angiographic features. The dissections with

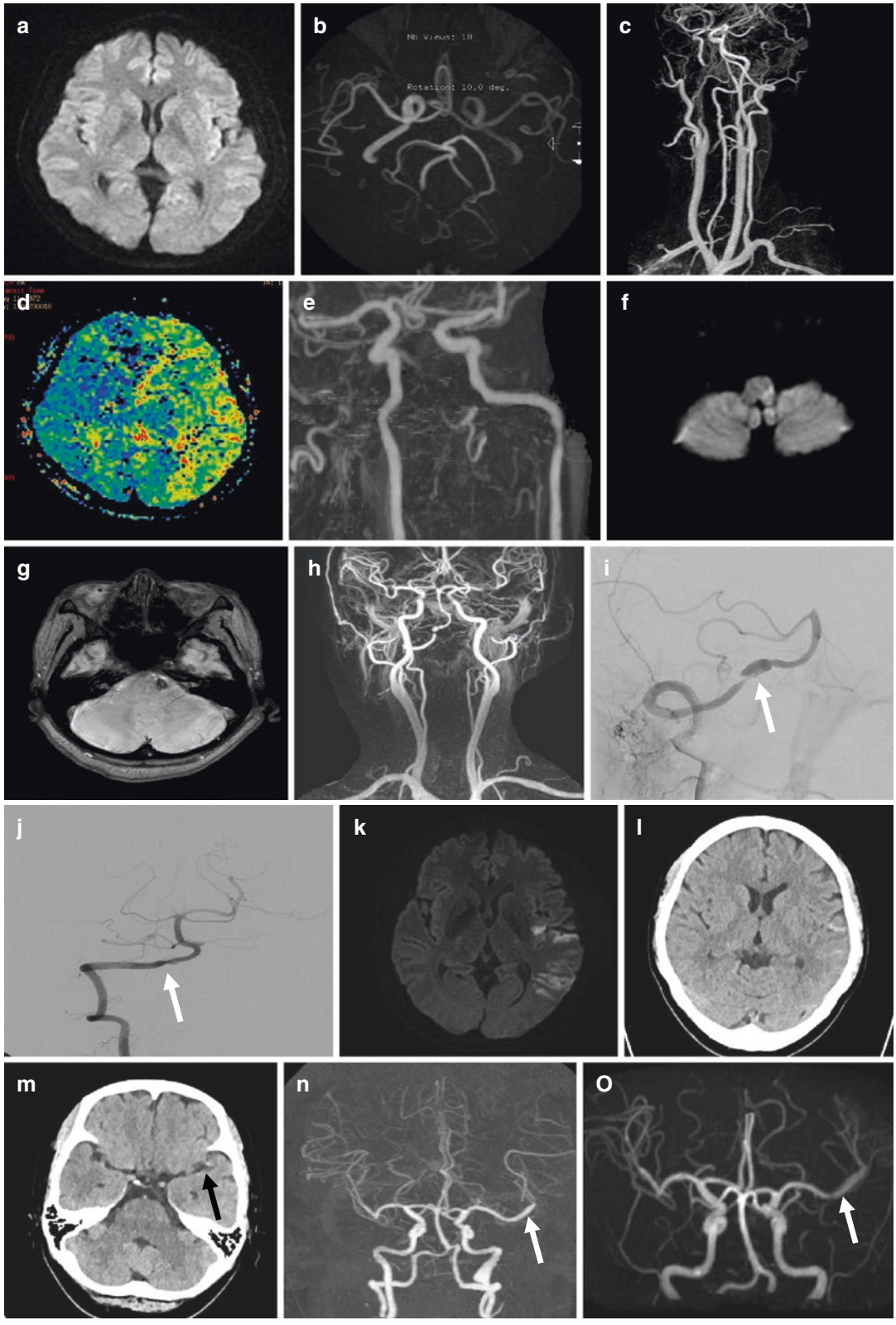
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Fig. 11.5 Phenotype of cervical artery dissection. Cerebral artery dissection occurs in various segments of the cervical and intracranial arteries. Images (**a**–**e**) indicates a carotid artery dissection. A 45-year-old man experienced a transient right-sided weakness. DWI (**a**) showed no abnormal lesions, but MRA (**b**, **c**) showed a severe stenosis of long segment of the left carotid artery. PWI (**d**) showed a perfusion delay in the left MCA territory. Follow-up MRA (**e**) revealed a significant resolution of the dissected carotid artery. Images shows a vertebral artery dissection (**f**–**j**). DWI (**f**) shows a lateral medullary infarction, and SWI shows acute thrombus in the distal left vertebral artery. MRA (**h**) and conventional angiography (**i**) showed severe stenosis of the bilateral vertebral arteries and dissecting aneurysm in the right distal vertebral artery (white arrow). Follow-up MRA (**j**) showed an improvement of stenosis and aneurysmal dilatation. Images (**k**–**o**) indicates a case of intracranial artery dissection. DWI (**k**) shows a left MCA infarction, and brain CT (**l**, **m**) showed subarachnoid hemorrhage and intramural hematoma (black arrow) in the left MCA. MRA (**n**) revealed a severe stenosis of the left distal MCA (white arrow), and follow-up MRA (**o**) showed a recannalization of left MCA but with a mild dilatation

arterial occlusion are most significantly associated with a poor outcome, whereas those with aneurysm and mildly stenotic features have favorable outcomes [42]. In general, patients with dissecting aneurysms carry a very low risk of clinical complications and good anatomic outcomes [42]. Therapeutic strategies include antiplatelet agents or anticoagulants and, occasionally, invasive treatments such as endovascular procedures. These options confer some risks, which must be applied by balancing harm and benefit and predicting the probable natural history. Antithrombotic therapy may no longer be required once the flow in the dissected artery has been restored.

Cervical artery dissection is relatively uncommon in the very elderly, possibly because of arterial stiffening or accumulating atherosclerosis during the aging process. Indeed, some age-related risk factors are negatively associated with arterial dissection. Lipid accumulation in the vessel wall and decreased compliance may change a weak artery into a resistant artery. Considering that females have more frequent vertebral artery dissection and occurrences of multiple dissections, sex hormones may contribute to the arteriopathies. It has been reported that hormones affect the integrity of vessel walls by changing collagen deposition, matrix metalloproteinases, and arterial compliance [15]. While there is no convincing evidence that the conventional vascular risk factors are related to the dissection, migraine is highly associated with patients with this disorder. Although the underlying mechanisms are unknown, there are a variety of overlapping genetic polymorphisms between migraine and arterial dissection, suggesting a common genetic predisposition. Migraine is also associated with a higher level of serum elastase activity, which usually indicates extracellular matrix degradation.

In terms of the pathophysiology of cervical artery dissection, it has been histologically proven that intima tears cause the luminal blood to burst subintimally, leading to intramural hematoma (Fig. 11.6). An alternative pathway is that the sudden intramural hematoma results from the rupture of the vasa vasorum from intrinsic factors. The pathological changes associated with cervical artery dissection primarily include the fragmentation of the elastic lamellae, focal loss of smooth muscle cells, accumulation of proteoglycans, and blood in the border of the media and adventitia. It is generally accepted that cervical artery dissection results from the interaction of a genetically determined frailty of the vessel wall and acquired factors such as minor trauma, blood dyscrasia, and infection. A significant association between the MTHFR 677TT genotype and cervical artery dissection has been noted. An association between cerebral artery dissection and connective tissue diseases, such as Marfan syndrome, neurofibromatosis type 1, Ehlers–Danlos syndrome, and Loeys–Dietz syndrome has also been suggested [43]. Connective tissue disorders usually involve dissections of multiple vessels, which favor the link between cervical artery dissection and underlying arteriopathy. However, a multifactorial genetic predisposition more frequently underlies the pathogenesis of cervical artery dissection as opposed to a single genetic disorder. The geneti-

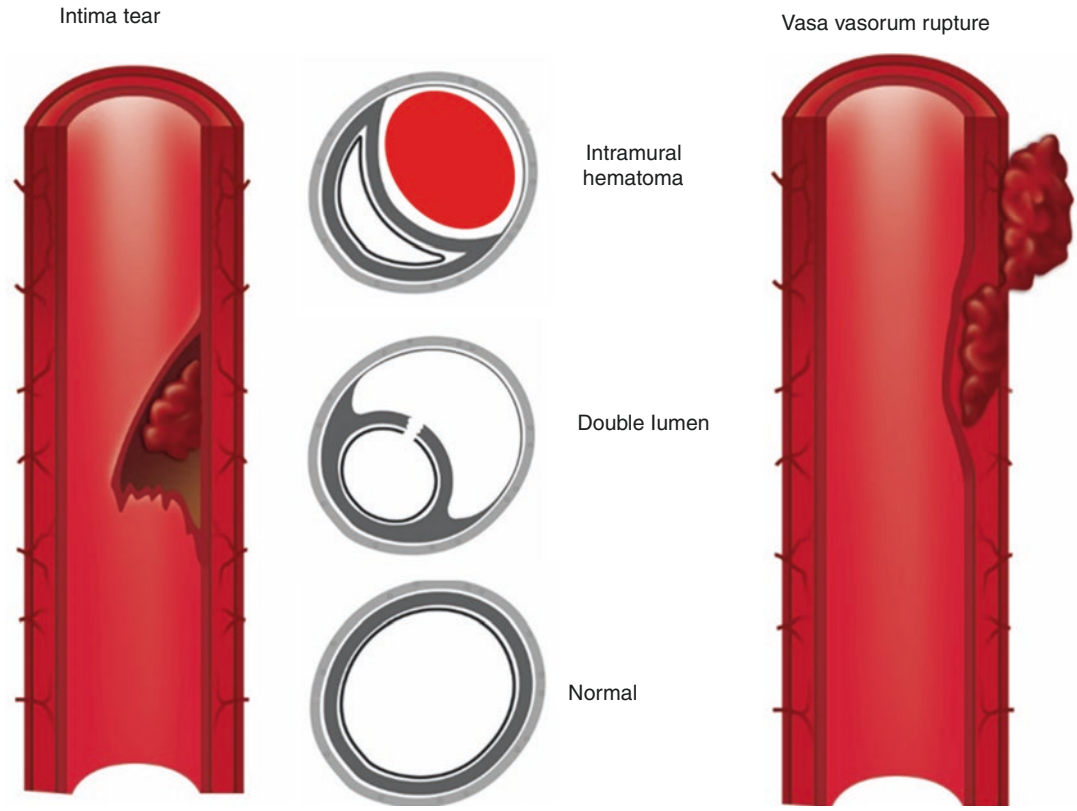

Fig. 11.6 Pathophysiology of cervical artery dissection

cally determined conditions prone to dissection share the pathogenetic feature of tunica media degeneration. An electron microscopy study of the skin of patients with cervical artery dissection displayed pieces of evidence of underlying connective tissue orders in 50%, while only 3% showed clinical manifestations [44]. In addition, cervical artery dissection commonly presents with aortic-root dilation, intracranial aneurysm, and arterial redundancies (kinks, coils, or loops) [45]. The abnormal development of neural crest-derived cells in the tunica media of the cervical and intracranial arteries is highly associated with dissection at multiple levels of the cerebral arteries. Thus, the patients with proven cervical artery dissection need extensive investigation for the underlying connective tissue disease. Shear stress is a strong trigger for the development of cervical artery dissection in predisposed individuals. Shear stress on the cervical arteries is highest at 90° of lateral rotation or 45° of rotation with neck extension [46]. Dissection induces complex flow patterns in vessels with distinct geometric properties, which might play a considerable pathophysiological role in the development, recurrence, and healing of the disease. As previously mentioned, the wall shear stress stabilizes vascular integrity and promotes remodeling. The wall shear stress might confer an adaptive role by inhibiting the growth of intimal tears, expansion of mural hematoma, and formation of luminal thrombi during the acute phase, eventually promoting anatomical recanalization. In contrast, minimal or no flow impairs arterial remodeling and reversibility, which is associated with a poor functional outcome. It was recently determined that the initial absence of antegrade flow reduces the likelihood of complete recanalization with a poor long-term outcome [42].

11.4.3 Primary Central Nervous System Vasculitis

Central nervous system (CNS) vasculitis is a heterogenous disease entity with the hallmarks of inflammation and destruction of cerebral arterial walls. It can be divided into primary CNS vasculitis and CNS vasculitis secondary to a systemic condition. In this section, we provide an overview of the primary type of CNS vasculitis. Primary CNS vasculitis is a rare inflammatory disease of unknown origin involving the medium-sized vessels of the brain and spinal cord [47]. The incidence peaks at 50 years affecting men and women equally. Neurological symptoms and signs are nonspecific and extremely variable according to the involved vessels and brain regions. Multi-territorial and bilateral acute stroke is the most common pattern found on MRI, while patients may experience recurrent strokes or diffuse progressive encephalopathy. Primary CNS vasculitis should be suspected in the setting of strokes of unknown causes with abnormal angiography. Widely adopted diagnostic criteria include the presence of neurologic or psychiatric symptoms, typical angiographic or histopathological features of vasculitis within the CNS, and exclusion of other mimicking diseases.

The common diagnostic tool for primary CNS vasculitis is a conventional cerebral angiography, while the gold standard for the confirmatory diagnosis of primary CNS vasculitis is cerebral and meningeal biopsy. Typical angiographic findings include segmental stenosis and dilatation of multiple mid-sized arteries in both hemispheres (Fig. 11.7). However, the sensitivity and specificity of angiographic findings are not optimal and it is unclear whether angiographic findings are well correlated with those from cerebral biopsy. In pathologically proven cases of primary CNS vasculitis, angiography was found to have a sensitivity and specificity of only about 30%. The low sensitivity is probably because a significant proportion of primary CNS vasculitis involves the distal segment of cerebral arteries below its spatial resolution. The advance in neuroimaging holds promise for differentiating primary CNS vasculitis from other non-inflammatory conditions. The advent of high-resolution MRI for the intracranial arteries may help to differentiate CNS vasculitis from other vasculopathies. In patients with multiple arterial stenoses, the enhancement of the arterial wall with gadolinium is more prominent in primary CNS vasculitis than in other mimicking arteriopathies [23, 48].

Given the non-specificity of cerebral angiography, patients with suspected primary CNS vasculitis should undergo biopsy. The biopsy provides essential information for identifying vasculitis and also in evaluating infectious and neoplastic diseases. In contrast, cerebral biopsy is not generally indicated in cases of negative angiography because conventional cerebral angiography is associated with a high negative predictive value for primary CNS vasculitis. Since primary CNS vasculitis involves vessels in a skipped and segmental pattern, the sensitivity is low with a false negative rate of 25% and a negative biopsy does not rule out the likelihood of CNS vasculitis. Thus, the site for biopsy should be carefully selected so that areas of radiological abnormalities and meningeal sampling are targeted. For tissue biopsy, open-wedge biopsy of a radiologically positive lesion is recommended to increase the biopsy efficiency. Typical histological findings include granulomatous vasculitis with vasculocentric mononuclear inflammation, diffuse lymphocytic vasculitis with occasional plasma cells, and necrotizing vasculitis characterized by transmural fibrinoid necrosis in the leptomeningeal and parenchymal arteries (Fig. 11.8) [49]. The intracranial arteries usually undergo stenosis or occlusion by thrombosis and inflammation in the vessel wall. The lesion is often accompanied by hemorrhagic transformation or hemorrhagic complications such as subarachnoid hemorrhage. The mechanism by which blood leaks into the subarachnoid space is not well understood, though the interaction between the inflammatory vascular lesion and ischemia reperfusion secondary to steno-occlusion is involved in this complication. The pathogenesis of primary CNS vasculitis is also not fully under-

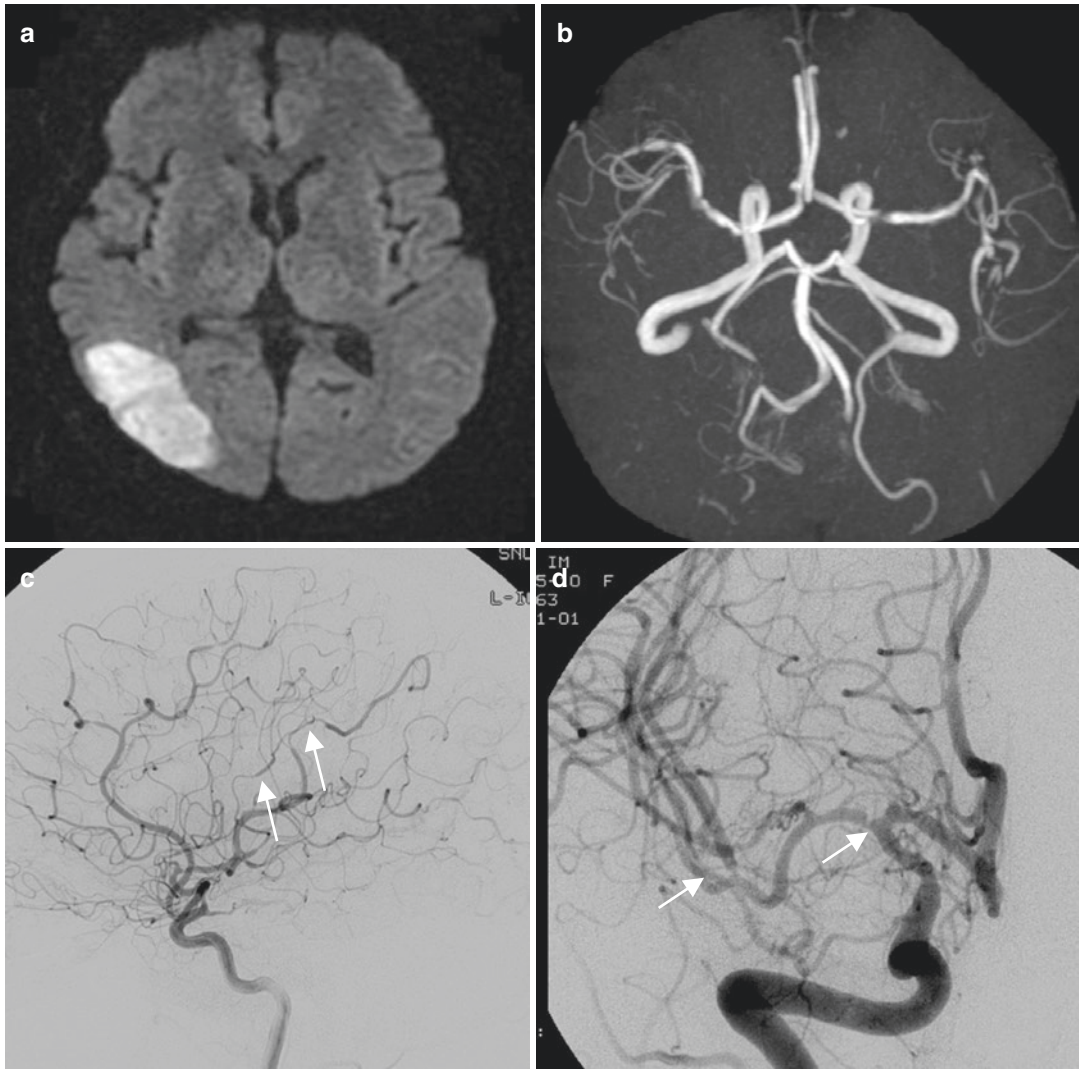

Fig. 11.7 Phenotype of primary CNS vasculitis. A 58-year-old woman visited us because of a sudden visual disturbance. She has no specific history suggestive of systemic vasculitis. DWI (**a**) showed an infarct in the right temporo-occipital area. MRA (**b**) showed a multiple segmental stenosis in the intracranial arteries. Conventional angiography (**c**, **d**) showed beaded patterns of stenosis in multiple intracranial arteries (white arrows). The clinical and angiographic phenotypes were well-controlled with immunosuppressive agents

stood. No clear genetic links have been noted in adult patients with the disease, and although the immunologic triggers have not been clearly identified, certain types of viral or mycobacterial organisms may contribute to the initiation of inflammatory cascades. The presence of memory T cells deposited in the vessel wall may represent the evidence of a cross-reaction to similar epitopes [50]. As reported in animal models of vasculitis, MMP 9 may play a primary role in the destruction of the vessel wall.

The low incidences of this disease entity and the lack of specific laboratory markers for diagnosis prompt consideration of a wide range of differential diagnoses. Radiological mimics of primary CNS vasculitis include reversible cerebral vasoconstriction syndrome (RCVS), infectious vasculitis, CNS manifestations of sys-

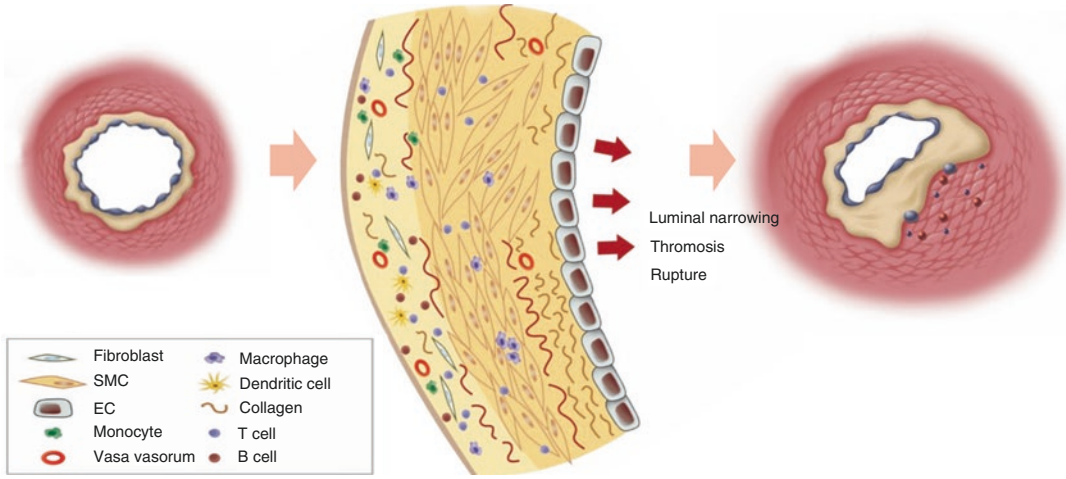

Fig. 11.8 Pathophysiology of primary CNS vasculitis. *EC* endothelial cell, *SMC* smooth muscle cell

temic vasculitis, and neoplastic conditions. The most common differential diagnosis is atherosclerotic disease. Atherosclerotic disease is more proximal, more eccentric, and involves shorter segments as compared to vasculitic lesions. RCVS is a noninflammatory vasoconstrictive syndrome characterized by severe headache and sometimes focal or diffuse neurologic signs. Cerebrospinal fluid analysis, which is essential for the differential diagnosis of the two diseases, generally shows findings of aseptic meningitis in primary CNS vasculitis and helps to exclude RCVS. Angiographic abnormalities are more diffuse in RCVS than in primary CNS vasculitis, and they typically resolve within 8–12 weeks. The convexity subarachnoid hemorrhage is present in 25% of patients with suspected primary CNS vasculitis [51]. This rate is comparable to the magnitude found in RCVS. However, the higher association with leptomeningeal enhancement supports the higher likelihood of a diagnosis of primary CNS vasculitis [52]. Vasculitis is a common mechanism of cerebrovascular complications mediated by infectious pathogens. Vasculitis arises from direct invasion of the pathogen itself or of inflammatory cells into the vessel wall, or indirectly by chemical stimulation of inflammatory exudates in the subarachnoid space. Infiltrative vasculitis occurs inward from the adventitia and is prominent in the large- and medium-sized arteries in the circle of Willis. Infectious pathogens that are most frequently associated with vasculitis are pyogenic bacteria, tuberculosis, *Treponema pallidum*, *Borrelia burgodorferi*, human immunodeficiency virus, hepatitis B and C virus, varicella zoster virus, cytomegalovirus, and Cryptococcus. Varicella zoster virus (VZV) is one of the more important pathogens linked to CNS vasculitis; therefore, cases of suspected primary CNS vasculitis should be evaluated for VZV vasculopathy. Infectious vasculopathy can be excluded by thorough microbiological testing of the cerebrospinal fluid. On the other hand, CNS vasculitis associated with systemic autoimmune diseases should also be differentiated from primary CNS vasculitis. Behcet's disease, systemic lupus erythematosus, Sjogren syndrome, and sarcoidosis can mimic all aspects of primary CNS vasculitis. Constitutional symptoms, systemic organ dysfunction, and elevation of acute phase reactants in serum suggest the presence of systemic disease rather than primary CNS vasculitis. Primary CNS vasculitis is a distinct disease entity from CNS vasculitis of other causes in that it rarely involves systemic organs or alteration of systemic inflammatory markers. Furthermore, primary CNS autoimmune disease such as NMDAR encephalitis may mimic the clinical presentation of primary CNS vasculitis. In the clinical setting, neuronal antibody testing should be performed. The radiological findings may be similar to intravas-

cular lymphoma or primary CNS lymphoma. Brain biopsy is mandatory to clinically distinguish the two disease conditions. Since the disease responds well to immunosuppressive therapy, early clinical suspicion is critical. Failure of immunotherapy should prompt reevaluation for an alternative diagnosis such as a neoplastic disorder, infection, systemic autoimmune disease, and reversible vasoconstriction syndrome.

11.5 Future Directions

Moyamoya disease, arterial dissection, and CNS vasculitis are radiologically similar arteriopathies with distinct pathophysiologies in relation to the degeneration and remodeling processes of the arterial wall. Enriched epidemiological observations and advanced imaging and laboratory profiles have enhanced our knowledge of the similarities and differences between the cerebral vessel wall diseases. Further investigation is necessary to determine the master switch and elucidate the downstream phenomenon in each disease. In the context of shared pathophysiology, small vessel disease is currently recognized as encompassing lacunes, microbleeds, and leukoaraiosis. This strategy can also be applied to the cerebral vessel wall diseases. Comprehensive multi-panel assays with high-throughput genetic or immunologic tests would offer the opportunity to classify cerebral vessel wall diseases as mechanical, inflammatory, autoimmune, or degenerative conditions.

Prompt diagnosis is necessary to improve the long-term outcome of patients with cerebral vessel wall diseases. Each cerebral vessel wall disease requires a distinct therapeutic approach. In moyamoya disease, hemodynamic support by direct or indirect bypass surgery may be helpful to prevent future ischemic events. Cervical artery dissection is usually treated using anticoagulant or antiplatelet agents, but occasionally by endovascular treatment, while various regimens of immunosuppressive therapy have been applied for CNS vasculitis. We are still in the early stages of optimizing the management of these cerebral vessel wall diseases. There is a need for an enhanced understanding of the therapeutic targets before the optimal treatment is achieved for each condition. In order to establish more effective therapeutic targets, we need to better comprehend the underlying pathophysiology and the shared associations among all the cerebral vessel wall diseases. Data regarding the natural history and genetic and molecular signatures associated with disease development should be accumulated based on the findings of large prospective multicenter cohorts. In addition, more histopathological data should be obtained with optimal targets and methods. Developments and applications of new vessel wall imaging techniques in conjunction with pathological data would enable the clear characterization of lesions with respect to injury type, injury extent, and vulnerability to thrombosis or rupture.

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Hemorrheologic Disease

12

Min Kyoung Kang

Abstract

How do you think we know hemorrheologic disease-related stroke? In most situations, patients and clinician have low awareness of hemorrheologic disease-related stroke because of its low incidence and uncertainty of diagnosis. However, considering the importance and the curability of the disease, up-to-date knowledge about pathophysiology and important differential points between classical stroke and hemorrheologic disease-related stroke are essential for neurologists. In this context, understanding the key concept of hemorrheologic disease will provide appropriate treatment strategy according to its pathophysiology. At each point, antiphospholipid syndrome must be checked for, especially in young stroke patients with undetermined etiologies. An expert's opinion is needed on the diagnosis of cancer-related stroke and cerebral venous thrombosis based on patients' clinical context and stroke pattern. For the diagnosis of other hemorrheologic diseases, the clinician needs to watch out for any laboratory clues. The emerging treatment option for hemorrheologic disease is non-vitamin K antagonist oral anticoagulants; however, prospective studies are needed to prove its efficiency for hemorrheologic disease-related stroke. Through the delicate suspicion of the clinician, we could reduce a patient's fear of uncertainty of diagnosis and recurrence in the long term.

12.1 Antiphospholipid Syndrome

Since the first report in Jamaica, understanding of the pathophysiology of antiphospholipid syndrome (APS) has been pursued for more than three decades, but it is still not totally understood. A typical APS has several established characteristics, such as arterial and venous thromboses, pregnancy-related morbidity, miscarriages, fetal growth restriction and deaths, and pre-eclampsia [1]. In fact, APS can be associated with various clinical symptoms, such as stroke, seizures, cognitive impairment, pulmonary embolism, heart disease, coronary artery disease, thrombocytopenia, livedo reticularis, osteonecrosis, renal failure, and distal gangrene (Fig 12.1). This autoimmune disease is diagnosed by certain types of autoimmune antibodies, not mutually exclusive but commonly referred to as antiphospholipid antibodies, such as lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti-β2-glycoprotein I (GPI) antibodies. Among these antibodies, the prelude to the coagulation cascade is binding to β2-GPI. Despite the high interest for APS, there are no robust epidemiological statis-

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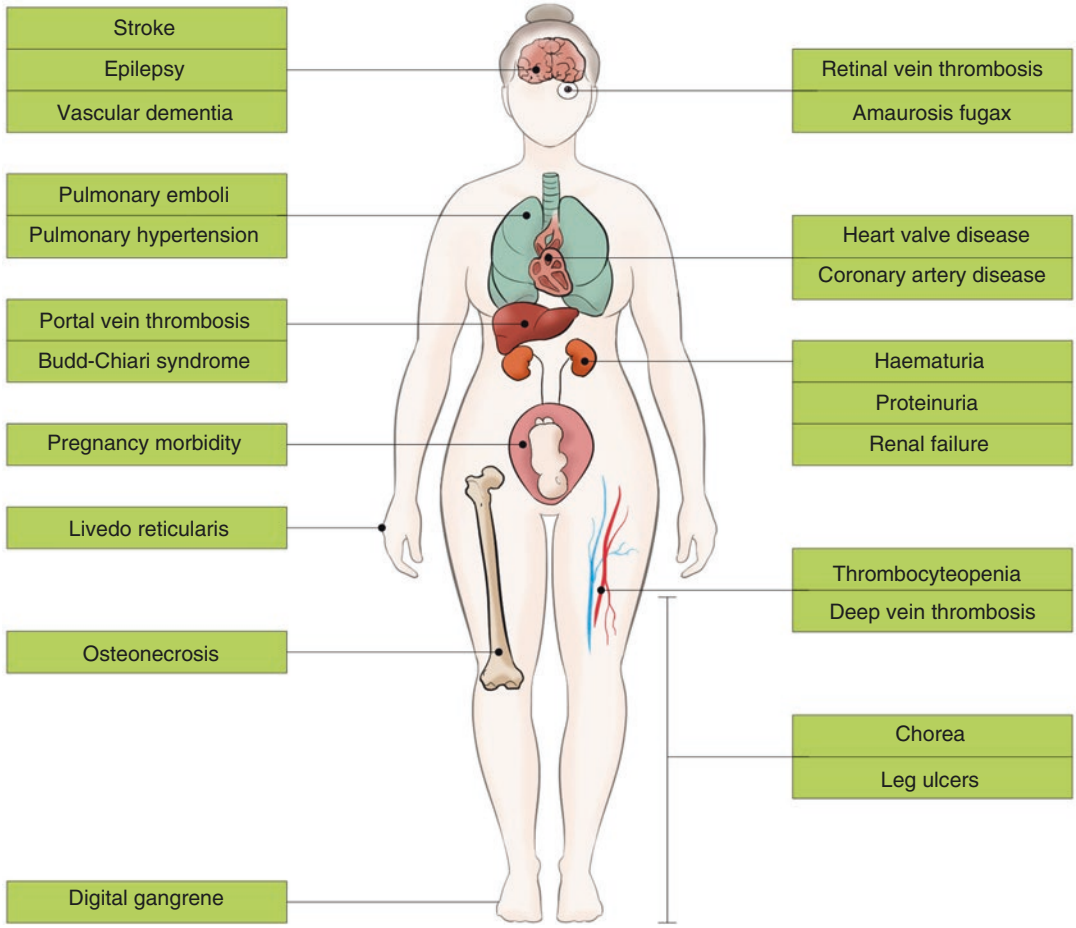

Fig. 12.1 Clinical manifestations of antiphospholipid syndrome. Adapted with permission from Nature Review Disease Primers, Copyright Springer Nature [1]

tics, as the methods of antibody detection are not established among worldwide laboratories.

12.1.1 Epidemiology of APS

There are no clear statistics on the epidemiology of APS, but the reported incidence of APS is 5 per 100,000 individuals per year, and its prevalence is approximately 40–50 cases per 100,000 individuals [2]. Despite efforts made to standardize immunoassays for the detection of antiphospholipid antibodies, considerable variations in interassay and interlaboratory aspects are still reported. For this reason, the robustness of epidemiological data of antiphospholipid antibody positivity and APS in the general population is limited.

In the cohort of the Euro-Phospholipid project, which started in 1999 as a multicenter, prospective study, approximately 5% of the total cohort experienced stroke and transient ischemic attacks. Interestingly, some studies showed that antiphospholipid antibodies were detected in 20% of young stroke cases. Specifically, 40% of the participants of the Euro-Phospholipid project had deep vein thrombosis, 20% had stroke, 14.1% had pulmonary embolism, and 11.1% had transient ischemic attack and obstetric morbidity [3].

12.1.2 Pathophysiology of APS

APS is an autoimmune disease that is usually caused by autoantibodies, such as LA, aCL, and anti-β2-GPI antibodies. Binding of antiphospholipid antibodies leads to dimerization of β2-GPI that enhances activation of inflammatory cells and endothelial cells, promotion of coagulation, and activation of complement system (Fig. 12.2) [4]. Autoantibodies bound to β2-GPI, especially via domain 1, can induce a strong prothrombogenic tendency in animal models through the injection of human anti-β2-GPI antibodies in mice. Through this process, the cascade through platelet and complement activation to the monocyte and vascular environment becomes the main route to thrombosis in APS.

In the two-hit theory, the first hit is the genetic predisposition to produce autoantibodies bound to β2-GPI. Although autoantibodies are always produced, signs and symptoms of APS do not always manifest [1]. The second hit is the trigger for promoting the production of autoantibodies. Inflammation, infection, smoking, pregnancy, and other procoagulant factors such as contraceptives, smoking, and surgery have all been reported as potential causes of the second hit (Fig. 12.2). Molecular mimicry between structures of infectious agents such as bacteria or viruses and β2-GPI-derived amino acid sequences is thought to be the cause of the formation of autoantibodies. In this context, it is better to see autoimmune antibodies collectively, as indicated by the term antiphospholipid antibodies, rather than highlighting each identity.

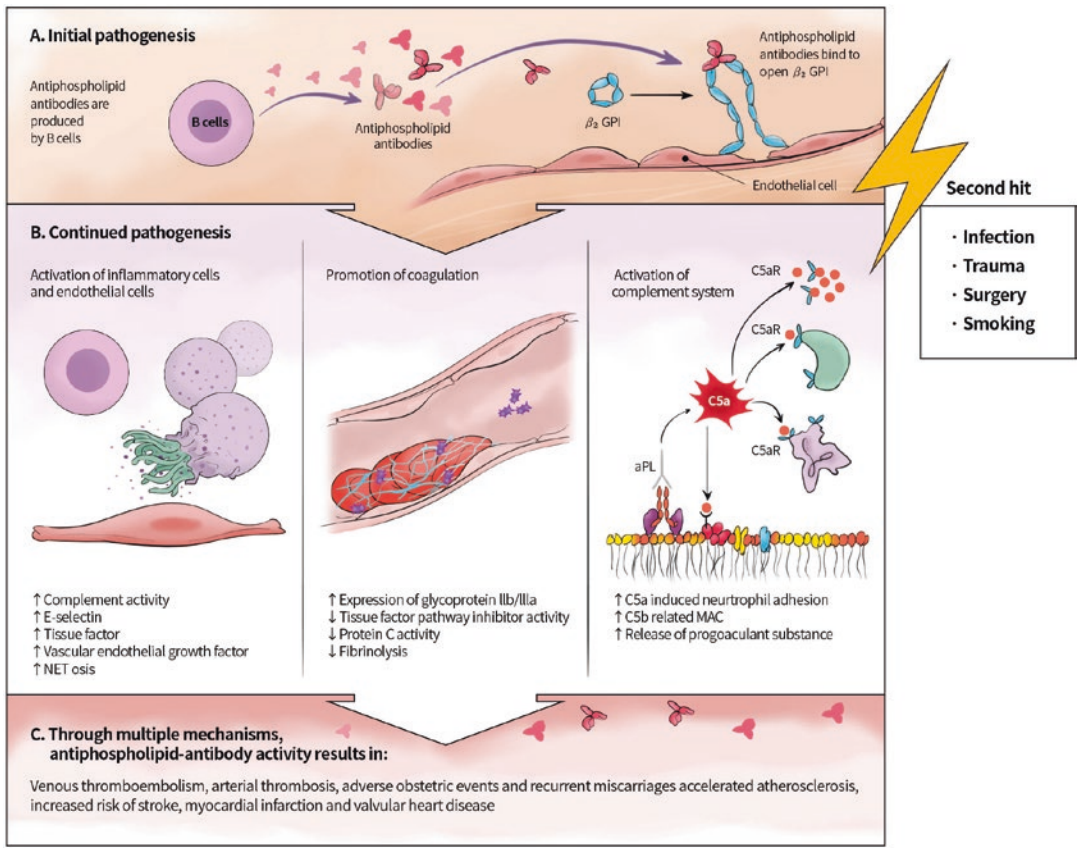

Fig. 12.2 Pathophysiology of antiphospholipid syndrome. Adapted with permission from New England Journal of Medicine, Copyright Massachusetts Medical Society [4]

12.1.3 Diagnosis of APS

APS could be diagnosed by an expert clinician who evaluates the patient's history and laboratory test comprehensively. Definitive diagnosis of APS follows a set of classification criteria (Table 12.1). However, the symptoms that do not fit with the criteria for definite APS need to be assessed in detail. These symptoms may also indicate thrombocytopenia, hemolytic anemia, thrombotic microangiopathy, valvular heart lesion, livedo reticularis, cognitive dysfunction, subcortical white-matter change, multiple sclerosis, chorea, or myelopathy. For laboratory criteria, assessment of antibody profile is the mainstay of diagnosis and helps in risk stratification of APS. High titer and detection of multiple autoantibodies provide more confidence in the diagnosis.

However, obtaining definitive APS diagnosis has several hurdles. First, there is a problem on the standardization of immunoassays for measurement of antiphospholipid antibodies. Profound interassay and interlaboratory variations are still reported. Considering the difference among laboratories, the diagnosis criteria were set at ≥99% for antibody titer for aCL. Second, in anticoagulated patients, a false positive is possible. Third, for exclusion of transient humoral change, the restriction sentence, "two positive results at least 12 weeks apart between tests" was included in the diagnostic criteria for APS. If an aCL result for only a single time point is available, the diagnosis may be delayed. Thus, integrated interpretation of all tests and symptoms is needed for APS diagnosis.

Table 12.1 Diagnosis of antiphospholipid syndrome

Clinical criteria (one or more)
1. Vascular thrombosis: One or more objectively confirmed episodes of arterial, venous, or small vessel thrombosis occurring in any tissue or organ
2. Pregnancy morbidity:
(a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation
(b) One or more premature births of a morphologically normal neonate before the 34th week of gestation due to eclampsia, preeclampsia, or placental insufficiency
(c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation
Laboratory criteria (one or more, present in two or more occasions at least 12 weeks apart using recommended procedures)
1. Lupus anticoagulant, detected according to the guidelines of the International Society on Thrombosis and Hemostasis
2. Anticardiolipin antibody of IgG and/or IgM isotype, present in a medium or high titer (greater than 40 GPL or MPL or greater than the 99th percentile), measured by a standardized ELISA
3. Anti-β2-glycoprotein-1 antibody of IgG and/or IgM isotype, present in a titer greater than the 99th percentile, measured by a standardized ELISA

12.1.4 Treatment of APS Treatment

APS is a relatively rare disease, and its evidence is scarce. The treatment decision was made based on expert opinion in many cases. Under the current diagnostic system that consists of symptoms and a special laboratory test, the primary prevention of APS is a great challenge. As a conventional cardiovascular risk factor, smoking cessation was recommended, and low-dose aspirin and hydroxychloroquine can be considered for patients with systemic lupus erythematosus (SLE) who are positive for LA. For secondary prevention for those who experienced a thromboembolic event, aspirin was recommended as evidence level A. Considering that platelet activation is one of the pathways of APS, aspirin is a reasonable option. However, oral anticoagulants, warfarin or non-vitamin K antagonist oral anticoagulants (NOAC), might have a role in the coagulation pathway and tissue factors pathway, especially in the refractory group (Table 12.2).

NOAC can be an emerging treatment option considering the mechanism of thrombosis in APS and the ease of use. Rivaroxaban was compared to warfarin in a multicenter randomized controlled trial [5]. In this trial, the peak thrombin generation was lower in the rivaroxaban group than in the warfarin group, which leads to the extension of the beneficial effect of warfarin to NOAC. Anti-inflammatory drugs, such as intravenous immunoglobulin, rituximab, eculizumab, and hydroxychloroquine, are also being studied in APS.

Table 12.2 Treatment of antiphospholipid syndrome

Clinical manifestation	Treatment
Venous thrombosis	Oral anticoagulation therapy (INR 2.0–3.0)
Arterial thrombosis	Oral anticoagulation therapy (INR 3.0–4.0) or LDA plus oral anticoagulation therapy (INR 2.0–3.0) or LDA alone
Antiphospholipid positivity with previous thrombosis	LDA plus therapeutic dose of LMHW
Pregnancy with antiphospholipid positivity	Prophylactic dose of LMWH for 6 weeks postpartum
Treatment-refractory antiphospholipid syndrome	Increased intensity of anticoagulation therapy (INR > 3.0) or add LDA, hydroxyquine or rituximab to oral anticoagulation

LDA low-dose aspirin, *LMWH* low molecular weight heparin

12.2 Cancer-Related Stroke

Since the declaration of war on cancer, many advances have been made in cancer treatment and diagnosis, but humans have not yet been able to conquer cancer. As the number of people with cancer increases, the incidence of cancer-related stroke has also increased. Moreover, as the duration of cancer is lengthening according to increased life expectancy, the incidence of cancer-related stroke has also increased.

Patients with cancer are at risk for the development of ischemic stroke. Malignancy activates the coagulation cascade by multiple mechanisms, by itself, and by treatment such as chemotherapy, radiotherapy, and surgery. Multiple site infarction and increased D-dimer level help in the diagnoses of cancer-related stroke. Low-molecular-weight heparin (LMWH) is thought to be the drug of choice, but there are emerging NOACs for cancer-related stroke. The diminished general medical condition of patients and this mechanistic uncertainty make it difficult to choose treatment options; hence, the expert needs to weigh the benefits and risks of treatment for cancer-related stroke.

12.2.1 Epidemiology of Cancer-Related Stroke

Cancer-related thrombosis was first described in 1876. Since then, many advances in diagnostic and therapeutic technology enable to extend the life expectancy of cancer patients. At present, 40% of the general population is likely to develop any type of cancer throughout their lifetime [5]. In addition, the survival rate of cancer patients has increased by 1.5 times compared to that at 10 years ago. Therefore, the management of cancer complications has become more interesting and important. Approximately 10% of in-hospital ischemic stroke patients have comorbid cancer, and cancer is also associated with early neurological deterioration, poor functional outcome, stroke recurrence rate, and mortality after stroke [6]. In a different light, approximately 7% of cancer patients experienced a twofold increased risk of ischemic stroke at 1 year since diagnosis. The most common type of cancer in patients with stroke and active cancer are lung, gastrointestinal, and breast cancer. The incidence of stroke correlates with advanced cancer stage, the highest in stage 4. Besides stroke, the manifestation of cancer-associated thrombosis includes pulmonary embolism, deep vein thrombosis, and nonbacterial thrombotic endocarditis (NBTE). Recently, many cancer patients live longer and have more therapeutic options; thus, cancer-related stroke becomes more important.

12.2.2 Pathophysiology of Cancer-Related Stroke

The exact pathophysiology of cancer-related stroke remains unknown. However, we think that it may be a multifactorial phenomenon. The following are considered key players: hypercoagulability by cancer itself; tumor microparticles and mucin circulating in the bloodstream; induced hypercoagulability by cancer that correlated with cancer type (highest in adenocarcinoma), advanced stage, and vessel invasion; tissue factor and procoagulant factor released by cancer cell; activated platelet, endothelial cell, and adhesion

molecules such as P- and L-selectin; neutrophil extracellular trap (NET) generated by stimulated neutrophil and inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1 and IL-6 produced by monocyte or macrophage are proposed to initiate the coagulation cascade of cancer-related stroke (Fig. 12.3). In addition, cancer patients have worsened classical risk factors of stroke. Systemic inflammation evoked by cancer promotes atherosclerotic plaque progression and rupture. A rare but important mechanism in cancer patients is increased embolic tendency due to atrial fibrillation or septic embolism.

Another key player is anticancer treatment. L-asparaginase for acute lymphoblastic leukemia, alkylating agent (cisplatin), mammalian target of rapamycin (mTOR) inhibitor (everolimus, temsirolimus), proteasome inhibitors (bortezomib), monoclonal antibodies (bevacizumab), vascular endothelial growth factor-receptor (VEGF)-targeted therapy (aflibercept), tyrosine kinase inhibitor (sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, lenvatinib, nilotinib, ponatinib), interferon-alpha, anti-estrogen treatment (raloxifene, tamoxifen), and radiotherapy are known to increase the risk of stroke [7]. They mainly evoke endothelial dysfunction. The VEGF pathway is a relatively well-documented mechanism of anticancer therapy. Inhibition of VEGF receptor hinders nitric oxide (NO) production by endothelial NO synthase via the phosphoinositide-3-kinase-protein kinase B/Akt pathway. Radiotherapy can also worsen atherosclerotic changes [8].

An interesting pathologic finding related to tumor is NBTE. NBTE presents as sterile eosinophilic vegetation or wartlike materials made of fibrin and platelet aggregates. It is believed to be caused by inflammation or a microorganism, but not by bacteria [5].

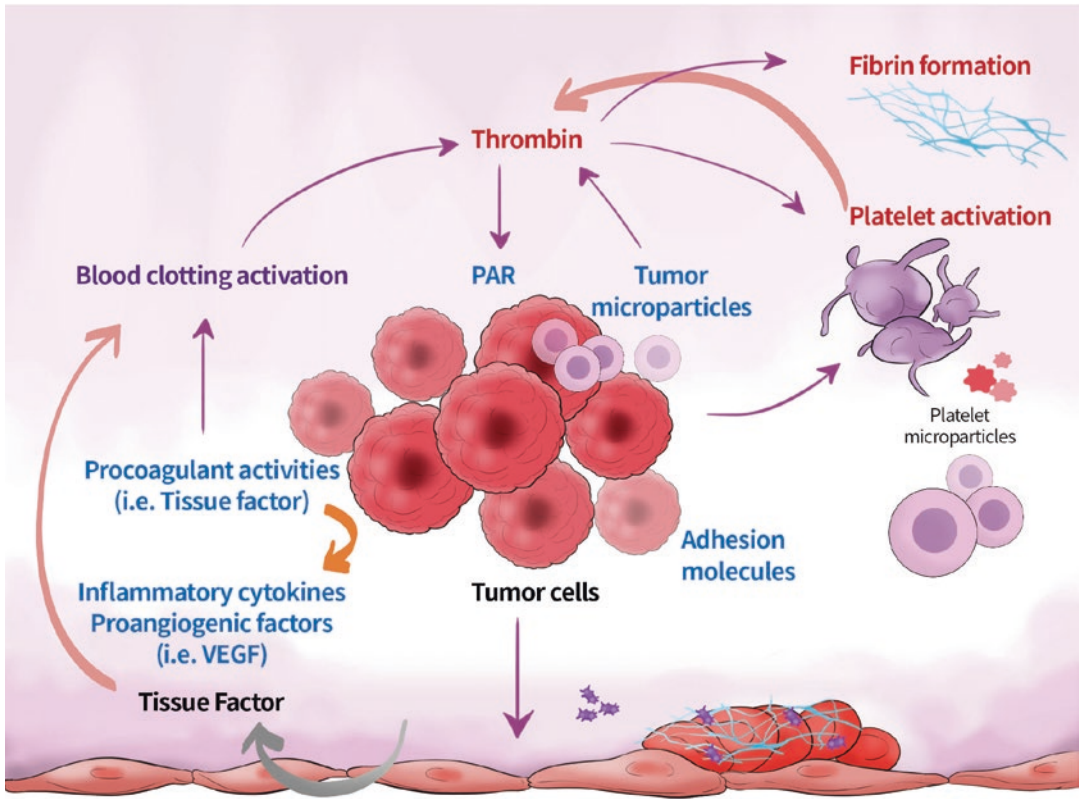

Fig. 12.3 Pathophysiology of cancer-related stroke. *PAR* protease-activated receptors, *VEGF* vascular endothelial growth factor

12.2.3 Diagnosis of Cancer-Related Stroke

There are no definite diagnostic criteria for cancer-related stroke. Therefore, when a stroke occurs in a cancer patient, the clinician must concentrate on the mechanism of stroke by careful consideration of the clinical settings: time from cancer diagnosis, cancer cell type, history of anticancer treatment, ischemic lesion, and laboratory tests. Proposed clues for cancer-related stroke include increased D-dimer level, C-reactive protein, fibrinogen, tumor marker, decreased platelet count, fibrinogen or hematocrit, multiple brain lesions that cannot be explained by single vessel territory, and echocardiographic evidence of NBTE [9]. Neurologists may obtain additional clues from transcranial doppler (TCD) imaging. In a prospective study, 50% of cancer-related stroke patients had signals of microemboli detected on TCD exams [10]. In addition, the presence of the microemboli was associated with high D-dimer levels. It suggests an active hypercoagulable state in many of these patients.

12.2.4 Treatment of Cancer-Related Stroke

The primary principle for the treatment of cancer-related stroke is the use of a precise approach. There is no concrete consensus on the management of cancer-related stroke, and their management slightly differed from other ischemic stroke patients. First, cancer must be eradicated as soon as possible. As described above, the key player is the cancer cell itself. Second, the clinician should prescribe medical treatment when the benefit of anticoagulation could surpass the risk of bleeding, considering underlying general medical condition and life expectancy. Third, the clinician should ensure that the prescribed treatment is the most appropriate method for the patient. For example, oral medication would not be appropriate for patients with obstruction of gastrointestinal tract due to cancer.

What medication is appropriate for this patient? Considering the main pathophysiology, anticoagulation could be a proper option; hence, warfarin and LMWH have been used thus far (Table 12.3). However, for many practical reasons such as consistency of the anticoagulant effect and the ease of administration, NOACs are emerging candidates for long-term coagulation [8]. Regarding cancer-associated venous thromboembolisms (VTE), research of NOAC uses for cancer-related thrombosis has been conducted. Edoxaban, rivaroxaban, and apixaban led to less recurrent thromboembolism but more events of major bleeding compared to LWMH. However, data on the utility of NOACs for cancer-related stroke is limited. An alternative for cancer-related stroke is antiplatelet therapy. Platelets activated by cancer itself or factors secreted by cancer play a role in cancer-related stroke, so antiplatelet agents might have a protective effect for cancer-related stroke properties. However, antiplatelet therapy has not been proven effective for the secondary prevention of cancer-associated stroke.

Table 12.3 Treatment of cancer-related stroke

Acute management	
LMWH	Dalteparin 200 U/kg QD Enoxaparin 1 mg/kg BID
Fondaparinux	5 mg (<50 kg), 7.5 mg (50–100 kg), 10 mg (>100 kg) QD
Unfractionated heparin	APTT-adjusted infusion (target APTT 2–2.5 X control)
Chronic management	
LMWH	Recommended for first 6 months as monotherapy Without warfarin in patients with proximal DVT or PE and metastatic or advanced cancer
NOACs	Minimum 3 months

LMWH low molecular weight heparin, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *NOAC* non-vitamin K antagonist oral anticoagulants

12.3 Cerebral Venous Thrombosis

Cerebral venous thrombosis (CVT) is caused by thrombosis, and its incidence is lower than strokes of other etiologies. Its vague neurologic symptoms and signs, such as headache, visual disturbance, and seizures, pose diagnostic challenges to clini-

cians [5]. The diagnosis of CVT depends on neuroimaging studies based on clinician's suspicion, especially in brain computed tomography (CT) and magnetic resonance (MR) imaging. Its pathophysiology is thought to be a combination of the anatomical structure of the cerebral venous system and systemic hypercoagulability due to infection, trauma, oral contraceptive, puerperium, and malignancy. The treatment strategy is based on anticoagulant, and the duration of the treatment varies with the presence of provocation factors.

12.3.1 Epidemiology of CVT

CVT is a rare disease. Given its vague presentation, diagnosis is still difficult, and this disease entity has been under-recognized so far. Despite sparsity of robust epidemiological evidence, the overall incidence of CVT is 1.32 per 100,000 person-year [11]. CVT accounts for 0.5%–1% of ischemic stroke cases. Especially, in young stroke patients, it occurs in seven cases per million, which is two times higher than that in the general population. Moreover, 5% of young stroke patients are diagnosed with CVT. In the International Study on Cerebral Vein and Dural Sinus Thrombosis study, approximately 45% of the patients were identified to have more than one cause of CVT, mainly as oral contraceptive use, thrombophilia, pregnancy, puerperium, and head and neck infections [12].

12.3.2 Pathophysiology of CVT

The Virchow triad is usually used to explain the pathophysiology of CVT (Fig. 12.4). Anatomically, superficial cerebral veins and sinuses lack tunica muscularis and valves, which allow bidirectional flow and therefore induce thrombus formation within the structure. In the

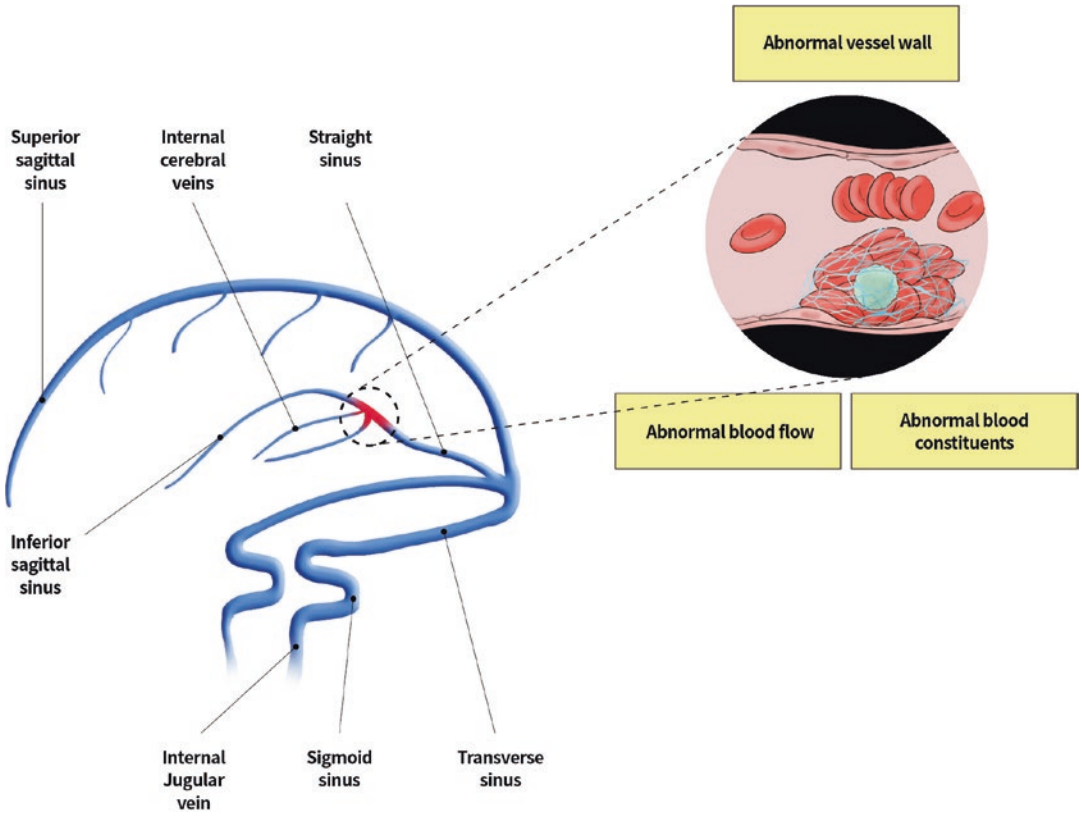

Fig. 12.4 Pathophysiology of cerebral venous thrombosis

superior sagittal sinus, scalp and cerebrospinal fluid (CSF) infections could evoke thrombosis due to anatomical adjacency. In case of a lateral sinus, the anatomical positioning near the mastoid increases their susceptibility to thrombosis induced by ear infection. Any blockage in the deep venous structure and poor venous outflow leads to the decreased CSF drainage, followed by increased the intracranial pressure. Another factor for CVT is systemic hypercoagulability. The hypercoagulable tendency is reported in patients not only with infection, but also cancer, nephrotic syndrome, inflammation, transient physiological states including dehydration and pregnancy, oral contraceptives, smoking, and head trauma [13]. Genetic causes are related to not only deficiency of prothrombin or protein C/S, but also AT3-deficient hyperhomocysteinemia.

12.3.3 Diagnosis of CVT

Experts' suspicion is a very important point in the diagnosis for CVT. Acute to subacute headache, young age, and bizarre neurology may be a clue to CVT. Clinical manifestations of CVT are less stereotyped than those of arterial stroke syndromes.

CVT is often presented as focal seizure or bilateral neurologic symptoms, frontal lobe dysfunction in the superior sagittal veins; headache, ear pain, tinnitus, uncommon aphasia or neglect in the transverse sinus; orbital pain, diplopia, ptosis, palsy of cranial nerve which pass through the cavernous sinus, mental status changes, and rapid neurological deterioration in the deep vein system. In severe cases, CVT of the deep vein system could result in coma. As above, the clinical presentation is dependent on the location of the thrombosis.

CVT diagnosis is made by suspicion through symptom and imaging evaluation. Pre-contrast CT, enhanced CT angiography, CT venography, brain MR imaging, MR angiography, and MR venography are mainly used to reveal infarction of atypical vascular territory, hemorrhage, or brain edema. In the CT protocol, radiologically important imaging findings that improve the visualization of thrombus are as follows: cord sign (thrombosed cortical and deep vein), dense triangle sign (visualization of the clot inside the sinus, in the posterior portion of the superior sagittal sinus), empty delta sign with contrast agent in the CT protocol, isointense on T1 imaging, hypointense on T2 imaging, and blooming effect of the gradient echo or susceptibility weighted imaging in the MR protocol.

In summary, if CVT is clinically suspected, brain imaging should be actively performed, considering the anatomic correlation with venous structure in the interpretation of symptoms.

12.3.4 Treatment of CVT

The first step in the treatment of CVT is the elimination of possible causes of thrombogenicity. The main purpose of CVT treatment is to remove thrombi and recanalization of the venous system. Clinicians may fear hemorrhagic complications of medications to treat CVT, especially in case of anticoagulation. However, anticoagulation facilitates recanalization and resolves deep venous thrombosis. Therefore, the use of anticoagulation is not a contraindication in the treatment of CVT. The recommended treatment is oral vitamin K antagonist (INR 2.0–3.0), unfractionated heparin, or LMWH. In addition, treatment dura-

Table 12.4 Recommended treatment durations of cerebral venous thrombosis

3 months	6–12 months	Indefinite
Provoked CVT	Idiopathic CVT	Recurrent CVT
Transient provocation factor – Infection – Trauma – Immobility – Medication	Mild thrombophilia – Heterozygous FVL – Heterozygous prothrombin	Severe thrombophilia – Antithrombin mutation – Protein C/S deficiency – Homozygous FVL mutation – Homozygous prothrombin mutation – Antiphospholipid antibody

CVT cerebral venous thrombosis, *FVL* factor V Leiden

tion of CVT depends on the presence of the trigger factor (Table 12.4).

Symptomatically, if a patient has a history of seizure due to CVT, antiepileptic drug should be used. Preventive prescription of an antiepileptic drug is not recommended. Decreased mental status due to increased intracranial pressure may be managed by mannitol, sedation, or endovascular treatment.

12.4 Other Hypercoagulability-Related Conditions

Hypercoagulability, the third component of Virchow's triad, may indicate systemic alterations in blood coagulability [14]. Hypercoagulability can be primary or secondary. Most primary hypercoagulable states are related to genetic background; deficiency of antithrombotic protein such as antithrombin, protein C/S, and increased prothrombotic protein such as factor V Leiden or prothrombin gene mutation. However, in this chapter, the authors will not elaborate on primary hypercoagulability because of its rarity. In this section, we focus on the cause of secondary hypercoagulability.

12.4.1 Myeloproliferative Disorder

Myeloproliferative disorders are a group of bone marrow stem cell disorders characterized by clonal expansion of abnormal hematopoietic cells [15]. It includes polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF). Venous and arterial thrombosis, including stroke, are major causes of morbidity and mortality in myeloproliferative disorders. The thrombosis induced by stem cell disorder can occur in large, small, or microvessels. Ischemic stroke occurs in 8% of patients with PV, 1.5% in patients with ET, and 3% in patients with MF [16]. ET is known to have the most favorable outcome. The proposed mechanism of stroke includes two aspects. First, the increase in blood cell counts correlates with the increased risk of stroke by hyperviscosity of blood and changed characteristics of blood cell, such as the cell membrane and procoagulant activation. Second, proteolytic activities, secretion of inflammatory cytokines, and expression of adhesion molecules were altered through Janus kinase 2 (JAK2), a gain-of-function mutation at the site of V617F. JAK2 mutation with erythrocytosis, leukocytosis, and thrombocytosis is a prognostic marker of stroke in myeloproliferative disease (Fig. 12.5). A clinician can evaluate the risk of stroke in patients with hematopoietic disease by using some tiered system, so we can decide on certain prophylactic agent and/or antithrombotic drugs. Aspirin, hydroxyurea, anagrelide, phlebotomy, and cytoreduction were recommended according to risk stratifications of myeloproliferative disease.

12.4.2 Pregnancy-Related Stroke

From the pregnancy period to the first postpartum period up to 8 weeks, the association with stroke increased up to fivefold. Pregnancy-related stroke occurred in 1 of 1500 pregnancies [17]. The pathophysiology of pregnancy-related hypercoagulability involves induced hypercoagulability due to increased procoagulant activity and changes in the vessels of the entire body [14]. Pregnancy induces elevation of the levels of coagulation factors V, VII, VIII, IX, X, and XII, fibrinogen, von Willebrand Factor, D-dimer, thrombin activatable fibrinolysis inhibitor (TAFI), and plasminogen activator inhibitor (PAI). It also induces a decrease in anticoagulant proteins, such as antithrombin, protein C, protein S, and tissue plasminogen activator [16]. These changes help minimize maternal blood loss during delivery. At the same time, however, these changes could predispose to stroke and placental vascular complications to the mother. These changes occur during the entire pregnancy period but are more pronounced in the third trimester until puerperium. Three weeks after delivery, altered blood coagulation and fibrinolysis generally returned to normal.

The treatment of pregnancy-related stroke was unfractionated heparin or LMWH instead of warfarin because of the teratogenic potential of the

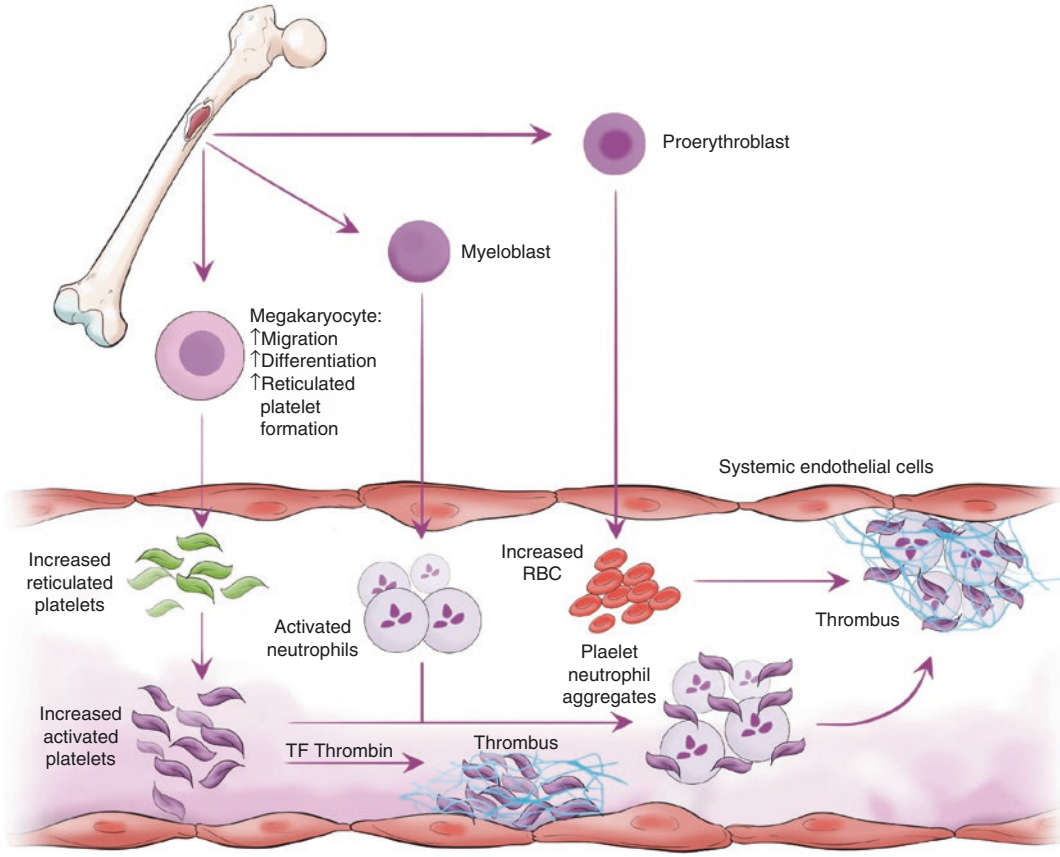

Fig. 12.5 Pathophysiology of myeloproliferative disease. Adapted with permission from Leukemia, Copyright Springer Nature [14]

latter. Low-dose aspirin was known to be safe, but clinicians should keep in mind early closure of patent ductus arteriosus in the fetus as a complication of aspirin therapy.

12.4.3 Oral Contraceptives and Hormonal Therapy

In women on conception by oral pill or assisted reproductive treatment, the risk of stroke is significantly high. The mechanisms of stroke by hormonal therapy are similar to those found in pregnancy, via the altered activity of blood coagulation and fibrinolysis. The risk of stroke is increased about two to sixfold with the use of oral contraceptives and hormone replacement therapy, despite the difference in the components of oral contraceptives [18]. The key player of the thrombogenicity of oral contraceptives is estrogen compounds. Estrogen has a direct effect on the vascular wall, either on the artery or venous system, mainly via the matrix metalloproteinase (MMP) pathway. MMP has a role in the cleavage of connective filaments, such as collagen and elastin in the vascular intima. It induces the metabolism of lipids and lipoprotein, increases the level of low-density lipoprotein and triglyceride, and decreases the level of high-density lipoprotein [16]. The main discordant point with pregnancy-related stroke is that protein C levels may increase, which may help identify a global hypercoagulable state. The level of protein C has been found to be higher in oral contraceptive users than in non-users. Progesterone-only oral contraceptives have generally no or little

effect on plasma lipoprotein levels, as wells as the risk of stroke [19]. The treatment of oral contraceptive-related stroke is to eliminate provocation factor as soon as possible and conversion to another therapy that has less effect on thrombogenicity.

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Paradoxical Embolic Stroke

13

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Abstract

Even after extensive work-up for stroke etiology, up to 40% of ischemic stroke patients do not have identifiable cause, who are considered cryptogenic stroke. Paroxysmal embolism refers to embolism originated from venous circulation entering arterial circulation, potential cause of the cryptogenic stroke. To the development of ischemic stroke with paradoxical embolism, there are essential components including embolic source in venous system, intracardiac or intrapulmonary communication with right-to-left shunt, and embolization to cerebral circulation. There are multiple image modalities including echocardiography, transcranial Doppler, MR and CT images which can provide diagnostic and functional information of the right-to-left shunt. Most common structure of right-to-left shunt is patent foramen ovale (PFO). Epidemiological data consistently have reported that higher prevalence of PFO in patients with cryptogenic stroke than controls. Recently, randomized clinical trials demonstrate benefit of endovascular closure of PFO in cryptogenic stroke patients with PFO than only medication for secondary prevention of stroke. However, there is a need for caution to interpret the results because it is difficult problem to determine whether the presence of PFO is the cause of paradoxical embolism or only incidental finding. Paradoxically, recurrent risk of stroke is lower in patients with a high probability of a PFO-related stroke than those with other etiology. There is a need for further studies to identify patients at high risk of paradoxical embolism and optimal treatment plan.

13.1 Paradoxical Embolism

Ischemic stroke is a pathophysiological heterogenous disease. Despite extensive stroke workup, there are up to 40% of patients whose underlying cause remained unexplained, commonly referred to cryptogenic stroke [1]. Cryptogenic stroke frequently demonstrates the pattern of embolic stroke without compelling source. Paroxysmal embolism refers to thromboembolism originated from the venous side of circulation to the arterial side through an intracardiac or extracardiac shunt. Essential components to develop paradoxical embolism are venous thrombosis (source of embolism), right-to-left shunt, and embolism into arterial circulation (Fig. 13.1). Increasing evidences suggest that paroxysmal embolism is one of the major hidden causes of cryptogenic stroke,

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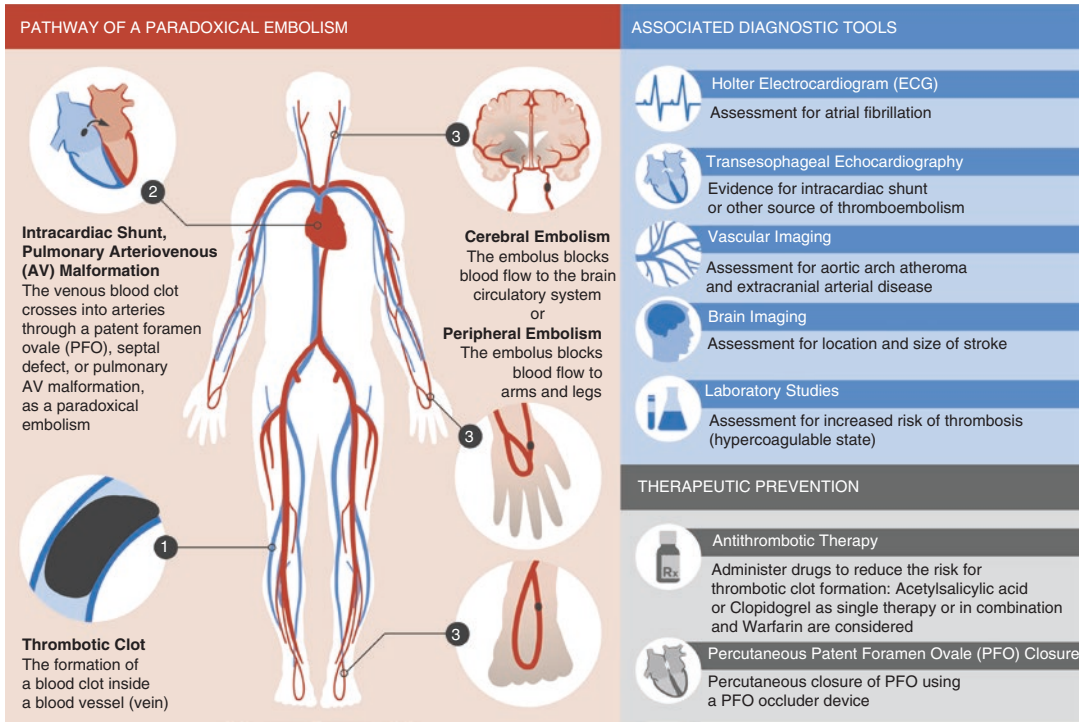

Fig. 13.1 Paradoxical embolism. Figure is from reference [1]

and the shunt structures may be potential treatment target to prevent recurrent stroke. In this chapter, we discuss the mechanism, intracranial/extracranial shunt, diagnostic method, and proper management for the prevention of paradoxical embolism based on currently available data.

13.2 Source of Embolus

Paradoxical embolism starts with the formation of blot clot in the venous circulation. Venous thrombosis, blot clot in vein, is relatively common medical problem with an annual incidence that exceeds 1 per 1000. Risk of venous thrombosis varies by race, with African-Americans having over fivefold greater incidence than Asian-ancestry populations, and an intermediate risk for European and Hispanic populations [2]. Along with the genetic susceptibility, recent surgery, trauma, immobilization, obesity, oral contraceptives, and coagulopathy are well-known predisposing factor for venous thrombosis. A large portion of venous thrombosis is asymptomatic, but both symptomatic and asymptomatic cases can be a source of pulmonary or paradoxical embolism. In patients with venous thrombosis, asymptomatic pulmonary embolism is also frequently found. Most common site of venous thrombosis is the deep vein of legs (deep vein thrombosis, DVT) [3]. In study of pulmonary embolism, about 90% of embolism seems to be originated from leg vein [4]. Superficial vein as well as deep vein can be the source of embolism.

Duplex ultrasound on leg vein is most commonly performed diagnostic study to find source of venous thrombi. However, failure to find the evidence of venous thrombi with ultrasound study is common in patients presumed due to paradoxical or pulmonary embolism. There are many possibilities of resolution of venous thrombus with anticoagulation, complete migration of thrombus, and thrombus in calf, upper extremities or pelvic vein which are usually unevaluated [3]. One recent study reported that 18% of

cryptogenic stroke patients who underwent pelvic MR venography had pelvic venous thrombosis [5]. For patients who highly suspected to paradoxical embolism, whole leg ultrasound, CT venography, MR venography and conventional contrast venography could be used as diagnostic tools with high diagnostic accuracy. Thrombosis in upper extremities is relatively rare but accounts for 4–10% of venous thrombosis [6]. Many cases in upper extremity are intravenous catheter-related thrombosis.

D-dimer is the degradation product of cross-linked fibrin and D-dimer level in blood correlate with the presence of fibrin clots. Because D-dimer level is elevated in cases with venous thrombosis, D-dimer test is frequently performed in clinical practice. However, D-dimer test has high sensitivity and poor specificity for venous thrombosis. In patients with clinically suspected venous thrombosis, low level of D-dimer should not be interpreted to obviate the possibility of venous thrombosis.

13.3 Right-to-Left Shunt

Without structure of right-to-left shunt, emboli originated from venous thrombosis travels into pulmonary circulation causing pulmonary embolism, which do not enter to arterial circulation. Cryptogenic stroke with paroxysmal embolism should accompany with the right-to-left shunt via intracardiac (patent foramen ovale, congenital heart defects) or extracardiac route (pulmonary arteriovenous malformation). In the cases of intracardiac shunt, the mean right atrial pressure is usually lower than the mean left atrial pressure which prevents right-to-left shunt flow and embolization. However, physiologic spontaneous transient reversal of the atrial pressure is present during early diastole and during isovolumetric contraction of the right ventricle of each cardiac cycle [3]. The reversed gradient can further increase with physiologic maneuver or conditions which increase pressure of right atrium or pulmonary vascular resistance such as postural change, inspiration, coughing, Valsalva maneuver, obstructive sleep apnea, chronic obstructive pulmonary disease, pulmonary embolism, right ventricular infarction, and positive end-expiratory pressure. These factors enhancing right-to-left flow can promote emboli travel into arterial circulation, which increases the risk of paradoxical embolism in the cases with structure of right-to-left shunt.

13.3.1 Patent Foramen Ovale

PFO is a hole between the left and right atrium, the most common congenital defects can act as intracardiac shunt. During fetal circulation, the hole works as physiologic route for oxygenated blood from the placenta to the systemic circulation. Spontaneous closure occurs at infancy, but the hole remains open in about 20–30% of general population; this condition is called PFO. There is no sex predominance and the size of PFO ranges from 1 to 19 mm in autopsy studies. Although it is not well known whether the size of PFO changes over time, the size of detected PFO is larger in older than young individuals in the cross-sectional studies. This finding might be due to spontaneous closing with aging in cases with small size of PFO, remaining only unclosed large size of PFO in elderly patients.

It has been widely debated whether PFO is a risk factor of ischemic stroke and paradoxical embolism for a long time. There were case reports of autopsy with systemic embolization and branched thrombus entrapped within PFO. In the cross-sectional studies, the prevalence of PFO is consistently higher in ischemic stroke patients than controls. PFO is more common in cryptogenic stroke than stroke with other causes, especially in young patients [7]. As another supporting evidence for the pathophysiological role of PFO on paradoxical embolism, PFO is a significant risk factor of death and arterial thromboembolic complications in patients with pulmonary embolism [8]. The presence of PFO is also a risk factor of stroke or transient ischemic attack in those who underwent implantation of transvenous pacemaker or defibrillator which may be the

Characteristics	Points
No history of hypertension	1
No history of diabetes	1
No history of stroke or TIA	1
Nonsmoker	1
Cortical infarct on imaging	1
Age(year)	
18–29	5
30–39	4
40–49	3
50–59	2
60–69	1
≥ 70	0
Maximum score	10

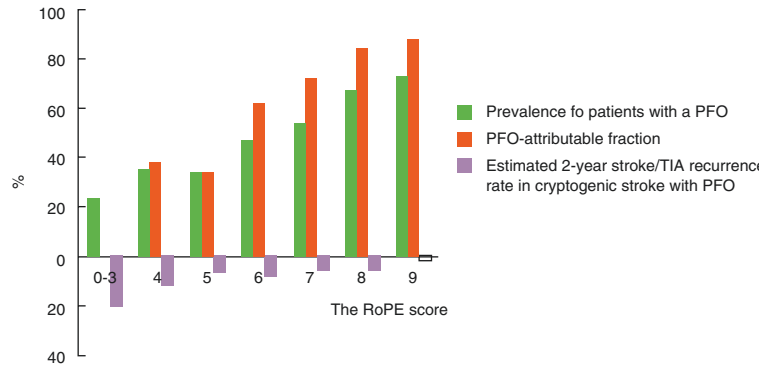

Fig. 13.2 Paradoxical embolism (RoPE) score. *TIA* transient ischemic attack. Figure is from references [14, 15]

source of venous thrombosis [9]. On the other hand, coexisting or preceding event of venous thrombosis is frequent in patients with suspected PFO-related strokes [10].

Considering the pathologic evidence of trapped thrombus in autopsy cases, PFO could be anatomical route of paradoxical embolism into cerebral circulation and risk factor of cryptogenic stroke. Epidemiologic data also support the relationship between PFO and cryptogenic stroke. However, because PFO is prevalent in general population (20–30%), it is difficult to determine whether PFO is the cause of stroke or only incidental finding when PFO is found in stroke patients. Clinical manifestations of PFO-related stroke are nonspecific, and there is no conclusive diagnostic test for paradoxical embolism. Based on Bayers' theorem and prior reports for the prevalence of PFO, probably one-third of PFO found in patients with cryptogenic stroke is likely to be incidental [7]. To estimate whether PFO is a cause of stroke and risk for recurrent stroke in patients with PFO, clinician should consider multiple anatomical and functional factors. There are many anatomical variants that may be linked with stroke risk in the patients with PFO; large size of PFO, long tunnel length (maximum overlap of the septum primum and septum secundum), aortic septal aneurysm, prominent Chiari network and Eustachian value [11]. These structures are considered to enhance direct flow toward PFO or increase in pressure of right atrium, which may predispose to paradoxical embolism in the cases with PFO. Higher degree of right-to-left shunt is more frequently found in patients with cryptogenic stroke than those with other causes [12]. Right-to-left shunt at rest without Valsalva maneuver (severe degree) and bidirectional flow through PFO are considered high risk of paradoxical embolism [13]. High degree of shunt is one component of RoPE score which estimates the likelihood of the PFO-related stroke (Fig. 13.2) [14]. However, prior studies are mainly based on cross-sectional design and inconsistent findings are also present. Underlying role of the anatomical and functional features with PFO on cryptogenic stroke is not fully elucidated. We need further data whether these findings are reliable risk markers for paradoxical embolism in PFO patients.

13.3.2 Atrial Septal Defect and Other Intracardiac Shunt

Along with PFO, there are other intracardiac communications which can be a route of paradoxical embolization including atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus, and Ebstein's anomaly. ASD, a hole in the wall between right and left atrium, allows intracardiac shunt for right-to-left flow and lowering of oxygen levels in arterial circulation. ASD is the third most common type of congenital heart defect with a dominance of female and an incidence of 56 per 100,000 live-

births [16]. The symptom and nature of ASD depend on the type, size, and coexisting factors. VSD is a defect in the ventricular septum and one of the most commonly encountered congenital heart defects at birth. About 2–5% of babies have VSD at birth, and small defects often are asymptomatic and close spontaneously during childhood [17]. Large VSD can increase pulmonary resistance and workload on heart and lung leading to multiple cardiopulmonary complications. Usually, VSD is associated with left-to-right shunt, but right-to-left shunt flow through ventricular shunt is possible and could be related to paradoxical embolism. In VSD patients, coexisting cardiac abnormalities (Eisenmenger syndrome and tetralogy of Fallot) are frequent, which can predispose to right-to-left flow.

13.3.3 Pulmonary Arteriovenous Malformation, Extracardiac Shunt

Pulmonary arteriovenous malformation (PAVM) is abnormal vascular communication between pulmonary artery and pulmonary vein which allows persistent right-to-left shut and passenger of venous thrombus into arterial circulation. One of the major functions of pulmonary capillary bed is filtering of small thrombi and bacteria from venous circulation. Defect in filtration and direct shunt by PAVM can increase the risk of paroxysmal embolism and brain abscess. PAVM is commonly asymptomatic, but can cause hypoxemia, cyanosis, exercise intolerance, hemoptysis, brain abscess, and stroke. There may be contributing factors of coexisting polycythemia or cerebral arteriovenous malformation with PAVM. PAVM could be acquired with severe liver disease or chronic infection. There is only limited data for stroke risk with PAVM. In studies with patients with PAVMs, the prevalence of stroke or TIA varied from 2.6% to 37.0% [18, 19].

Unlike intracardiac shunt structures, venous flow can enter arterial side though PAVM even without reversal of the pressure gradient to right-left. PAVM is a relatively rare vascular disease, occurring at a frequency of 0.02% [20]. The male-to-female ratio varies from 1:1.5 to 1.8. Approximately 50–70% of PAVMs are present in the lower lobes. PAVM can be single or multiple, unilateral or bilateral. Single PAVMs range from 42% to 74%, and bilateral PAVMs range from 8% to 20% [21, 22]. PAVM can be classified as simple or complex types on the basis of their vascular architecture. Simple type has a single segmental feeding artery and complex type has multiple segmental feeding arteries. It is not well known whether characteristics of PAVM including the presence of respiratory symptoms, feeding artery size, degree of the right-to-left shunt are associated with stroke risk [23].

Sporadic or acquired PAVMs are possible, but >80% of PAVM occur in patients with an inherited condition called hereditary hemorrhagic telangiectasia (HHT), an autosomal dominant disorder. For the patients with confirmed or suspected HTT, screening for brain and PAVM is recommended [18]. In HTT patients, the prevalence of PAVMs has been estimated between 15% and 33%. In one clinical report of patients with PAVM and HTT, most patients were asymptomatic until stroke and did not previously diagnose for PAVM [23]. In Asians, PAVM may be less associated with HHT than Western populations [24].

Not all patients with PAVM need treatment. Most PAVMs remain stable in size, with approximately 25% enlarging slowly. Growing of PAVM occurs most during pregnancy or puberty which supports the influence of hormone. Common indications for treatment of PAWM are progressive growth, feeding artery size >3 mm, symptomatic hypoxemia, paroxysmal embolism, or brain abscess.

13.4 Diagnosis

Because stroke is a heterogenous disease, it is a difficult problem to determine whether right-to-left shunt is a cause of stroke by paradoxical embolism or incidental finding in the stroke patients with right-to-left shunt. To evaluate the likelihood for paroxysmal embolism, we should

comprehensively consider the pattern of ischemic stroke in the brain, conventional risk factors, and the presence and characteristics of right-to-left shunt.

13.4.1 Brain Image

At brain image, paroxysmal embolism is expected to have similar infarction pattern of embolic stroke. Embolic stroke commonly shows multiple infarct lesions in different vascular territories with scattered or cortical-subcortical involvements. Presence of silent brain infarction in different vascular territory also suggests the presence of embolic cause. In angiographic study, occlusion of cerebral artery at acute phase and resolution of the occlusion later strongly indicate embolic stroke. If patients with image pattern of embolic infarction do not have other sources of embolism, clinician should concern the possibility of paroxysmal embolism especially in young patients. Even in cryptogenic stroke, brain infarct pattern may vary according to the shunt characteristics and coexisting anatomical variants [15]. Cortical involvement is one component suggesting stroke attributable to the PFO [14]. However, stroke with paradoxical embolism can present with patterns of small vessel disease or other causes of stroke. Currently, there is no standardized image criteria and it should be improper to diagnose paradoxical embolism only by findings of brain image at stroke.

13.4.2 Study for Shunt

Detection of intracardiac or extracardiac shunt is important to both diagnosis and treatment plan for cryptogenic stroke. As diagnostic test for shunts, commonly available tools are transcranial Doppler (TCD), echocardiography, cardiac CT, and MR images. Echocardiography is the most popular study for the investigation of cardiac source of stroke. It can provide information on intracardiac shunt and other embolic cause in heart (myxoma, intracardiac thrombus, valvular disease). For more accurate detection of shunt with echocardiography, peripheral injection with agitated saline or echocardiac contrast is required with Valsalva maneuver. For detection of right-to-left shunt including PFO, transthoracic echocardiography (TTE) can be easily performed non-invisibly with relatively good sensitivity and specificity [3]. However, TTE is inappropriate for detection of small shunt, and transesophageal echocardiography (TEE) is more recommended for detection of PFO. TEE also has merits over TTE with clearer images on aorta, atrium, atrial appendage, and atrial septum that are important structures on cardioembolic source. On the other hand, TEE needs fasting and cooperation of the patient during procedure, which was frequently unsuccessful in acute stroke patients. On the TEE examination with intracardiac shunt-like PFO, microbubble signal enters left atrium within three cardiac cycles after appearance of microbubble in right atrium. In extracardiac shunt-like PAVM, bubbles enter left atrium after 3–8 cardiac cycles.

Along with echocardiography, TCD can be used to evaluate the presence and degree of intracardiac and extracardiac shunt. With peripheral injection of agitated saline and Valsalva maneuver, microbubble signals in middle cerebral artery can confirm the presence of shunt structures. The degree of the shunt on TCD examination could be quantified based on the number of microbubble signals as 0 = absent shunt (Grade 0); 1–20 = small shunt (Grade 1); >20 with no curtain = moderate shunt (Grade 2); >20 with curtain effect = large shunt (Grade 3) [25]. In cases with poor temporal window for TCD study, microbubble signals also can be accessed in extracranial or peripheral limb artery. Compared to TEE, TCD study has merits of good sensitivity, simplicity, noninvasiveness, and high feasibility [26].

Recently, the use of CT and MRI has increased for diagnosing intracardiac and extracranial shunt due to feasibility and no need for Valsalva maneuver. Electrocardiographically gated multidetector CT can detect intracardiac shunt with relatively good accuracy and provide detailed images of cardiac structures. The diagnostic accuracy of magnetic resonance image for cardiac shunt remained controversial, but maybe useful for noninvasive quantification of

shunt flow. PAVM can be diagnosed with radionuclide perfusion lung scanning, CT, MRI, and pulmonary angiography. On plain chest X-ray, PAVM is frequently apparent as oval mass lesion with uniform density. Contrast enhanced computed tomography is the diagnostic imaging modality of choice for PAVM with higher detection rate for PAVM rather than conventional pulmonary angiography (98% vs 60%) [27]. Pulmonary angiography remained as gold standard for the evaluation of PAVM for not only identification but also angioarchitecture of pulmonary vasculature. There is screening technique using ear oximetry for detection of cardiac shunt. If there is enough shunt flow during Valsalva maneuver, mixed desaturated venous flow causes drop of oxygen saturation in arterial side. Compared to the result of TEE, the sensitivity and specificity of ear oximetry are 0.756, 0.706 in one preliminary study [28].

13.5 Treatment and Prevention for Paradoxical Embolism

For patients who have intracranial or extracranial shunt and suspected with paradoxical embolization by the shunt, the treatment and preventive strategy should be individualized based on underlying shunt structure and risk of recurrence. Main clinical concerns are (1) whether shunt structure is the cause of stroke or incidental finding; (2) obliteration of the shunt may be preventive for recurrent stroke; and (3) optimal medication plan.

13.5.1 Patent Foramen Ovale

Although PFO could be a route for paradoxical embolism, there is long-term debate in whether PFO is a significant risk factor for ischemic stroke. Cross-sectional studies consistently show high prevalence of PFO in stroke patients compared to controls. However, many population-based cohort studies do not find increased risk for ischemic stroke in those with PFO [29]. These findings suggest that fraction of primary stroke risk attributable to the PFO may be low in the general population, especially in the elderly. Therefore, primary stroke preventive treatment for PFO is not indicated to the healthy people without prior embolic events in the absence of other significant complications. Major controversy in the clinical practice is preventive plan for patients with ischemic stroke who have PFO. To set optimal preventive plan, we should access the underlying etiology of the primary stroke. Because PFO is common in the general population, PFO in stroke patients could be both cause of paradoxical embolism or incidental finding not related to stroke. Risk of Paradoxical Embolism score (RoPE) is a 10-point clinical scoring system to predict the likelihood of PFO in patients with cryptogenic stroke based on 12 component databases (Fig. 13.2) [14]. The RoPE score is calculated with the evidence of cortical stroke on neuroimaging, the absence of conventional risk factors (hypertension, diabetes mellitus, smoking, previous TIA, or stroke) and young age; these factors are related with the likelihood of paradoxical embolism. In the stroke patients with PFO, high RoPE score suggests that the discovered PFO is likely to be cause of stroke than incidental finding. Paradoxically, stroke recurrent rates decrease as the RoPE score increases [14, 30]. Indeed, many observational studies failed to find increased risk for recurrent stroke with the presence of PFO. These paradoxical features could be explained that the recurrent risk in patients with PFO-related stroke may be lower than those with other conventional stroke mechanisms.

If the underlying cause of primary stroke is suspected to paradoxical embolism through PFO, closing of the shunt may be the fundamental prevention of recurrent embolism. PFO, a hole between atrial septum, can be closed with heart surgery or endovascular devices. Recently, there are randomized control trials based on the hypothesis that PFO closure using endovascular devices may have stroke-preventive effects. Table 13.1 summarizes results of the randomized trials. In the earlier studies of CLOSER I, PC, and RESPECT trials, PFO closure group had lower risk for recurrent throm-

Table 13.1 Trials of patent foramen ovale closure for stroke prevention

Trial name (year of publication)	No. of patients	Mean or median no. of years of follow-up	Comparator	Primary outcome	Hazard ratio[a]	*P* value[a]
Trials with negative findings						
CLOSURE I (2012)	909	2	Antiplatelet therapy, warfarin, or both	Composite of stroke or transient ischemic attack at 2 years, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years after randomization	0.78	0.37
PC (2013)	414	4.1 (PFO closure group), 4.0 (medical-therapy group)	Antiplatelet therapy or anticoagulation[b]	Composite of death, stroke, transient ischemic attack, or peripheral embolism	0.63	0.34
Trials with positive findings						
Gore REDUCE (2017)	664	3.2	Antiplatelet therapy	Ischemic stroke and new brain infarction on imaging	0.23	0.002
CLOSE (2017)	473	5.3	Antiplatelet therapy or anticoagulation[b]	Stroke	0.03	<0.001
RESPECT extended follow-up (2017)	980	5.9	Antiplatelet therapy or warfarin	Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization	0.55	0.046

CLOSE denotes Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence, CLOSURE I Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale, Gore REDUCE Gore HELEX Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients with Patent Foramen Ovale (PFO), PC Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism, and RESPECT Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment. Table is modified from *Stroke and Vascular Neurology* 2018; 3;e000173 [31]

[a]The hazard ratio and *P* value are for the expected probability of stroke or other primary outcome after closure of the PFO versus medical treatment in the intention-to-treat analysis

[b]Anticoagulation refers to any form of anticoagulation

boembolism than medical treatment group, but the difference did not reach statistical significance. On the other hand, two more recent trials of Gore REDUCE and CLOSE succeeded in demonstrating that PFO closure is preventive for stroke recurrence compared to only medical treatment. The Gore REDUCE trial demonstrated 77% relative reduction of recurrent strokes with PFO closure compared to medication group; the number needed to treat of PFO closure to prevent one new stroke is 28 at 2 years. The CLOSE trial showed 4.9% absolute risk reduction of recurrent stroke for 5 years with PFO closure; the number needed to treat with PFO closure to avoid one stroke at 5 years is 20. The discrepant results between the early and later trials might be due to the more stringent criteria to include only patients whose PFO was suspected to be a cause of primary stroke [32]. CLOSE trial only includes patients with large shunt (>30 microbubbles) or an atrial septal aneurysm which are supporting findings of PFO-related stroke. Gore REDUCE trial excluded patients who had suggesting features of any other cause including atherosclerosis on cerebral artery or aortic plaque,

cardioembolic source, and image pattern of small-vessel occlusive disease. In the later trials with more strict inclusion criteria, recurrent stroke risk was significantly lower in those who received endovascular PFO closure than controls who received only medication. Furthermore, subgroups with large shunt or coexisting atrial septal aneurysm, suggesting PFO-related stroke, have more benefit with PFO closure. Stroke preventive effect of PFO closure is also found in the RESPECT extended follow-up study [33]. In the above five trials, success rate of PFO-closing rates ranged from 89.4% to 99.6%. Procedure-related complications and adverse events are relatively infrequent with vascular injury, device-related embolization, incomplete closure, and residual shunt on PFO. One concern with PFO-closing device is increased risk of newly developed atrial fibrillation [34].

Until 2017, major guidelines of stroke do not recommend PFO closure as preventive treatment for stroke patients with PFO. The guidelines are published prior to the recent randomized trials and did not reflect the results. Considering the positive results in the multiple trials, PFO closure could be beneficial to prevent recurrent stroke to selected patients who are suspected to PFO-related stroke. However, clinician should not routinely decide PFO-closing to all stroke patients who have not identifiable causes; about 40% of all stroke patients are undetermined etiology. The PFO trials showing beneficial findings selectively included patients <60 years who are more likely to have stroke-related PFOs. If patients are of old age or have multiple conventional risk factors, which suggest atherosclerotic or other stroke mechanism rather than PFO, it is hard to expect the preventive effect of PFO closure. Currently, there is a lack of specified consensus or guidelines who is the candidates of PFO-closing in stroke patients. For planning of PFO closure should be decided based on individual's characteristics including radiological and functional studies for PFO and coexisting conventional risk factors (Table 13.2). Although reported complication rate is low with endovascular PFO closure, critical adverse event is possible.

Table 13.2 Features suggesting a causative relationship between PFO and paradoxical embolism in stroke

History
Sedentary period prior to onset
Valsalva at onset
Absence of common stroke risk factors
Anatomy
Atrial septal aneurysm
Large PFO size
Prominent Eustachian valve
Physiology
Shunt at rest
Spontaneous Doppler flow
Many bubbles cross on contrast injection
Neuroimaging and laboratory testing
Past "silent" strokes
Embolic stroke topography
Hypercoagulable state

PFO patent foramen ovale
Table is from *Curr Atheroscler Rep* 2007; 9;319–325 [35]

13.5.2 Arterial Septal Defect and Ventricular Septal Defect

ASD can introduce complications of paradoxical embolization, cerebral abscess, arrhythmia, right ventricular heart failure, and pulmonary hypertension. Generally, ASD closure is indicated to the patients with right ventricular overload [36]. Surgical repair of VSD is indicated for significant aortic regurgitation, pulmonary hypertension, and refractory heart failure. Due to the limited data, there is lack of direct evidence whether ASD or VSD closure can reduce risk of stroke recurrence. Unlike PFO, ASD and VSD are relatively uncommon in adulthood. If the intracardiac communications are found at work-up for ischemic stroke and there is no other compelling cause of stroke, clinicians should consider the possibility of paradoxical embolism and the need of therapeutic closing of the heart defects. Considering the mechanism of paradoxical embolism and prior positive data from trials with PFO closure, closure of ASD or VSD might be reasonable to prevent further cryptogenic stroke in the absence of other cause of embolism.

13.5.3 Pulmonary Arteriovenous Malformation

The prevalence of PAVM is reported very low in general population. Therefore, if PAVM is detected in stroke patients with pattern of embolic stroke and without other plausible causes, treatment of PAVM should be considered for prevention. Treatment of PAVM could be done by endovascular embolization or microsurgery. Success rate of endovascular embolization is as high as 98%, and neurological complication rate is low after successful embolization [22].

13.5.4 Antiplatelet or Anticoagulation for Paradoxical Embolization

Optimal medication plan is another debate for PFO-related stroke. For the prevention of venous thromboembolism, anticoagulation is considered to be more effective than antiplatelet [37]. Because paradoxical emboli are originated from venous thromboembolism, anticoagulation may be more preventive to the patients who presented with cryptogenic stroke through supposed paradoxical embolism. Indeed, some study data suggested anticoagulation might be more reasonable than antiplatelet for secondary prevention in cases with PFO [38]. However, anticoagulation with vitamin K antagonist is consistently associated with higher bleeding risk than antiplatelet. Therefore, current guidelines do not support routine use of anticoagulant for patients with PFO or cryptogenic stroke except in coexistence of deep vein thrombosis. The prior trials of endovascular PFO closure had control groups treated with antiplatelet. There is a lack of conclusive data comparing the preventive effects of PFO closure and anticoagulation. New oral anticoagulants (NOAC) are alternative anticoagulants which are at least as effective as vitamin K antagonist for prevention of thromboembolism in patients with atrial fibrillation and have lower risk of bleeding than vitamin K antagonist. Ongoing trials for NOAC on embolic stroke of undetermined source might provide further information for the optimal medication strategy for paradoxical embolism.

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Hemorrhagic Diseases

14

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Abstract

The cerebrovascular event of strokes can be classified as ischemic strokes and hemorrhagic strokes. Hemorrhagic stroke occurs in approximately 10–15% of all cerebrovascular strokes. Mortality and morbidity rate is reported to be high among patients with hemorrhagic stroke.

The most typical hemorrhagic strokes are intracerebral hemorrhage, subarachnoid hemorrhage, hemorrhage due to arteriovenous malformation, and arteriovenous fistula. Computed tomography, magnetic resonance imaging, and digital subtraction angiography are used for differential diagnostic evaluations and planning of the treatment. Especially determining the cause of the stroke is essential. After a diagnosis of the hemorrhagic stroke, tailored management including medical, surgical, endovascular or radiosurgical treatment is required to prevent further neurological deteriorations.

In this chapter, epidemiology, diagnostic evaluation, management of intracerebral hemorrhage, subarachnoid hemorrhage, cerebral arteriovenous malformation, and cerebral dural arteriovenous fistula will be discussed.

14.1 Intracerebral Hemorrhage

Spontaneous intracerebral hemorrhage (ICH) accounts for 10–15% of all strokes; however, its contribution to overall stroke mortality and disability is over-proportionally high [1]. Fifty-eight percent of ICH patients die within the first year, and 2/3 of survivors remain moderately or even severely disabled [2]. Various forms of cerebral small vessel diseases underlie the majority of spontaneous ICH. Additional causes include cerebral amyloid angiopathy (CAA), vascular malformations, cerebral sinus vein thrombosis, tumors, vasculitis, and antithrombotic medication.

However, spontaneous ICH is usually caused by rupture of small perforating arteries secondary to hypertensive changes [3–5]. In developed countries, the incidence of hypertensive ICH has decreased with the improvement of blood pressure control [6]. In developing countries, the burden of ICH has not decreased [7]. The out-

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come of ICH is variable, depending on hematoma volume, location, an extension to ventricles, and other factors [8]. In this review, we will summarize the epidemiology, pathophysiology, risk factors, diagnosis, clinical manifestation, general management, prognosis, and outcomes.

14.1.1 Epidemiology

ICH accounts for approximately 8–15% in western countries [9] and 18–24% in Japan [10] and Korea [6]. The data on the frequency of hemorrhagic stroke are contained in a systematic review performed by the Global Burden of Diseases, Injuries and Risk Factors study in 2010, which included 58 studies from high-income countries and 61 studies from low-income countries; this study estimated that in 2010, a total of 5,324,997 people worldwide experienced a hemorrhagic stroke [11] The incidence of ICH is substantially variable across countries and ethnicities. Eighty percent of all ICH cases occurred in low to middle-income countries, clearly indicating that the major global burden lies in these regions. Unlike ischemic stroke, the age-specific incidence of ICH is higher in low-middle income countries than in high-income countries [11]. Another recent inpatient database study from the Netherlands based on retrospective cohort study reported that the incidence of ICH per 100,000 was 5.9 in 35–54 years, 37.2 in 55–74 years, and 176.3 in 75–94 years old in 2010 [12]. For all ages, the annual incidence rate per 100,000 persons was higher in men than in women; 5.9 vs. 5.1 in people aged 35–54 years, 37.2 vs. 26.4 in those aged 55–74 years, and 176.3 vs. 140.1 in those aged 75–94 years [13].

The rate of early fatality is high among patients who have had an ICH: The median one-month case fatality after ICH was 40.1% in a systematic review of 36 population-based studies conducted in 1983–2006 [14]. A worldwide stroke epidemiology study revealed that early stroke case fatality (21-day to 1-month) varied substantially among countries and study periods; the case fatality rate was 25–30% in high-income countries while it was 30–48% in low- to middle-income countries [15]. A decrease in the ICH fatality rate might be attributed to the improvement of critical care [16, 17].

14.1.2 Classification

Spontaneous ICH can be classified as either primary or secondary depending on the underlying cause. Primary ICH accounts for 70~80% of cases and is due to spontaneous rupture of small vessels damaged by hypertension or CAA. Primary ICH is also classified by location as lobar versus non-lobar and supratentorial versus infratentorial [18].

Lobar ICH is commonly the result of CAA. Amyloid deposition in small-sized to medium-sized cortical perforators may lead to the rupture of these vessels, resulting in asymptomatic microhemorrhages or symptomatic lobar hemorrhages [19] (Fig. 14.1a). Non-lobar ICH is most often the result of long-standing hypertension resulting in lipohyalinosis of small perforating arteries of the basal ganglia, thalamus, pons, and cerebellum, leading to deep hemorrhages, often with extension into the ventricles [17] (Fig. 14.1b–e). The most common locations of hypertensive ICH are the putamen, thalamus, subcortical white matter, pons, and cerebellum.

Secondary ICH is associated with a number of congenital and acquired conditions such as vascular malformations, tumors, coagulation disorders, use of anticoagulants and thrombolytic agents, cerebral vasculitis, drug abuse, and cerebral venous thrombosis.

14.1.3 Pathophysiology

14.1.3.1 Hypertensive Vascular Change

ICH is usually caused by ruptured vessels that are degenerated due to long-standing hypertension. Responsible arteries show prominent degeneration of the media and smooth muscles [4]. Fibrinoid necrosis of the sub-endothelium with micro-aneurysms and focal dilatations may be seen in some patients. Lipohyalinoses, promi-

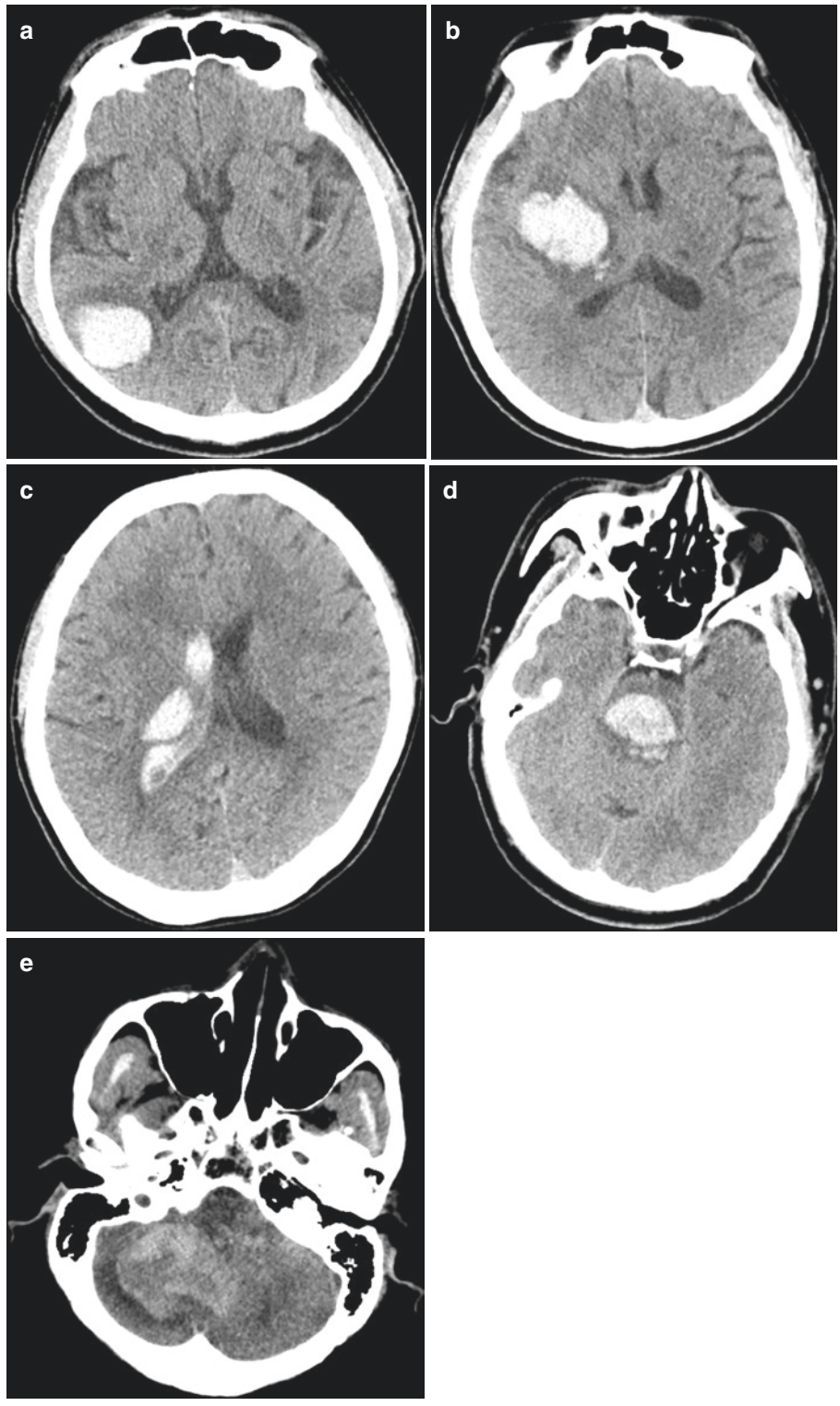


Fig. 14.1 Various types of ICH. (**a**) Lobar ICH, (**b**) ICH on basal ganglia, (**c**) Thalamic ICH with IVH, (**d**) ICH on pons, and (**e**) ICH on cerebellum

nently related to long-standing hypertension, is most often found in non-lobar ICH [16], whereas CAA is relatively more common in lobar ICH.

14.1.3.2 Cerebral Amyloid Angiopathy (CAA)

CAA is characterized by the deposition of amyloid-β peptide at capillaries, arterioles, and small- and medium-sized arteries in the cerebral cortex, leptomeninges, and cerebellum [20]. CAA in the cerebral small vessel leads to sporadic ICH in elderly people, commonly associated with variations in the gene encoding apolipoprotein E epsilon 2 and 4 in chromosome 19 [21]. Duplication of the APP locus on chromosome 21 is also found in families with familial early-onset Alzheimer disease and CAA. CAA-related ICHs occur mainly in the elderly subjects while a rare familial syndrome may manifest in relatively young patients.

14.1.4 Risk Factors

Older age, hypertension, African-American ethnicity, low LDL cholesterol, and low triglycerides increased the risk of ICH [22]. Hypertension is the most important modifiable risk factor for spontaneous ICH. Those with Stage 3 hypertension at baseline have five times the risk as those without hypertension [22]. Anticoagulation-related ICH is nowadays increasing because of the increased use of oral anticoagulation in the elderly population. Warfarin users were at a much higher risk of ICH compared with no therapy, with a marked association with an international normalized ratio >3 [23]. Antiplatelet therapy can increase the risk of ICH with a small but significant increase. Another study reported that sympathomimetic drugs and chronic kidney disease were also associated with ICH.

Cerebral microbleeds (CMBs) were more prevalent with advanced age and males and associated with hypertension, diabetes mellitus, and cigarette smoking [24]. The prevalence of CMBs is the highest in spontaneous ICH (79%), followed by atherothrombotic brain infarction (46%), and other types of infarction (39%) [25]. Among all patterns of CMB topography, the strictly lobar CMB type is the most established specific pattern for a small vessel disease that is CAA, which is commonly seen in lobar ICH in the elderly. Similar to lobar ICH, CMBs in CAA have a posterior cortical predominance and they also tend to cluster in the same lobe [26].

14.1.5 Diagnosis and Imaging

Non-contrast Computed tomography (CT) scan is highly sensitive and specific for ICH and will reveal not only the location and amount of hematoma but also intraventricular extension, mass effect, hydrocephalus and early signs of brain herniation. Magnetic resonance imaging (MRI) can be as sensitive as CT but delayed MRI is better utilized as an adjunct tool to aid in the determination of the underlying cause of the ICH (such as CAA, vascular malformations, and underlying tumor). CT angiography is very sensitive for identifying associated vascular abnormalities and contrast extravasation as "spot sign" [27]. Contrast extravasation during angiography is associated with ongoing bleeding and worsening outcome. Repeat imaging study should be considered for evaluation of any neurologic deterioration or for follow-up of any underlying lesion or vasculopathy.

14.1.6 Clinical Manifestation

ICH showed dynamic disease progress and neurologic symptoms usually aggravate over minutes or a few hours. The clinical manifestations vary by the size and location of ICH. Headache is more common in patients with large hematomas and is attributed to traction on meningeal pain fibers, increased intracranial pressure, or blood in the cerebrospinal fluid. Vomiting due to increased intracranial pressure is reported in about 50% of patients with hemispheric ICH, and more common in patients with cerebellar hemorrhages [16]. Decreased mental status indicates large ICHs that involve the brainstem reticular activat-

ing system. Seizures can be delayed but most frequently occur at the onset of ICH. About 50–70% of seizures occur within the first 24 h, and 90% occur within the first 72 h, with an overall risk of seizures of about 8% within 1 month of symptom onset [28]. The only factor independently associated with the occurrence of early and late seizures is cortical involvement of the lobar ICH. Patients with a supratentorial ICH involving the basal ganglia or thalamus have contralateral sensorimotor deficits. In patients with an infratentorial ICH, signs of brainstem dysfunction occur such as an ocular motor or other cranial nerve abnormalities, and contralateral motor deficits [4]. About 10% of patients have dementia before their first stroke, 10% develop new-onset dementia after their first-ever stroke, and more than 30% develop dementia after a recurrent stroke [29]. The most frequent underlying vasculopathies in ICH are CAA and deep perforating vasculopathy, both of which have been associated with cognitive impairment of either the vascular or Alzheimer's type.

14.1.7 Management

14.1.7.1 Emergent Management and Prevention of Hematoma Expansion

ICH is a dynamic phenomenon, and urgent therapy must be taken to fight against hematoma expansion. Indeed, over 20% of patients experience a decrease in the Glasgow Coma Scale (GCS) score between prehospital assessment and admission to hospital [30]. Securing airway, breathing, and circulation is essential to preventing secondary injury from hypoxia and hypertension. Intubation is indicated in a patient with GCS ≤8 or significant respiratory distress. And patient with intraventricular hemorrhage with hydrocephalus, mass effect, or brain herniation should be considered ventriculostomy and hyperosmolar therapy.

Approximately one-third of patients demonstrate significant hematoma expansion within the first 24 h of onset, explaining their early neurological deterioration, which further aggravates outcome. The mechanisms underlying hematoma expansion are not entirely clear, but the initial hematoma leads to twisting of the surrounding tissues which predisposes other potentially diseased microvessels to tear successively and thereby produce a "hemorrhagic avalanche" [31]. Additional therapeutically amenable forces predisposing to continued bleeding include an elevated blood pressure and a coagulopathy. Therefore, management of hypertension and correction of coagulopathy are essential to prevent hematoma expansion which would be the crucial factor for poor prognosis.

14.1.7.2 Management of Hypertension

Initial post-ICH blood pressure (BP) is often much higher than the last premorbid level (mean increase of 40.7 mm Hg). And not only recent premorbid BP increase but also poststroke factors may contribute to elevated BP in acute ICH. Elevated admission BP was significantly associated with increased odds of death or disability [32]. Lowering arterial blood pressure in acute ICH has been studied in several trials. The INTERACT-2 trial comparing early lowering of SBP to <140 mm Hg with <180 mm Hg showed no increase in adverse events in the aggressive treatment group [33]. There was no significant difference in death or severe disability at 90 days. Ordinal analysis of modified Rankin scores indicated improved functional outcomes with intensive lowering of BP [33]. Based on the INTERACT-2 trial, the current AHA/ASA guideline states that early aggressive BP lowering to 140 mmHg or lower is safe and can be effective to improve functional outcomes [34].

In the multicenter Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II trial used intravenous nicardipine, ICH patients with a GCS of 5 or more were randomized within a 4.5 h time window to an intensive systolic BP target of 110–139 mmHg or a standard target of 140–179 mmHg [35]. The primary outcome was death or disability (modified Rankin Scale 4~6) at 3 months after randomization. There was no significant difference in the primary end points of death or disability (38.7% in intensive lowering

group vs 37.7% in the standard treatment group) and the rate of hematoma expansion [35]. However, the study showed a higher incidence of adverse renal events (9.0% vs 4.0%, $p = 0.002$) in the intensive treatment than the standard treatment group [35]. The mean minimum SBPs of the two groups during the first 2 h were 128.9 ± 16 and 141.1 ± 14.8 mm Hg, respectively; thus, it is likely that the neutral results of the trial were a result of the already good BP management in the group receiving standard treatment. Of note, the much lower minimum SBPs in the intensive treatment group in the ATACH II trial might explain the higher incidence of renal adverse events. In addition, efforts should be taken to ensure stability and consistency in BP lowering, not only in the first 24 h but also in the several days following ICH.

A wide range of agents is available for BP control, though a lack of comparative effectiveness studies means that there is no one ideal recommended drug in the context of acute ICH. Current guidelines cite labetalol and nicardipine as agents to consider as first-line treatment, given their short half-life and ease of titration [36]. Labetalol, a combined selective alpha 1 adrenergic and nonselective beta-adrenergic receptor blocker, has a rapid onset (2–5 min) after intravenous administration and can be given as a bolus without invasive BP monitoring. It is not dependent on renal or hepatic function and therefore may be used in those with renal or hepatic impairment. The second-generation calcium channel blocker nicardipine has an onset of action of 5–10 min and has cerebral and vasodilatory properties that may improve cerebral perfusion. The new third-generation calcium channel blocker clevidipine has a rapid onset (<1 min) and is easily titratable; therefore, several studies have confirmed its efficacy and safety in BP reduction in hypertensive crises in cardiac surgery or emergency department settings [37]. Thiazide should be used with caution because it may cause hyponatremia and worsen cerebral edema in patients with large hemorrhage. In a recent randomized trial, spironolactone was shown to be very effective for patients with resistant HTN [38].

14.1.7.3 Reversal Strategies for Vitamin K Antagonists

Anticoagulant agents are frequently used for the prevention and treatment of a wide range of cardiovascular diseases. Indeed, approximately 12–20% of patients presenting with ICH are taking oral anticoagulants [39]. The most often used anticoagulants are heparin and its derivatives; vitamin K antagonists (VKA) and antiplatelet agents, including aspirin and thienopyridine derivatives such as clopidogrel. The most important complication of treatment with anticoagulants is hemorrhage and each of specific clinical situations requires a careful and balanced assessment of the benefits and risks of reversing anticoagulants. In well-controlled patients in clinical trials, treatment with VKA increased the risk of major bleeding by 0.5%/year and the risk of intracranial hemorrhage by about 0.2%/year [40].

The most straightforward method to counteract the effect of VKA is the administration of vitamin K. However, VKA anticoagulants via inhibiting the synthesis of vitamin K dependent coagulation factors in the liver. Rapid replacement of deficient coagulation factors is preferred for reversal of anticoagulation in cases of clinically significant bleeding. Substitution of vitamin K is crucial but, not enough for an immediate reversal of VKA, as measurable effects take hours to days especially oral administration. Prothrombin complex concentrates (PCC), containing all vitamin K-dependent coagulation factors, are more useful. In a prospective study, in patients using VKAs and presenting with bleeding, the administration of PCC resulted in at least satisfactory and sustained hemostasis in 98% of patients [41]. Moreover, in contrast to fresh frozen plasma (FFP) which are stored in blood banks, PCC are readily available, do not need compatibility testing before transfusion, and can be infused over a few minutes without volume overloading. For all patients taking vitamin K antagonists, vitamin K 10 mg and 3-factor or 4-factor PCC should be administered intravenously for patients with the international normalized ratio (INR) ≥1.4. If repeat INR 15–60 min after PCCs administration shows continued INR elevation above 1.4, consider further correction

with 2–4 units FFP. Reversal of unfractionated heparin is recommended for patients who develop ICH with prolonged activated partial thromboplastin time (aPTT) while on heparin infusion. Intravenous protamine sulfate is the antidote of choice and each milligram of protamine will neutralize approximately every 100 units of heparin given in past 2–3 h. If repeat aPTT remains elevated, repeated at half of the initial dose should be administrated, maximum 50 mg dose.

14.1.7.4 Reversal of Non-vitamin K Antagonist Oral Anticoagulants (NOACs)

NOACs comprise the factor Xa inhibitors apixaban, edoxaban, and rivaroxaban and the direct thrombin inhibitor dabigatran. NOACs are safer than VKA in terms of major bleeding for stroke prevention and they carry about a 50% lower risk of ICH compared to VKA. These agents have relatively stable pharmacokinetic and pharmacodynamic properties; therefore, do not need for repeated dose adjustments.

For patients taking factor Xa inhibitors, activated charcoal can be administrated to prevent drug absorption (within 2 h of drug exposure). Depending on the severity of the clinical situation and in view of the half-lives of the direct Xa inhibitors, the cessation of medication may be sufficient to reverse the anticoagulant effect; however, PCC (50 units/kg) is recommended if the hemorrhage occurred within 3–5 half-lives of drug exposure. In the ANNEXA-4 trial, an infusion of andexanet alfa, a recombinant, genetically modified factor Xa can reverse rapidly by a partial rebound of the oral and parenteral anticoagulant effect including rivaroxaban, apixaban, and edoxaban [42]. It has not been approved by the FDA for clinical use.

Direct thrombin inhibitors (DTIs; e.g., dabigatran, argatroban, and bivalirudin) have good and relatively stable bioavailability after oral ingestion and have the significantly less adverse effect of causing bleeding than VKA. Dabigatran was shown to be effective in the prevention and treatment of both venous and arterial thromboembolism. Furthermore, the half-lives of most of the agents are relatively short; hence, in the case of less serious bleeding, interruption of the treatment will be sufficient to reverse the anticoagulant effect. However, reversal of coagulopathy is indicated if the patient presents within 3–5 half-lives of drug exposure. Idarucizumab (5 g intravenous divided into two doses) is a fragment of an antibody that is an only currently licensed specific antidote for the oral direct thrombin inhibitor dabigatran [43]. Monitoring of the anticoagulant effect of thrombin inhibitors is difficult and the ecarin clotting time may be accurate than aPTT but is not readily available in most routine clinical settings. Practically applicable measure for monitoring the anticoagulant effect may be the diluted thrombin time, which needs to be standardized for the specific agent that was used [44].

14.1.7.5 Reversal of Antiplatelets

Cyclooxygenase inhibitors such as aspirin and the P2Y2G inhibitors clopidogrel, prasugrel, and ticagrelor irreversibly block their targets in platelets and thereby attenuate platelet aggregation. In current clinical practice, bleeding can almost always be managed with local hemostatic procedures or conservative strategies without interrupting aspirin use. Rather, interruption of aspirin has been associated with an increased risk of thromboembolic complications. In a multicenter, randomized open-label trial, platelet transfusion seems inferior to standard care for patients taking antiplatelet therapy before ICH with increased mortality or dependence at 3 months (OR 2.1, $p = 0.0114$) [45]. Platelet transfusion is not recommended for nonsteroidal anti-inflammatory drugs (NSAIDs) or glycoprotein (GP) IIb/IIA inhibitor-related ICH. Nevertheless, under special clinical circumstances, such as ICH need to undergo a neurosurgical procedure, the anti-hemostatic effect of aspirin needs to be reversed immediately. The most rigorous measure to achieve that is the administration of platelet concentrate after the cessation of aspirin. Another approach is the administration of de-amino d-arginine vasopressin (desmopressin) which can be considered in ICH associated with cyclooxygenase inhibitors or ADP receptor inhibitors.

14.1.7.6 Management of IVH

Intraventricular hemorrhage (IVH) can occur in isolation or more frequently as part of parenchymal ICH in up to 45% of patients with ICH. Because it is associated with poor outcome, external ventricular drain (EVD) placement should be considered in patients with GCS ≤8, significant IVH with hydrocephalus due to obstruction of cerebrospinal fluid circulation or evidence of transtentorial herniation [46]. Moreover, intraventricular clots cause inflammation of the ependymal layer and fibrosis of the arachnoid granulations, leading to delayed communicating hydrocephalus. In the recent multicenter, randomized placebo-controlled CLEAR-III trial, a dose-dependently better result of the intraventricular clot lysis was observed in intraventricular t-PA administrated patients, but this showed no benefit of the overall outcome [47]. Subgroup analysis showed reduced mortality in patients with large IVH.

14.1.7.7 Surgical Intervention

The randomized, controlled STICH trial and the subsequent STICH-II demonstrated no benefit for early surgery with hematoma evacuation in patients with supratentorial ICH [48, 49]. Subgroup analysis shows a small survival benefit in patients with lobar hematoma location without significant improvement in functional outcomes. STICH II revealed a trend toward improved outcomes, particularly in those patients whose GCS was between 9 and 12 initially. However, in cases of cerebellar ICH, emergency craniotomy for hematoma evacuation is generally recommended given the high morbidity from the rapid development of brainstem compression (Fig. 14.2). Surgical indications include >3 cm sized hematoma, upward herniation, brainstem compression or hydrocephalus which is not sufficient with EVD alone and further neurological deterioration [50]. With respect to the benefit observed in patients with malignant middle cerebral artery infarction, hemicraniectomy should be considered when targets the space-occupying effect of the massive hematoma.

Recent, less invasive techniques for hematoma evacuation may be promising. The Minimally Invasive Surgery plus tPA for Intracerebral Hemorrhage Evacuation (MISTIE) phase II trial evaluated the stereotactic guided clot catheterization and intermittent dosing of intraventricular tPA to facilitate clot liquefaction and aspiration [51]. It suggested that the procedure is safe and showed a trend toward improved outcomes in the surgical patients compared with the medically treated patients. And MISTIE II study also revealed the association of hematoma evacuation and reduction of brain edema in the surgically treated group. The ongoing MISTIE III trial has added a stereotactic CT-guided Endoscopic Surgery arm and the results are expected soon. Preliminary data showed that the newer trans-Sylvian, trans-insular minimal invasive approaches may yield better results due to relative sparing of cortical function [39]. Evidence from clinical trials suggests that craniotomy is indicated for lobar ICH because the clot reaches the surface of the brain and because access is easy and safe. Meanwhile, EVD catheters may be better for patients with deep ICH. These principles do not apply to aneurysmal or cerebellar ICH [52].

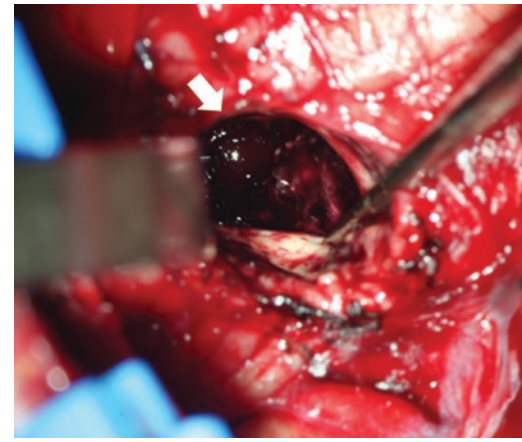


Fig. 14.2 Surgical view of craniotomy and hematoma evacuation for intracerebellar hematoma. After suboccipital craniotomy and minimal corticectomy, thick hematoma was observed in the cerebellar hemisphere

14.1.7.8 Critical Care of Intracerebral Hemorrhage

Patient with ICH has up to 16% risk of clinical seizures within 1 week which are defined as early

seizure [53]. Among them, 50–70% of seizures occur within the first 24 h, and 90% occur within the first 72 h, with an overall risk of seizures of about 8% within 1 month of symptom onset [54]. The incidence of late seizures is around 4 new cases/100 person-years, with a median delay between ICH and seizures of 9 months [55]. The lobar ICH with cortical involvement is an independent predictor of both types of seizures [54]. In contrast with early seizures, the occurrence of late seizures has been associated with worse functional outcome. In addition, the incidence of subclinical seizures which can be detected through the continuous electroencephalography after ICH is 29–31%. Clinical seizures should be treated with antiepileptic medications, as should electrographic seizures accompanied by mental change.

Fever (>37.5 °C) is very common (about 40%) in patients with ICH, particularly in cases of intraventricular extension due to damage to any structures of the central temperature homeostasis pathways [56]. Sustained fever after ICH is an independent risk factor associated with poor outcome and death [57]. However, insufficient data is available to establish whether treatment of fever leads to an improved functional outcome. We consider therapeutic normothermia as a basic principle of neuroprotection and recommend early treatment of elevated body temperature associated with increased duration of sedation or mechanical ventilation.

It has also been shown in many small trials that hyperglycemia (blood glucose levels >140–200 mg/dl) on admission is associated with hematoma expansion as well as higher morbidity and mortality rates in patients with ICH [58]. There are no specific recommendations for lowering the blood glucose levels to a certain level in acute ICH. Also, hypoglycemia (<40–50 mg/dL) may lead to neurological deterioration in ICH patients; therefore, it is reasonable to target glucose level at 100–150 mg/dL for patients with ICH.

Because of their immobility and paresis, patients with ICH are at high risk for deep venous thrombosis (DVT), with the rate of symptomatic DVT at 1–5%. And consecutively, the incidence of symptomatic pulmonary embolism (PE) is ~0.5–2% [59]. and about half of the PE are fatal. Thigh-length graduated compression stockings did not prevent DVT based on the Clots in Legs Or sTockings after Stroke-1 (CLOTS-1) trial [60]. In contrast, the use of elastic stockings combined with intermittent pneumatic compression devices decrease the rate of DVT in patients both hemorrhagic and ischemic stroke and may lead to a better outcome [61]. Other recent guidelines recommend the initiation of mechanical VTE prophylaxis, preferably with intermittent pneumatic compression devices at the time of admission [62]. Prophylactic doses of subcutaneous unfractionated heparin might be started in patients with stable hematomas within 48 h of admission [39].

14.1.7.9 Prognosis and Outcomes

ICH is the most debilitating type of stroke. Known poor prognostic factors of ICH include large hematoma volume, hematoma expansion, GCS score on admission, an intraventricular extension of hemorrhage, hemorrhage location, old age, contrast extravasation on CT scan (spot sign) and anticoagulant use [16] (Table 14.1). The most widely used simple clinical grading scale for evaluating 1-month prognosis is the ICH score, which includes age, GCS score at admission, ICH volume,

Table 14.1 Poor prognostic factors of intracerebral hemorrhage

Intracerebral hematoma volume (≥30 ml)
Expansion of intracerebral hemorrhage
Low Glasgow Coma Scale (GCS) at initial presentation
Intraventricular extension of hemorrhage on initial computed tomography
Infratentorial origin of intracerebral hemorrhage
Old age (≥80 years old)
Contrast extravasation on computed tomography (“spot sign”)
Anticoagulant use
Hyperglycemia at admission
Chronic kidney disease (estimated glomerular filtration rate < 60 mL/min/m^2)

Table is from An SJ, Kim TJ, Yoon BW. Epidemiology, Risk Factors, and Clinical Features of Intracerebral Hemorrhage: An Update. Journal of stroke. 2017;19(1):3–10 [16]

ICH location, and intraventricular extension [8]. These prognostic factors may help to stratify the 30-day mortality risk and functional outcomes at 1 year. Hyperglycemia at admission was also associated with an increased risk of 30-day mortality and, chronic kidney disease was also reported to be associated with poor outcome [16]. Most patients die from ICH due to presumed poor outcome leading to the early withdrawal of care such as do-not-resuscitate (DNR) decisions within the initial hospitalization in the United States [63]. The current AHA/ASA guidelines recommend early and aggressive care after ICH and postponement of any new DNR orders until at least the second full day of hospitalization [34].

14.2 Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) is defined as the extravasation of blood into the subarachnoid space which is the area between the arachnoid membrane and the pia mater surrounding the brain. Trauma to the brain is the most common cause of SAH. Besides trauma, spontaneous SAH can be classified into aneurysmal, nonaneurysmal, and perimesencephalic causes. Around 80–85% of the SAH are caused by rupture of an intracranial aneurysm, and rest of SAH are caused by vascular malformations, vasculitis, etc. [64] As traumatic SAH is beyond the scope of this chapter, and the preponderance of morbidity and mortality of SAH is related to aneurysmal SAH, the chapter focuses on this entity.

14.2.1 Epidemiology

Intracranial aneurysms usually arise from the branching points of arteries which are assumed to have hemodynamic stress on the wall, and it occurs in 1–2% of the population [65]. Annual rupture rate of an intracranial aneurysm is 0.95% from UCAS study [66]. The reported Age-adjusted average annual aneurysmal SAH incidence varies from 2.0 to 22.5 cases per 100,000 persons widely across the world, and it is known to participate in 5–10% of all strokes in the United States [67, 68].

Comparing to other subtypes of stroke, aneurysmal SAH tends to present at younger age. Therefore, loss of productive life is relatively greater than that of other subtypes of stroke [69]. Mortality of aneurysmal SAH within 30 days is approximately 45%, and 30% of the survivors suffer neuropsychological effects and decreased quality of life [70].

The pathophysiology of the intracranial aneurysm is not well defined. However, family history, a genetic disorder related to the connective-tissue disorder and polycystic kidney disease is a commonly reported risk factor [71, 72]. Risk factors associated with SAH can be categorized to modifiable and nonmodifiable risk factors. Modifiable risk factors include hypertension, current smoking, alcohol abuse, use of sympathomimetic drugs, whereas, nonmodifiable risk factors include female gender, black race, Hispanic ethnic group, genetic disorders and an aneurysm larger than 7 mm [71, 73, 74].

14.2.2 Clinical Manifestations

The hallmark presenting symptom of aneurysmal SAH is an abrupt onset of a severe headache which can be observed up to 97% [75, 76]. The patients usually describe their headaches as the worst headache of their life. And in 10–40% of patients, headaches due to a warning leak or "sentinel" a headache can occur 5–20 days before the full presentation of the SAH [77]. Although a severe headache is one of the most important symptoms of aneurysmal SAH, it can commonly occur during physical or psychological stress during daily activities. The previous study reports that a headache due to aneurysmal SAH is only 1% of all headaches evaluated in the emergency department [78]. Furthermore, a sentinel headache can be easily regarded as a migraine headache or other headaches which can lead to four times more morbidity and mortality comparing to properly diagnosed sentinel headache [79]. Therefore, careful documentation of the onset, character, severity, and associated symptoms or

findings that accompany a headache should be taken from the patient's history to avoid misdiagnosis and potential lifesaving [74, 80].

Seizure is another important symptom that present up to 26% of patients with aneurysmal SAH [81–84]. It can be the cause of aneurysmal rebleeding which can lead to intracranial hypertension and herniation. The poor grade in Hunt and Hess scale and Fisher scale is well-known risk factor post aneurysmal SAH seizures [85]. And early seizures at the onset of aneurysmal SAH symptoms are often a sign of rebleeding and a predictor of poor clinical outcomes [81, 85].

With more severely affected aneurysmal SAH cases, patients present with altered mental status. The range of altered mental status can vary from mild lethargy to deep coma. The initial mental status at arrival to the hospital is regarded as the degree of encephalopathy, and it is the major determinant of the prognosis [80]. These patients had a 2.8-fold increase in death or severe disability based on the modified Rankin Scale at 1 year, even when controlling for age, severity at presentation, and aneurysm size [86].

Other symptoms or signs associated with aneurysmal SAH include nausea, vomiting, photophobia, neck stiffness, focal neurologic deficits, and sudden death [87]. As these symptoms or signs are not specific with aneurysmal SAH, as a result, they can easily lead to misdiagnosis.

14.2.3 Grading Scales Used with Aneurysmal SAH

A variety of grading scales were introduced which correlates with prognosis, vasospasm, and aneurysm rupture rate. Although some of the factors overlap with each other, each grading scales represents the nature of aneurysmal SAH.

The Hunt–Hess classification and the World Federation of Neurosurgical Societies classification are the most commonly used grading systems correlated with long-term prognosis [88, 89]. These two grading systems are based on the severity of encephalopathy which is the most important factor in the outcome of patients with aneurysmal SAH. Aneurysm rupture causes immediate brain dysfunction and late events such as vasospasm and delayed cerebral ischemia (DCI) which is potentially related to poor outcome; however, its mechanism is poorly understood [90, 91].

The Fisher scale and modified Fisher scale is the grading system which correlates with the risk of vasospasm [92, 93]. These scales are based on the amount of SAH and intraventricular hemorrhage presented on CT images. Currently, the mechanism of vasospasm is unclear, but it is believed that by-products from hematoma degradation have an important role in arise of vasospasm.

PHASES score is one of the grading systems which prediction of risk of rupture of an intracranial aneurysm [94]. This grading system is a result of systemic analysis of prospective cohort studies. Although it is not a systemic for the prognosis of aneurysmal SAH, it gives an idea of factors that cause the rupture of an aneurysm. According to PHASES score Population (race), Hypertension, Age, Size of the aneurysm, Earlier SAH from another aneurysm, and Site of an aneurysm are the risk factors of an aneurysm.

14.2.4 Diagnostic Evaluation

In patients with suggestive history and physical examination of aneurysmal SAH, brain CT without contrast enhancement is the first step to confirm the presence of bleeding in subarachnoid space which presents typical star shape hemorrhage localized to the basal cistern (Fig. 14.3) [87, 95]. The sensitivity of the CT scan is close to 100% in the first 3 days after the onset of symptoms, and declines to 50% by 5–7 days after the onset of symptoms [96, 97]. Besides time from rupture of the aneurysm, various factors can influence the sensitivity and specificity of non-contrast head CT, which includes the scanner, the radiologist, the amount of the hemorrhage, the patient's hematocrit level (<30%), and the presence of motion or bone artifact [64, 98–100].

If the CT shows negative results, MRI can be an alternative method to diagnose aneurysmal SAH. Although MRI takes more time to scan the

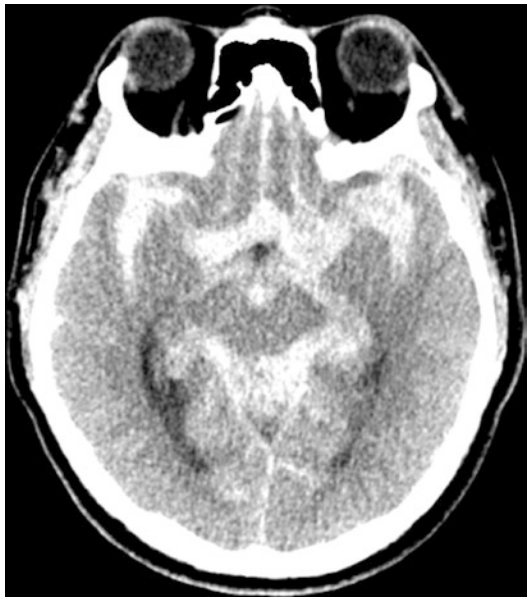


Fig. 14.3 Typical diagnostic image of SAH on CT is a hyperattenuating material seen filling the subarachnoid space, most commonly apparent around the circle of Willis and extending to sulci, fissures, and ventricles

brain image, it has the additional advantage of better sensitivity for detecting chronic bleeding than that of CT. MRI with fluid-attenuated inversion recovery, proton density, and gradient-echo sequences are reported to have high sensitivity to heme in the cerebrospinal fluid [101]. Due to longer study time is required than CT, usually MRI is not the first choice for aneurysmal SAH unless the patient is stable; however, there are physicians who prefer MRI as the first diagnostic choice.

If there CT or MRI is negative from patients with suspicious aneurysmal SAH, detecting blood or xanthochromia in cerebrospinal fluid by lumbar puncture (LP) can be another option [102]. LP has several drawbacks which are an invasive and time-consuming procedure with difficulty in distinguishing between subarachnoid hemorrhage and trauma during the procedure [97]. Furthermore, the sensitivity and specificity of CT and MRI are very high, the value of LP after negative CT or MRI is decreasing. As a result, LP as a diagnostic tool for aneurysmal SAH is in the debate. However, from a recent meta-analysis, there is still a chance of missing aneurysmal SAH by approximately 1% [103]. The value of LP as a diagnosis tool for aneurysmal SAH is diminishing due to low diagnostic yield and high sensitivity and specificity of CT and MRI, it still takes place in American Heart Association and American Stroke Association (ASA) guidelines published in 2012, which recommend to use after negative CT to adequately rule out SAH [95]. LP has an additional value that it can diagnose other cause of headaches, including idiopathic intracranial hypertension (pseudotumor cerebri), spontaneous intracranial hypotension, encephalitis, or meningitis and measure intracerebral pressure during the procedure [104]. Therefore, although LP can be an unnecessary procedure in the near future in diagnosing aneurysmal SAH, it should be kept in mind in the worst scenarios.

Once aneurysmal SAH is diagnosed, the next step is determining the specific location of the aneurysm which is ruptured. CT angiography can be performed immediately after the initial CT, and it can provide the essential information which is required for the surgical treatment [105]. MR angiography can be used as an alternative method also can be used for detecting an aneurysm. CT angiography and MR angiography can detect aneurysms as small as 2–3 mm, but tiny blister aneurysms or aneurysms filled with thrombi may be missed [106]. Although CT angiography and MR angiography provide reliable sensitivity, still they do not give information whether it is ruptured or not.

Digital subtraction angiography (DSA) remains the gold standard for diagnosing an aneurysm and for defining relevant anatomy for treatment [105]. Two-dimensional angiography in DSA provides information on vascular burden and dynamics of the blood flow. In some cases, it can also detect extravasation of blood from the aneurysmal dome which needs urgent treatment. With a combination of three-dimensional angiography reconstructions provides more sensitivity and more accurate anatomical data of the aneurysm and surrounding vessels which can be helpful in planning treatment [80].

14.2.5 Management

The goal of management of aneurysmal SAH is to prevent further neurological deterioration by rebleeding, brain edema, vasospasm, and hydrocephalus. Especially, the path to securing the ruptured aneurysm from rebleeding is the most important goal. Therefore, the management of aneurysmal SAH can be determined into three phases: management prior to secure of the ruptured aneurysm, securing the ruptured aneurysm, and management after securing the ruptured aneurysm. Before securing the aneurysm, the management of aneurysmal SAH management is basically focused to prevent rebleeding and minimize the encephalopathy which can result in high mortality and morbidity. Then surgical of endovascular treatment is performed to secure the ruptured aneurysm. Finally, management to prevent further neurological deterioration by delayed complications such as vasospasm, and hydrocephalus follows.

14.2.5.1 Management Prior to Secure of the Ruptured Aneurysm

Rebleeding is most common within the first 24 h, some studies report that the risk of rebleeding is highest within 2 h [107, 108]. Longer time to aneurysm treatment, worse neurologic status on presentation, initial loss of consciousness, previous sentinel headaches, larger aneurysm size, and hypertension are risk factors of rebleeding [109, 110]. Although early definitive treatment of ruptured aneurysms can reduce the risk of rebleeding, over 12% of patients decease during transportation to the hospital [109, 111].

Seizure; Antiepileptic Drugs

Seizure can be both cause and result of rebleeding and it is also a predictor of bad prognosis [81, 85]. Seizure-like episodes have been reported in up to 26% of patients with aneurysmal SAH, most occurring before arriving at the hospital [81–84]. The risk of seizures increases with poor Hunt and Hess grade and Fisher grade [85]. And delayed seizures occurred in 3–7% of patients [84, 85]. Routine prophylactic antiepileptic drug use in patients with aneurysmal SAH is commonly used by physicians; however, still, there are no randomized controlled trials for the safety and effectiveness of antiepileptic drugs in aneurysmal SAH [112]. Guideline from ASA suggests that short-term prophylactic antiepileptic drug can be used in the immediate posthemorrhage period, meanwhile, the routine long-term use of anticonvulsants is not recommended [95].

Hypertension

High blood pressure is regarded as a risk factor of rebleeding in aneurysmal SAH; therefore, there is the general consensus of strict control of hypertension unless the aneurysm is treated. However, the specific parameters for blood pressure have not been defined. According to ASA guideline maintaining systolic blood pressure less than 160 mmHg and mean arterial pressure less than 110 mmHg is recommended with Class I; Level of Evidence B [95]. In our institute, target blood pressure in aneurysmal SAH is under 140 mmHg which is widely used by many practicing neurosurgeons and endovascular specialists [74]. Blood pressure must be carefully controlled not to effect on lowering cerebral blood flow and an increase of intracranial pressure. Therefore, labetalol, nicardipine, and clevidipine are agents recommended for controlling hypertension [95].

Antifibrinolytic Therapy

Antifibrinolytic therapies such as aminoepsilon caproic acid or tranexamic acid can be considered to reduce the risk of aneurysmal rebleeding in case of an impossible situation of early secure of the aneurysm. Studies on the early and short-term use of antifibrinolytics showed benefits on prevention of rebleeding, but there were no significant benefits on long-term outcomes [113, 114]. ASA guideline suggests short-term (<72 h) therapy with antifibrinolytics is reasonable (Class IIa; Level of Evidence B), but it should be carefully used on a case-by-case basis [74, 95].

Other Medical Management

Various medical problems occur in patients with aneurysmal SAH, includes fever, electrolyte imbalance, cardiac decompensation, and deep vein thrombosis. Fever is one of the most com-

mon medical complications of aneurysmal SAH. Presence of fever in patients with aneurysmal SAH is associated with worse outcomes [115, 116]. As fever induces cerebral metabolism which leads to the production of metabolic byproducts such as various cytokines and free radicals, it can accelerate the encephalopathy procedure. Therefore, induced normothermia reduces episodes of cerebral metabolic crises [117]. Evidence of encephalopathy which can be measured with poor Hunt and Hess grade and presence of intraventricular hemorrhage are strong predictors of fever [118].

14.2.5.2 Securing the Ruptured Aneurysm

Once the aneurysm is ruptured, securing the ruptured point to prevent rebleeding is the most important goal of the management of aneurysmal SAH (Fig. 14.4a). There are two major treatments, which is an option in securing the ruptured aneurysm. One is surgical clipping and the other is endovascular treatment. Recently, flow diversion device such as pipeline device emerged as a new treatment method for the treatment of aneurysmal SAH in the endovascular division [119, 120]. Each treatment method will be described in this section.

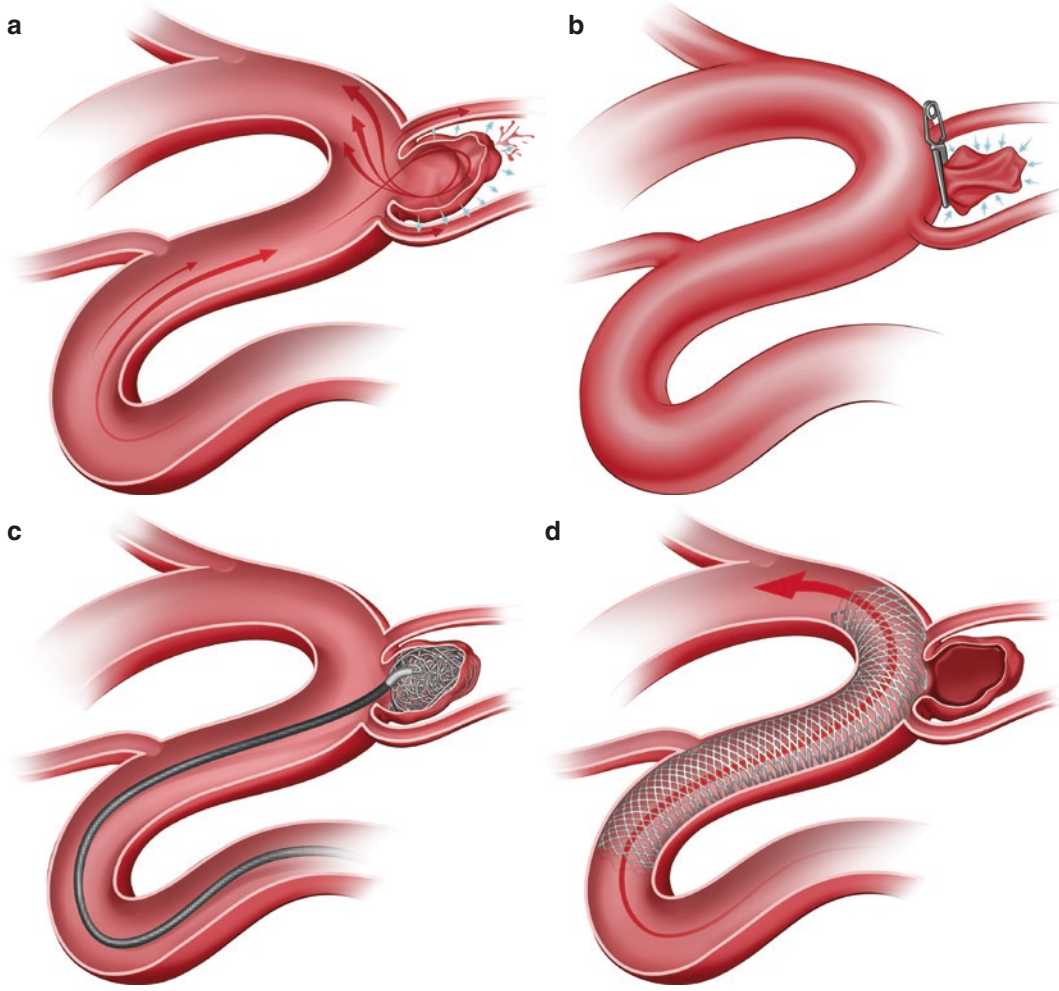


Fig. 14.4 Nontraumatic subarachnoid hemorrhages are usually caused by rupture of the aneurysm. (**a**) a ruptured aneurysm from origin of posterior cerebral aneurysm. Various treatment can be considered, including aneurysmal neck clipping (**b**), endovascular coiling (**c**), and flow diverting devices (**d**)

External Ventricular Drainage

Acute hydrocephalus is common in aneurysmal SAH with intraventricular hemorrhage which causes early neurologic decline. External ventricular drainage can be the treatment option for symptomatic hydrocephalus which can provide ICP monitoring as well as CSF drainage. Acute hydrocephalus can end up with intracranial hypertension and cerebral ischemia eventually cerebral herniation unless it is treated properly. Therefore, identification of the presence of the hydrocephalus on CT is essential to step on the management of aneurysmal SAH.

Microsurgical Clipping

Surgical clipping of a ruptured aneurysm is performed under craniotomy. Usually, subarachnoid hemorrhage spread throughout subarachnoid spaces and adhere to arachnoid and surrounding vessels. Careful dissection is performed around the cerebral arteries under the surgical microscope, to minimize the brain tissue injury. Once the aneurysm is exposed, titanium clip(s) is applied to the aneurysmal neck for mechanical closure of the aneurysm sac (Fig. 14.4b). This procedure preserves blood flow to the normal arteries and prevents rebleeding of the ruptured aneurysm. The majority in the surgical strategy of aneurysmal SAH is similar to that of the unruptured aneurysm. But it has various factors that can alter the surgical difficulties, and it has a larger chance of intraoperative rupture of the aneurysm. In case of presence of cerebral edema, drainage of cerebrospinal fluid via ventriculostomy from Paine's point or fenestration of lamina terminalis could be necessary and additional craniectomy with/without temporalis muscle resection could also be required. And in case of large amount hematoma in cisternal space or intraparenchymal hematoma could alter the anatomic relation in the surgical field. To deal with intraoperative rupture of the aneurysm, proximal control of the parent artery is essential. In the case with difficulty in exposing the proximal parent artery for temporary clipping, the physicians must not hesitate to expose the cervical internal cerebral artery.

Endovascular Treatment

Endovascular treatment of a ruptured aneurysm is performed under fluoroscopic guidance usually via the femoral artery or radial artery. Microcatheter is carefully navigated up to the parent artery of the aneurysm and the tip of the microcatheter is advanced into the aneurysm sac. Metal coil is carefully deployed inside the aneurysm sac, forming a framework like a bird cage (Fig. 14.4c). Once the framework is done, additional coils are introduced to fill the aneurysm sac. This process arrests intraaneurysmal blood flow and proceeds induced thrombus formation which leads to preventing rebleeding of the ruptured aneurysm.

Recent reports present successful results in the treatment of large proximal internal cerebral artery aneurysms with flow diversion devices [121]. Various devices have been introduced to the market, such as Pipeline, Surpass, SILK, FRED, and p64. High metal coverage of flow diversion device forms static intraaneurysmal blood flow which leads to intraluminal thrombus formation (Fig. 14.4d). There are studies that show that flow diversion devices can be used in a selective case in aneurysmal SAH, such as small or blister aneurysm [119, 120].

14.2.5.3 Management After Securing the Ruptured Aneurysm

Cerebral Edema

Global cerebral edema is reported in up to 20% of patients with aneurysmal SAH which is the cause of increased intracranial pressure [122]. Early global cerebral edema is caused by the ictal intracranial circulatory arrest at the time of aneurysm rupture. Various factors can lead to delayed cerebral edema which are cytotoxic effects of blood products, microvascular ischemia, and autoregulation dysfunction [123]. Both early and delayed global cerebral edema can present loss of consciousness. This is an independent predictor of mortality and poor outcomes.

Vasospasm and Delayed Cerebral Ischemia

Vasospasm and DCI is one of the most serious complications associated with aneurysmal

SAH. One-third of patients suffer from SCI who survive the aneurysmal SAH and results in poor outcome in half of the patients with this complication [124]. Approximately 70% of aneurysmal SAH patients present narrowing of cerebral arteries angiographically which is also known as vasospasm. Vasospasm generally starts 3–4 days after aneurysm rupture, peaks at 7–10 days, and resolves by 14–21 days [125] (Fig. 14.5a, b). DCI is a clinical syndrome of focal neurologic deficits that develop in 30% of aneurysmal SAH patients. Delayed cerebral ischemia generally occurs 4–14 days after aneurysm rupture [91]. Delayed cerebral ischemia is one of the major causes of morbidity and mortality after aneurysmal SAH [64]. There is a common belief among physicians that vasospasm is the cause of cerebral ischemia, but each may occur independently of the other. In addition, a recent study suggests that various factors contribute to DCI [126]. Amount of hemorrhage and presence of intraventricular hemorrhage are the most widely known factors of vasospasm and this is also represented on Fisher grade and modified Fisher grade [92, 93].

Classically, induced hypertension, hemodilution, and hypervolemia, the so-called triple-H therapy has been used for the management of hypoperfusion after aneurysmal SAH [127]. However, triple-H therapy was not supported by any controlled studies and adverse effect followed by serious complications arises. Recent systemic review study reports that only induced hypertension seemed beneficial in increasing cerebral blood flow [128], but the single-blind randomized clinical trial of induced hypertension in DCI showed no significant benefit in patients' outcome [129]. However, ASA guideline suggests that induced hypertension is recommended for patients with DCI unless the patient has initial hypertension or cardiac problem and maintenance of euvolemia and normal circulating blood volume is recommended whereas prophylactic hypervolemia is not recommended [95]. Therefore, in current status, maintaining normotension or induced hypertension with euvolemia in aneurysmal SAH must carefully apply to the aneurysmal SAH patients on a case-by-case basis.

Nimodipine is a calcium antagonist that is thought to reduce the rate of cerebral vasospasm

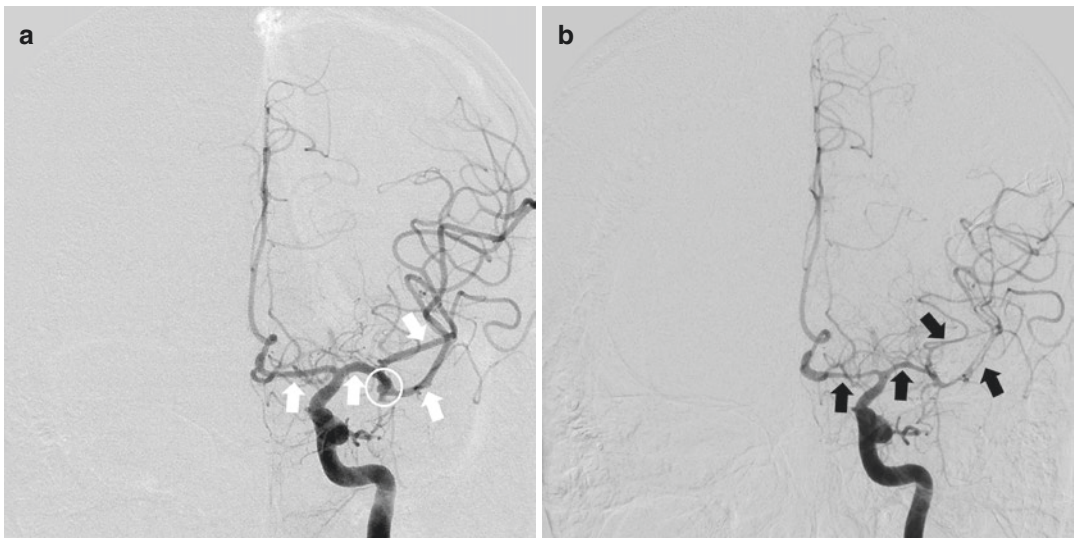


Fig. 14.5 A 57-year-old female administrated due to ruptured aneurysm on left MCA bifurcation. Severe headache with mild fever occurred 10 days after the aneurysmal neck clipping and DSA revealed broad vasospasm at ACA and MCA. (**a**) White circle, MCA aneurysm; White arrow, normal ACA and MCA; (**b**) Black arrow, ACA, MCA with vasospasm

by reducing the influx of calcium into the vascular smooth muscle cells. A Cochrane Review that includes a large randomized controlled trial shows a reduced risk of poor outcome [130]. The administration of nimodipine to reduce the risk of poor outcome and DCI is the only level IA evidence recommended by the ASA [95]. Use of nimodipine showed significant reduction of the risk of angiographic vasospasm; however, no measurable effect was observed on the development of DCI or on clinical outcomes [90, 91]. A Cochrane review of randomized trials indicated that nimodipine reduced the risk of poor outcomes in one-third of patients with aneurysmal SAH [130]. Oral nimodipine is recommended to be administered to all patients with SAH according to the ASA guideline [95].

Transcranial Doppler ultrasonography is widely used as a noninvasive screening for vasospasm after aneurysmal SAH [95]. Perfusion CT or MRI or diffusion MRI can also be used for patients who have a new neurologic deficit. One vasospasm is detected in major cerebral arteries which are not improved by intravenous nimodipine infusion or induced hypertension, selective intraarterial chemical balloon angioplasty under fluoroscope can be considered as a treatment of choice [95]. In addition, balloon angioplasty before the development of vasospasm is not recommended [95].

Hydrocephalus

Both acute and delayed hydrocephalus can develop in patients with aneurysmal SAH. Acute hydrocephalus occurs due to extravasated blood to subarachnoid cistern or ventricles which arrest the normal cerebrospinal fluid circulation. The incidence of hydrocephalus varies from 15% to 85% in patients with subarachnoid SAH [95]. If the hydrocephalus causes encephalopathy which presents in neurologic impairment, a placement of an external ventricular drainage can be performed. Lumbar drainage can be an alternative treatment for acute hydrocephalus. Both external ventricular drainage and lumbar drainage have the capability of removing some contents of the by-products from extravasated blood which could reduce the risk of vasospasm. However, lumbar drainage should not be used in patients with obstructive hydrocephalus and increased intracranial hypertension due to the intraparenchymal hematoma.

One-third of acute hydrocephalus patients caused by aneurysmal SAH suffer from chronic symptomatic hydrocephalus. The mechanism of the chronic symptomatic hydrocephalus is not clearly defined; however, it is generally believed that it is caused by damage of the arachnoid villi, which absorbs cerebrospinal fluid, by extravasated blood. [131]. Permanent diversion of cerebrospinal fluid generally ventriculoperitoneal shunt could be considered to improve neurological impairment including cognitive dysfunction, gait disturbance, and urinary incontinence.

Medical Complication

Multiple medical complications are common in aneurysmal SAH patients; therefore, they should be treated in a neurocritical care unit if possible [132]. There are various goals for aneurysmal SAH patients including euvolemia, normothermia, avoidance of hypoglycemia or marked hyperglycemia, electrolyte balance, and adequate ventilation to avoid exacerbating elevated intracranial pressure. Majority of these goals were described in prior paragraphs; other than these medical problems, deep venous thrombosis should be taken care of in patients with aneurysmal SAH, especially among immobilized patients due to low mental status. Routine prophylaxis with pneumatic compression is recommended. Under risk evaluation of patients with plan of multiple invasive procedures, unfractionated heparin can be considered, starting 24 h after securing the ruptured aneurysm and continuing until patient's mobilization [133].

14.2.5.4 Guidelines

The latest guideline is from a writing group of the American Heart Association and American Stroke Association guidelines published in 2012 for the management of aneurysmal SAH [95]. This chapter generally follows this guideline; however, data from recent systemic reviews, clinical studies were added for further discussion in the management of aneurysmal SAH. Half a

decade has already passed in the current situation; therefore, a new guideline is expected in near future.

14.3 Cerebral Arteriovenous Malformation

Arteriovenous malformations (AVMs) are vascular abnormalities consisting of fistulous connections of arteries and veins without normal intervening capillary beds. Three morphologic features are typical of these lesions: feeding arteries, draining veins, and a dysplastic vascular nidus composed of a tangle of abnormal vessels that acts as a shunt from the arterial to venous system [134]. There is a direct transmission of arterial pressure to venous structures, leading to increased cerebrovascular blood flow, dilatation and tortuous growth of vessels [135]. As a result of this anatomic cerebrovascular changes, this process may bring about significant hemodynamic changes in the brain, such as reversal of venous flow, venous hypertension, and low-resistance AVM shunt "stealing" blood away from surrounding tissue [136]. The most common presentation symptom is intracerebral hemorrhage, followed by a seizure. And the current treatment of AVMs includes microsurgical resection, stereotactic radiosurgery alone, preoperative endovascular embolization followed by microsurgery or radiosurgery, or observation only.

14.3.1 Etiology

Although the pathogenesis of AVMs remains unknown, their angioarchitectural characteristics and presentation at any age indicate that they are probably either embryonic or acquired. Although most AVMs do not occur hereditarily, rare cases of familial occurrence have been reported [137]. AVMs which are related to the genetic disease are very rare. There are no clinically distinguishable features found between acquired and congenital AVMs, but the acquired type tends to be diagnosed or occurred at in their earlier age [137, 138].

Usually, AVMs are found to be a single lesion in the vast majority of the cases, clinical series reported 1~9% incidence of multiple AVMs. Multiple AVMs can occur without apparent cause or in association with syndromic conditions, such as hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu syndrome), Wyburn–Mason syndrome, or soft tissue vascular malformations [139, 140].

14.3.2 Epidemiology and Presentation

The exact incidence of AVMs is an unclear and rather rare disease. The incidence rate of AVMs is estimated from 0.89 to 1.34 cases per 100,000 person-years in different population-based studies [141–143], and the prevalence of AVMs is presumed about 0.2% [135]. AVMs are accounted for 38% of all intracranial hemorrhage in patients between 15 and 45 years of age [144] and patients are usually initially seen in the third or fourth decade in life [145].

The most common presenting symptom of symptomatic AVMs is cerebral hemorrhage followed by seizure, headache, and focal neurological deficit due to mass effect or hemodynamic disturbance [135]. Hemorrhagic presentation of AVMs accounts for 30–72% of patients [146]. Intraparenchymal hemorrhage is the most common type, and it can also present intraventricular hemorrhage or subarachnoid hemorrhage [147]. The second most common symptom AVMs is symptomatic epilepsy, which is present in about 15–35% of patients [143].

14.3.3 Risk of Hemorrhage of Untreated AVMs

Because of the hemorrhagic stroke of cerebral AVMs could result in a serious complication, it is important to identify risk factors which are related to AVM rupture. The average annual hemorrhagic risk of untreated AVMs is about 2–4%,

but it differs from various risk factors and can be as low as 0.9% without any associated risk factors [140, 146, 148]. Cumulative hemorrhage rate was 2% in the first year, 14% at fifth year, and 31% at tenth year follow-up [149].

History of previous AVM hemorrhage, deep-seated location or infratentorial location or AVM and a deep venous draining system are typical risk factors which increase the bleeding risk of AVM [145, 146, 150]. Recent meta-analysis study of future hemorrhage risk of AVM showed that the annual rate of hemorrhage risk of unruptured AVM was 2.2%, meanwhile 4.5% in previously ruptured AVM [151]. Other risk factors are an intranidal or an extranidal aneurysm associated with AVMs and narrowing or occlusion of draining vein [151].

However, cautions are needed in interpreting these results, as the increased risk associated with these characteristics was inconsistent among various studies; the subgroup analysis was performed with a low event rate, and the number at risk for each of these subgroups was small after a short period [152].

Clinical outcome of ruptured cerebral AVMs differs from the extent of injury to adjacent brain structures. Hemorrhage which occurred in near eloquent area, deep white matter pathway, and basal ganglia can be associated with poor clinical outcomes.

14.3.4 Radiologic Findings

The first diagnostic examination which is performed in patients with suspected cerebral AVMs is usually CT and MRI, as the most common presentations, are not specific for AVM (hemorrhage, seizure, headache, and focal neurological deficit) [153].

Non-contrast brain CT is usually the initial imaging tool based on the clinical presentation, to evaluate for any hemorrhage. The AVM usually does not cause mass effect, unless in case of hemorrhage. Instead, there may be hypoattenuation and volume loss in the brain parenchyma surrounding the nidus, relating to gliosis or hemosiderin deposition from previous hemorrhage or chronic hypoperfusion [154]. For evaluation of possible underlying vascular malformation, CT angiography is chosen for next step, which is relatively noninvasive, only requiring an injection of contrast material into a vein. Enhancing nidus, flow-related aneurysms, or prominent draining veins will be well identified in CT angiography, but not as well depicted as on DSA.

On conventional MRI, dilated arterial feeding arteries, the nidus, and draining veins appear as flow voids. Hyperintensity in T2 and FLAIR involving the adjacent brain parenchyma frequently relates to gliosis [154] (Fig. 14.6a, b). MRI with MR angiography could be a useful noninvasive follow-up imaging tool after treatment of cerebral AVM with radiosurgery, which showed 80% of sensitivity and 100% of specificity compared with conventional DSA [155].

Despite of improvement of accuracy in noninvasive imaging modalities, DSA is the gold standard for evaluation of cerebral AVMs (Fig. 14.6c, d). DSA can evaluate image characteristic mentioned above, it can also find very small flow-related aneurysms, which makes it possible for the planning of endovascular embolization and evaluation of precise nidal extent for preradiosurgical planning. However, CT and MRI are required to recognize the relation between vascular structure and brain parenchyma, and it has a risk of permanent neurological deficit accounted for 0.1–1.0% [156].

14.3.5 Classification

For prediction of treatment outcome, several grading systems have been used for cerebral AVMs usually based on anatomical features. The Spetzler–Martin grading system is the most widely used scale for this purpose, which was originally developed not only to predict the outcome of microsurgical treatment of the cerebral AVMs but can also be used to predict the radiosurgical treatment outcome [157]. This scale includes major factors important in determining the difficulty of AVM resection: the size of the AVM, the pattern of venous drainage, and

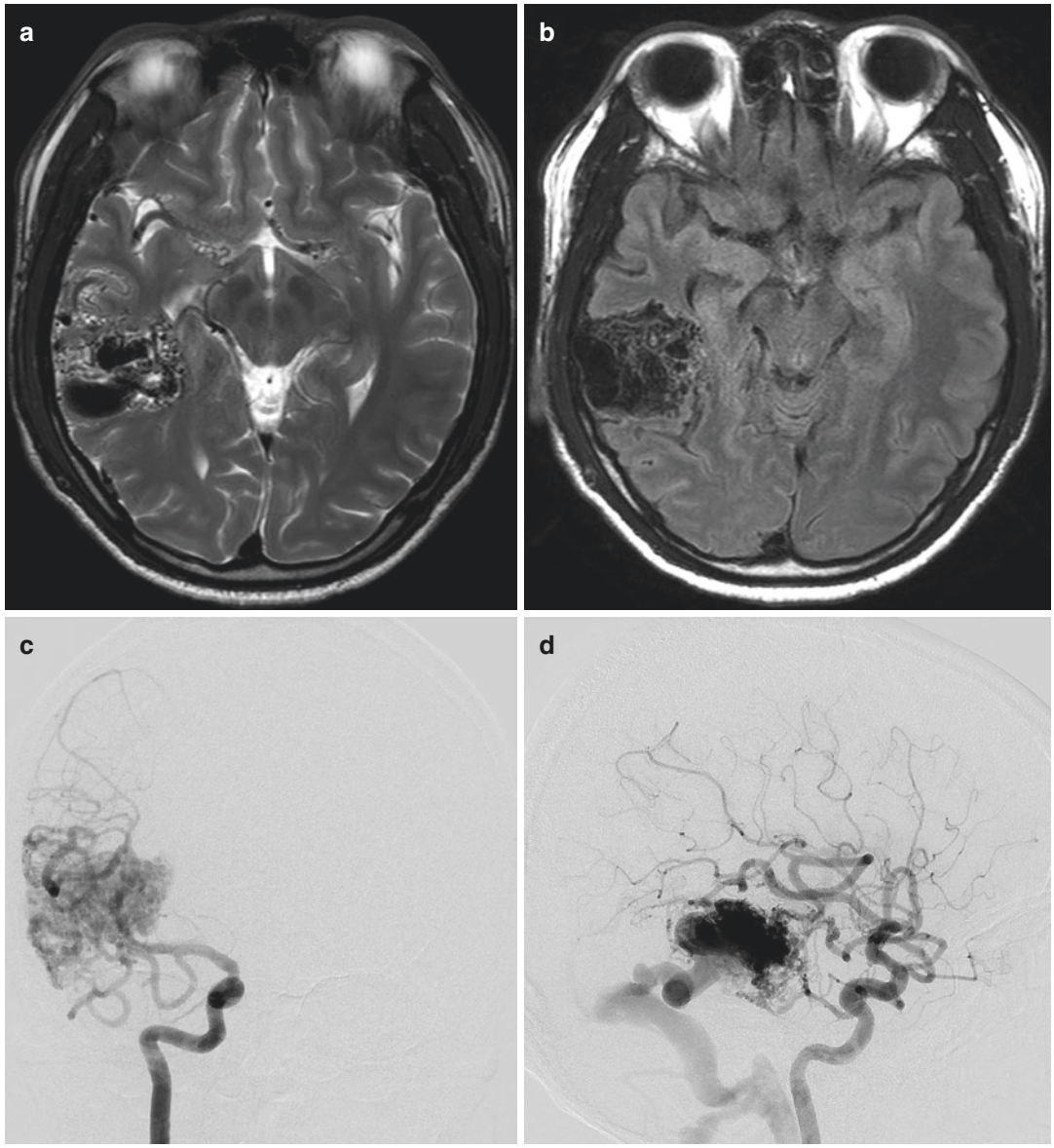


Fig. 14.6 A 29-year-old male presented with a headache and dizziness. About 5 cm entangled vascular mass with signal voids in right temporal lobe (**a** T1 weighted MRI, **b** FLAIR MRI). DSA revealed engorged feeding arteries from right MCA and PCA branches supplying nidus and engorged draining vein into right transverse sinus via vein of Labbe was noted (**c**, **d**)

the eloquence of adjacent brain. A numerical value is assigned for each of the factors (Table 14.2): the diameter, <3 cm (1 point), 3–6 cm (2 points), or >6 cm (3 points), presence of deep venous drainage (1 point), and involvement of an eloquent location such as the motor, sensory, language, and visual cortex or basal ganglia (1 point). Complete resection of grade I lesion would require relatively minor technical difficulties and resulted in no or minor mortality and morbidity. But the highest grade (grade V) lesion would be associated with poor outcome of surgical morbidity and mortality. The authors defined grade VI as "inoperable"

Table 14.2 Spetzler–Martin Grade and Supplementary grade

Spetzler–Martin Grade	Points	Supplementary grade
Size (cm)		Age (year)
<3	1	<20
3–6	2	20–40
>6	3	>40
Venous drainage patterns		Bleeding
Superficial	0	Yes
Deep	1	No
Eloquence		Compactness of the Nidus
No	0	Yes
Yes	1	No

This table is from Lawton MT, Kim H, McCulloch CE, Mikhak B, Young WL. A supplementary grading scale for selecting patients with brain arteriovenous malformations for surgery. Neurosurgery. 2010;66(4):702–13; discussion 13 [158]

lesion because of surgical resection wound almost inevitably resulted in totally disabling deficit or death.

Recently, some clinicians use simplified Spetzler–Martin grading system. Class A includes grades I and II, class B includes grade III, and finally class C includes IV and V. The advantages of this modification include simplification, a larger sample size for each group for analysis of clinical series, and a system that reflects current decision-making [159]. In addition, supplementary grading system which is added to Spetzler–Martin grading system is also introduced to stratify surgical risk more evenly [158] (Table 14.2).

For the prediction of treatment outcome of radiosurgery for cerebral AVMs, the Virginia Radiosurgery AVM scale (VRAS) and the radiation-based AVM score (RBAS) have been introduced [160, 161].

14.3.6 Treatment

The main goal of AVM treatment is the prevention of intracranial hemorrhage and further brain injury. Treatment planning for AVM depends on the risk of subsequent hemorrhage, which is determined by the demographic, historical, and angiographic features of individual patients. History of hemorrhage, deep venous drainage, stenosis or occlusion of venous outflow, and flow-related aneurysms make subsequent hemorrhage more likely. Four therapeutic approaches have evolved to treat AVMs: surgery, radiosurgery, embolization, and conservative treatment. There is a lack of consensus about the choice of treatment, and the specialty of the physician who first sees a patient with an AVM often determines management [162].

14.3.6.1 Observation

There was no widely accepted consensus whether observation or performing invasive treatment to whom diagnosed unruptured cerebral AVMs. Because some clinicians take into account patients diagnosed with an unruptured cerebral AVMs who were also considered candidates for invasive treatment due to the possibility of hemorrhage. Otherwise, the opposite side insists an observation policy because of the low incidence of annual hemorrhage risk of unruptured cerebral AVMs [140].

Therefore, the multicenter randomized clinical trial of unruptured brain AVMs trial (ARUBA) was conducted [163]. The patients with an unruptured cerebral AVMs were randomized to observation or invasive therapy (endovascular, surgical, or radiosurgery), which was stopped because of superiority of the observation. But this study has been criticized on many points. Generally grade 1 or 2 are good candidates for surgical resection, skillful surgeons have reported success rate of microsurgery up to 95% which were confirmed on MRI or angiography [164]. The data were not analyzed according to the type of invasive treatment, specific characteristics of the lesion's location, and patient's risk factor which can affect the outcome of treatment [165]. In addition, it generally takes 2–5 years to assess treatment outcome of stereotactic radiosurgery (SRS) due to a characteristic of the treatment process. However, the ARUBA study terminated at 33 months which considered too short for determining the outcome of SRS.

14.3.6.2 Embolization

Embolization involves occluding blood flow by introducing occlusive materials into feeding

arteries and nidus of an AVM. There are two main types of liquid embolic materials, *N*-butyl-2-cyanoacrylate (NBCA) and Onyx [166]. NBCA is a classical liquid embolic material. However, it is difficult to handle and highly adhesive resulting in some complications such as gluing of the microcatheter to the vessels. Recently, Onyx is widely used as an alternative to NBCA for treatment of DAVFs and AVM.

The purpose of embolization in AVMs can either be curative or adjuvant therapy. Curative embolization can be performed in selective cases if the size of the AVM is small and have one or two feeding arteries. And it can be performed prior to the microsurgical resection or stereotactic radiosurgery (SRS) to reduce the blood flow and shrink the size of the nidus of the AVM. During the embolization, it is important not to violate the draining veins as it can result in devastating outcomes. Complications of embolization of the AVM have been reported in up to 14% of cases [167–169]. Majority of the complications are minor complications which are related to endovascular procedures; however, severe complications including major hemorrhage, major stroke, and death have also been reported.

14.3.6.3 Microsurgical Resection

Since the first reported craniotomy was done for resection of cerebral AVMs, surgical skill was developed incredibly with the introduction of operating microscope, brain navigation, and development of surgical instruments [170]. After craniotomy is done, arterial feeders are isolated and ligated. After gentle dissection around the nidus with complete resection, ligation of the draining vein is the last step in surgery. When doing dissection or cauterization, damage to surrounding structures (basal ganglia, deep white matter tract, functional cortex) or massive bleeding from incomplete ligation results in the poor clinical outcome or even death.

For assessment of postoperative surgical outcome and risk, the Spetzler–Martin grade has been used. Surgical resection is usually strongly recommended to the treatment of low-grade cerebral AVMs if surgically accessible with low risk [171] because when experienced surgeons conducted microsurgical resection of low-grade cerebral AVMs, high cure rate with low complication rate has been reported [164]. Grade III AVMs are heterogeneous entity, which is size <3 cm with superficial venous drainage in the eloquent area have a similar risk of low-grade cerebral AVMs. Otherwise cerebral AVMs in size of 3–6 cm with superficial draining vein located in the eloquent area have similar operative risk as that of high-grade cerebral AVMs [172]. High-grade cerebral AVMs are often not amenable to surgical treatment alone because of high surgical morbidity and mortality rate. These AVMs can be approached by a combined multimodal approach of a combination of embolization, radiosurgery, or surgery [171].

14.3.6.4 Stereotactic Radiosurgery

Over the past 40 years, SRS has been accepted as an appropriate management option for treatment of cerebral AVMs and shown to be effective even for small AVMs located in critical areas of the brain where the surgical risk would be considered unacceptable [173, 174]. The complete obliteration rate of the cerebral AVM usually depends on the volume of the lesion and the delivered radiation dose to the margins of the lesion. Lesions which respond most favorably to SRS were AVM with a volume less than 4 cm^3 treated radiation dose of 18 Gy or more (77.3%). Whereas larger lesion with less marginal dose (<18 Gy) achieved less successful rate (48.3%) [161].

The limitation of the SRS of cerebral AVMs area complete obliteration could take a long time, even for several years, the patients are exposed continuously to ongoing hemorrhagic risk, and patients can experience radiation-induced complications [161]. Also, SRS is not therapeutically effective for all lesions, large, high-grade Spetzler–Martin, VRAS, RBAS showed poor response to SRS; physicians should consider alternative treatment methods for overcoming the weakness [175]. Other factors related to poor treatment response of AVM to SRS are changes of nidal morphology after SRS due to resection of hemorrhage, treatment planning error [176, 177].

To improve treatment success rate of SRS for large or high-grade AVMs, a neoadjuvant endovascular embolization of nidus and feeding vessels with materials such as *N*-butyl-2-cyanoacrylate or ethylene vinyl alcohol copolymer, has been developed [175]. As a result volume reduction of a large AVM nidus may improve the obliteration rate after SRS of the residual AVM. Neoadjuvant embolization also reduces surgical morbidity by occluding deep arterial feeding vessels, minimizing the need for extensive dissection into deep white matter pathways adjacent to the AVM [178].

14.4 Cerebral Dural Arteriovenous Fistula

14.4.1 Epidemiology and Pathophysiology

Intracranial dural arteriovenous fistulas (DAVFs) are abnormal arteriovenous shunts between dural arterial feeders and dural venous sinus or cortical veins. DAVF is distinguished from AVM in that an abnormal shunt is made in dura mater and that there is no parenchymal nidus. DAVFs are rare diseases, accounting for 10–15% of all intracranial malformation [179–182]. In addition, DAVFs constitute approximately 6% of supratentorial and 35% of infratentorial vascular malformation [180, 182]. These abnormal shunts are mainly located at the dural leaflets around venous sinus, especially at the transverse–sigmoid sinus (50%) (Fig. 14.7), cavernous sinus (16%) (Fig. 14.8), tentorium (12%), superior sagittal sinus (8%), anterior cranial fossa (Fig. 14.9), foramen magnum (Fig. 14.10) and other locations [183]. DAVFs do not show a clear difference in sex ratio and mainly occur in the age of 50s and 60s, and rarely occur at younger ages including children [179]. In addition, there is no clear evidence that DAVFs are associated with genetic factors.

Most DAVFs are presumed to be idiopathic, but some cases of DAVFs occur secondary to concomitant disease including head trauma, previous brain surgery, infection, cancers, or dural venous sinus thrombosis [179, 184, 185]. The pathophysiological mechanism of DAVF formation is not fully understood. However, DAVF is thought to be caused by progressive steno-occlusion of a dural venous sinus and be a dynamic disease. The fistulous connection between meningeal arteries and venous sinus or cortical veins may develop as the result of the elevation of the venous sinus pressure. This pathological process is presumed to progress via the opening up of preexisting micro-shunt or de novo formation of fistula from neoangiogenesis [166, 179, 186, 187]. As a result, the venous sinus and the venous tributaries related to the affected sinus are exposed to arterial pressure. With an elevation of the pressure within the venous sinus, the normal venous outflow is affected. Therefore, the normal antegrade venous outflow is converted to the retrograde flow through cortical veins that cause venous hypertension. However, DAVF is not a static disease and can be changed dynamically over time; additional recruitment of additional feeders from external carotid arteries (ECA), recanalization of thrombosed sinus and spontaneous resolution of the fistula due to thrombosis may occur.

Cavernous sinus DAVF (CSDAVF), which is a unique subtype of DAVF, means the abnormal fistulas between internal carotid artery (ICA) and/or ECA and cavernous sinus (CS) and is also called cavernous carotid fistula (CCF) (Fig.14.8). CSDAVF is divided into direct type and indirect type. Direct CSDAVFs that are defined as a high-flow direct shunt between the ICA and CS are usually developed at the cavernous segment of ICA due to skull base fracture, rupture of an aneurysm at the cavernous segment ICA, and iatrogenic causes. Indirect CSDAVFs that may develop spontaneously are usually low-flow shunt between meningeal branches of ICA and/or ECA and CS. Several medical comorbidities, such as postmenopausal status, pregnancy, diabetes mellitus, connective tissue diseases, and hypertension may affect the formation of indirect CSDAVFs [179].

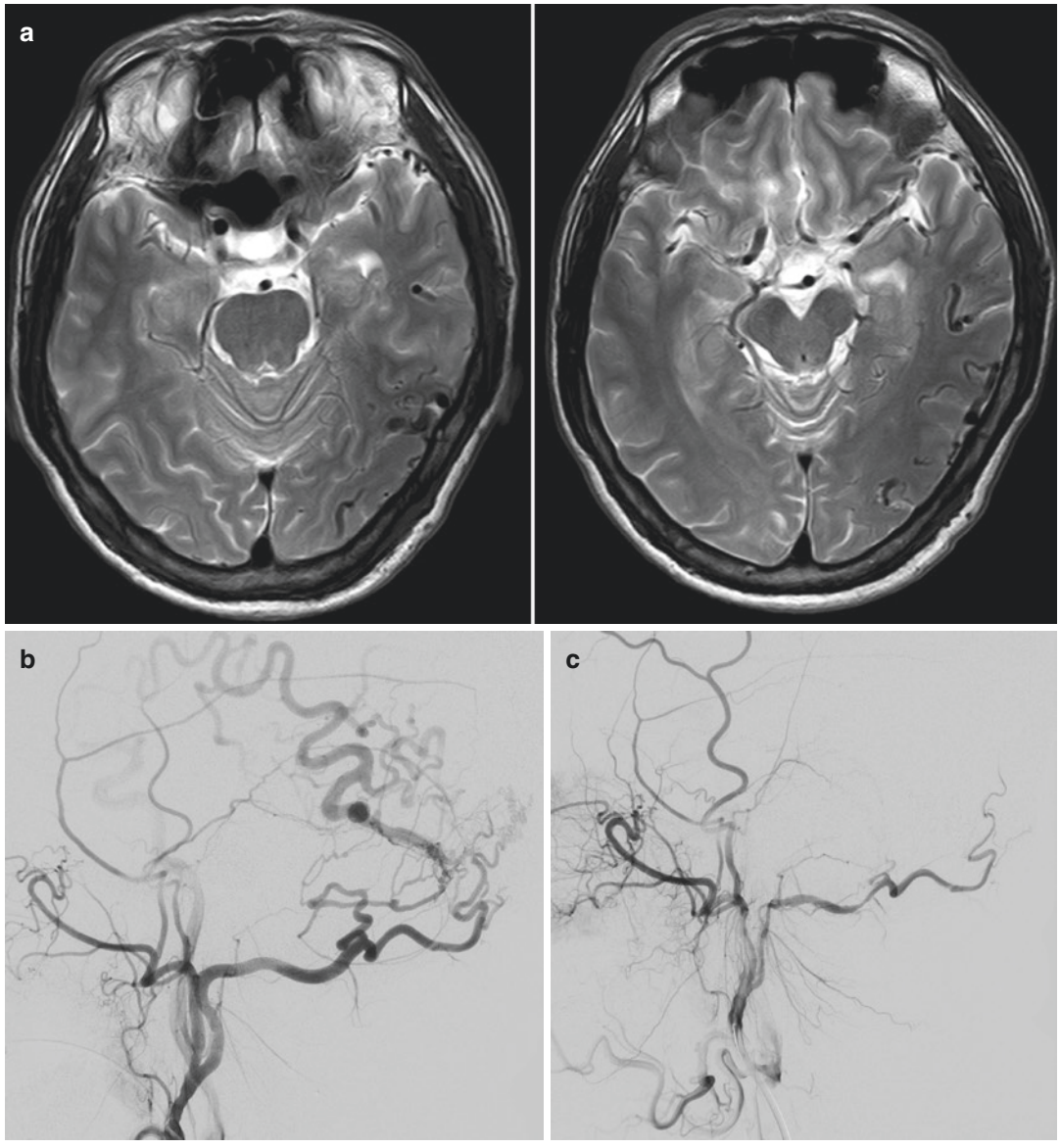
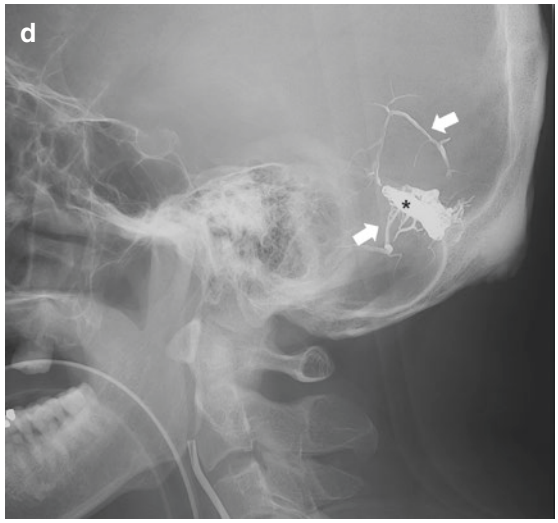


Fig. 14.7 A 43-year-old woman presented with a seizure. (**a**) T2-weighted magnetic resonance images show the flow voids from large arterialized draining veins. (**b**) Digital subtraction angiography (DSA) shows the dural arteriovenous fistula (DAVF) at the left transverse sinus. Main feeding arteries are the stylomastoid branch and transmastoid branch of occipital artery and the middle meningeal artery. DSA also shows that the DAVF has retrograde cortical venous reflux without antegrade flow and trapped segment of left transverse sinus with reflux into the arterialized and enlarged subarachnoid veins (Borden type III 2). (**c**, **d**) The DAVF was obliterated with transarterial embolization using Onyx and transvenous embolization using coils. White arrow, Onyx cast; Asterisk, Coils



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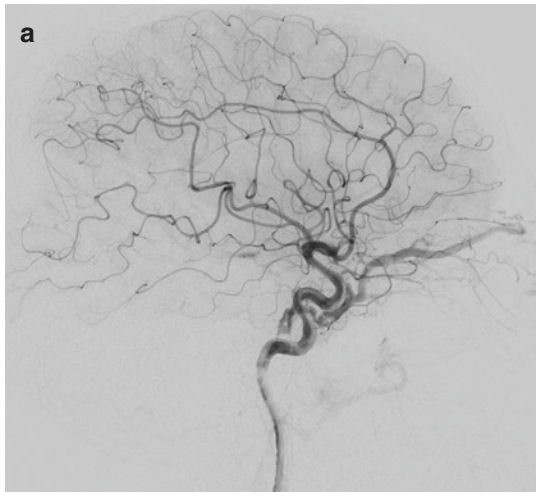


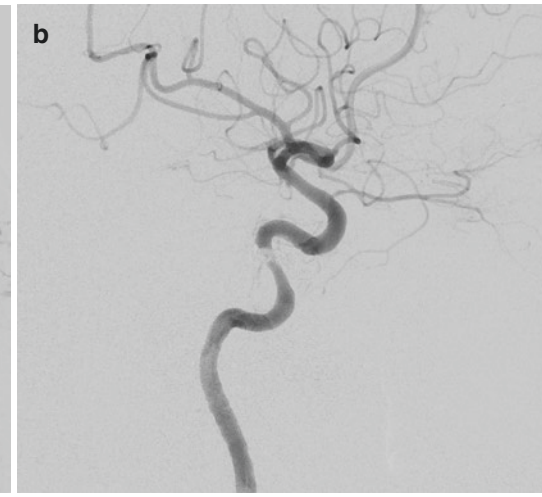
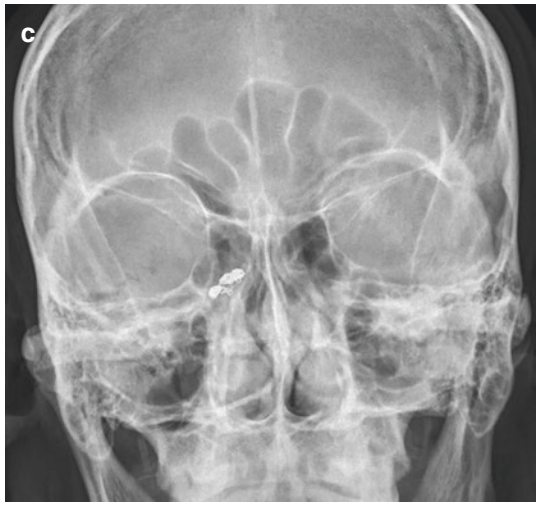


Fig. 14.8 A 53-year-old man presented with right eyeball pain, proptosis, chemosis, and limitation of right extraocular muscle movement. (**a**) Digital subtraction angiography shows a cavernous sinus dural arteriovenous fistula and the fistula between meningeal branches of internal carotid artery and cavernous sinus. In addition, there is a retrograde blood flow into the superior ophthalmic vein that causes the presenting symptoms. (**b**, **c**) The fistula was obliterated with transvenous embolization using coils



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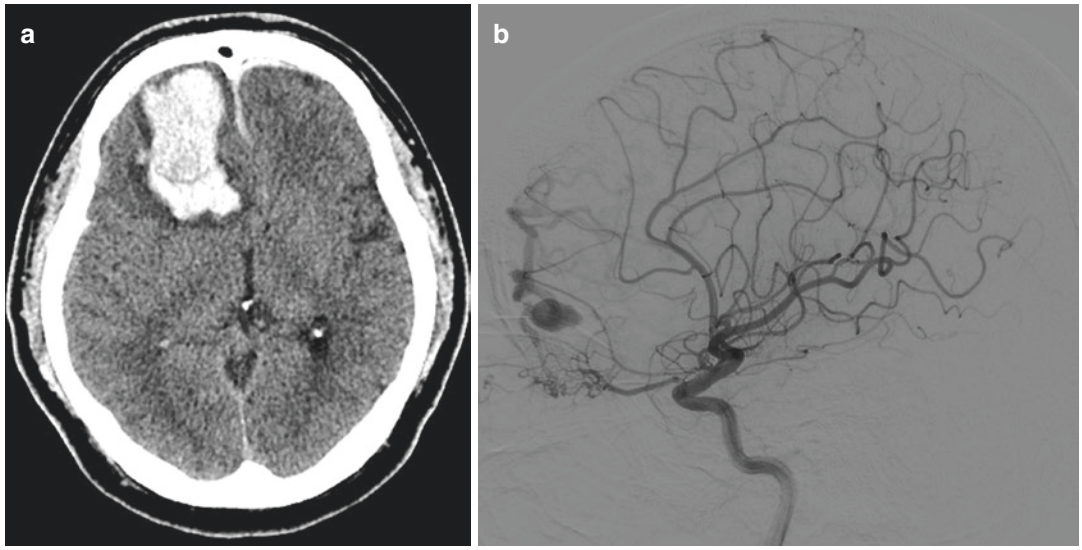
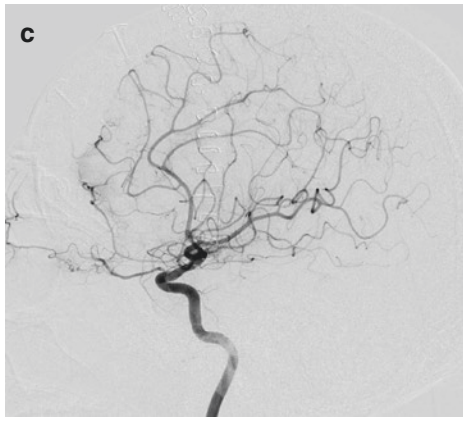


Fig. 14.9 A 48-year-old man presented with consciousness degradation. (**a**) Computed tomography shows a large amount intracerebral hemorrhage at right frontal lobe and subdural hemorrhage around falx. (**b**) Digital subtraction angiography shows a dural arteriovenous fistula (DAVF) at anterior cranial fossa. The arterial feeders are ethmoidal branches of the right ophthalmic artery and direct cortical venous reflux with venous ectasia (Borden type III 3 and Cognard type IV). (**c**) The DAVF at anterior cranial fossa was treated safely and effectively using microsurgery



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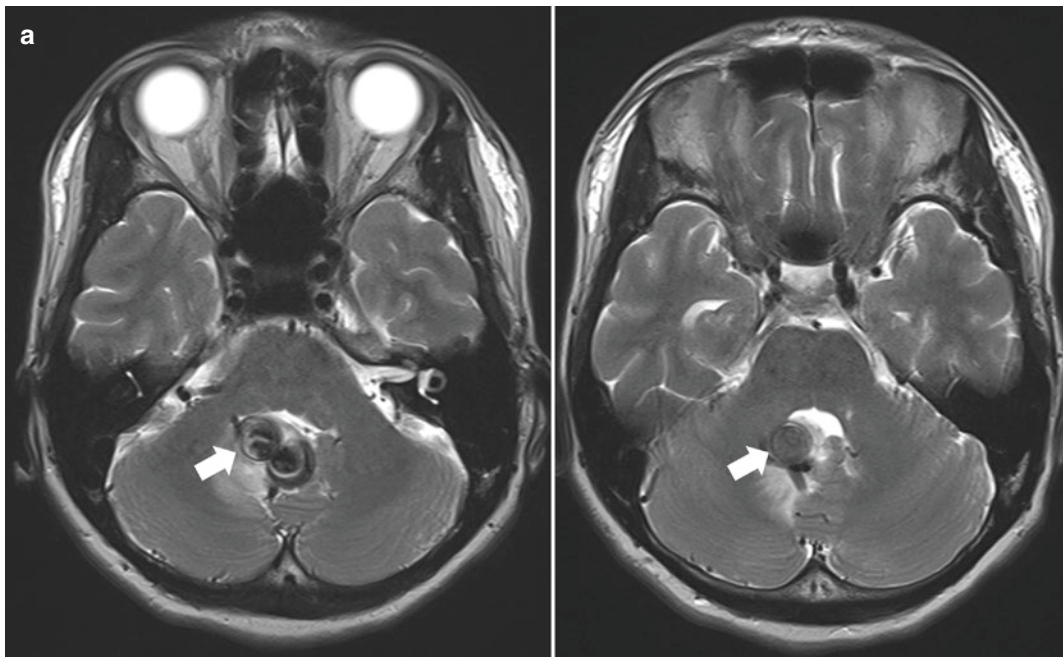

Fig. 14.10 A 41-year-old woman presented with a severe headache and ataxic gait. (**a**) T2-weighted magnetic resonance images show the vasogenic edema at right cerebellar peduncle and hemisphere and venous ectasia. (**b**) Digital subtraction angiography (DSA) shows a dural arteriovenous fistula (DAVF) at the foramen magnum. The arterial feeders are a stylomastoid branch of the right occipital artery, neuromeningeal trunk of right ascending pharyngeal artery and meningeal branch of the right vertebral artery. DSA also show retrograde venous reflux into the cortical and perimedullary vein, venous ectasia and venous aneurysm. (Borden classification III 3) (**c**) Endovascular treatment failed to obliterate the DAVF. Therefore, microsurgery was performed to obliterate the fistula. (**d**) The fistula was completely obliterated after microsurgery. White arrow, venous aneurysm; White circle, fistula point; Asterisk. Posterior inferior cerebellar artery

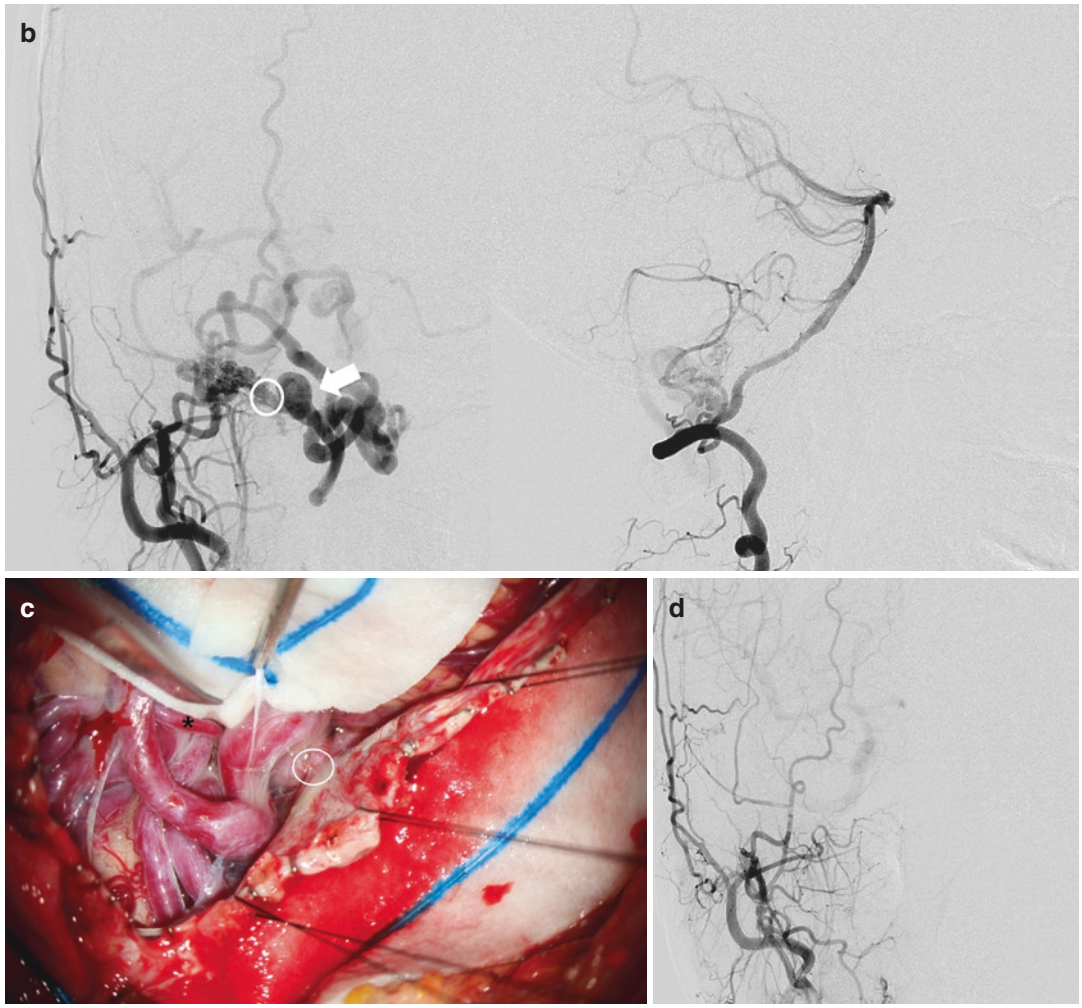

Fig. 14.10 (continued)

14.4.2 Imaging and Classification

When patients show symptoms related to intracranial lesions or test for health screening, CT or MRI is usually taken first. CT alone cannot confirm the presence of DAVFs but can detect intracranial hemorrhage and vasogenic edema caused by venous hypertension. MRI can detect not only intracranial hemorrhage and vasogenic edema, but also the flow voids from large arterialized draining veins, venous ectasia, dilated leptomeningeal and medullary vessels, parenchymal enhancement and venous sinus occlusion or thrombosis (Figs. 14.7a and 14.10a) [179]. Digital subtraction angiography (DSA) remains the gold standard for the diagnosis of DAVFs. The aim of DSA is not only to diagnose DAVFs but also to identify the arterial feeders, the site of the fistula, the presence of venous ectasia, and the pattern of venous drainage. DSAs for ECAs, ICAs, and VAs should be acquired because one DAVF can have various arterial feeders. The acquisition of DSA images should begin at the early arterial phase and proceed to the late venous phase. Superselective angiography of all potential arterial feeders is also very helpful to understand the anatomic structure of DAVFs and to establish a treatment plan.

DAVFs except CSDAVFs are usually classified based on their venous drainage characteris-

tics that determine the natural history and treatment recommendations. Borden classification (Table 14.3) and Cognard classification (Table 14.4) are most commonly used for classification of DAVFs [188, 189]. CSDAVFs that are also called CCFs are usually classified based on their shunt flow (high-flow and low-flow fistula) and their angiographic characteristics. Barrow classification is most widely used for classification of CSDAVFs [190]. Barrow et al. classified CSDAVF into four types: Type A fistulas are direct high-flow shunt between the ICA and the CS; Type B, C, and D fistulas are indirect, low-flow dural shunts. Type B is a fistula between meningeal branches from the ICA and the CS (Fig. 14.8), Type C is a fistula between meningeal branches of the ECA and the CS and Type D is a fistula between meningeal branches of both ICA and CEA and the CS [190].

Table 14.3 Borden classification

Type I	Drainage into meningeal veins, spinal epidural veins or into a dural venous sinus
	Normal anterograde flow in both the draining veins and other veins draining into the system
	Equivalent to Cognard type I and IIa, with a favorable natural history
Type II	Drainage into meningeal veins, spinal epidural veins or into a dural venous sinus
	Retrograde flow into the normal subarachnoid veins
	Equivalent to Cognard type IIb and IIa + b
Type III	Direct drainage into subarachnoid veins or into an isolated segment of the venous sinus (which results from a thrombosis on either side of the dural sinus segment)
	Equivalent to Cognard type III, IV and V

The content of table is from Borden JA, Wu JK, Shucart WA. A proposed classification for spinal and cranial dural arteriovenous fistulous malformations and implications for treatment. Journal of neurosurgery. 1995;82(2):166–79 [188]

Table 14.4 Cognard classification

Type I	Confined to sinus
	Antegrade flow
	No cortical venous drainage/reflux
Type II	IIa
	Confined to sinus
	Retrograde flow (reflux) into sinus
	No cortical venous drainage/reflux
	IIb
	Drains into sinus with reflux into cortical veins
	Antegrade flow
	IIa + b
	Drains into sinus with reflux into cortical veins
	Retrograde flow
Type III	Drains directly into cortical veins (not into sinus) drainage (40% hemorrhage)
Type IV	Drains directly into cortical veins (not into sinus) drainage with venous ectasia (65% hemorrhage)
Type V	Spinal perimedullary venous drainage, associated with progressive myelopathy

The content of table is from Cognard C, Gobin YP, Pierot L, Bailly A-L, Houdart E, Casasco A, et al. Cerebral dural arteriovenous fistulas: clinical and angiographic correlation with a revised classification of venous drainage. Radiology. 1995;194 (3):671–80 [189]

14.4.3 Clinical Manifestations

DAVFs in some patients are often diagnosed without any symptoms, but symptoms, when present, raged from mild symptoms such as tinnitus to fatal intracranial hemorrhage. The symptoms depend on the location of the fistula and venous drainage pattern. DAVFs that drain into the transverse sinus or sigmoid sinus often accompany pulsatile tinnitus. In addition, headache and cranial bruit are also common symptoms. Patients with these symptoms can undergo conservative management according to the venous drainage pattern, and DAVFs may occlude spontaneously.

However, patients with DAVFs also present with intracranial hemorrhages such as ICH, SAH, and/or SDH (Fig. 14.9a) and non-hemorrhagic neurologic deficits including seizures, focal cortical dysfunction, cranial nerve dysfunction, dementia, Parkinsonism, cerebellar dysfunction (Fig. 14.10a), myelopathy, quadriparesis, dysphasia, aphasia, and symptoms related to increased intracranial pressure. Intracranial hemorrhages are caused by the rupture of a fragile arterialized vein or hemorrhage transformation of cerebral venous congestion [179]. Non-hemorrhagic neurologic deficits are usually caused by focal or global cortical venous congestion and these symptoms usually develop more gradually over several days to weeks [179, 188].

In cases of DAVFs that cause these aggressive symptoms, neurosurgical treatments may be required to prevent further neurological deterioration.

The patients with CSDAVFs often present with the classical clinical symptoms such as eyeball pain, proptosis, chemosis, bruit, and limitation of extraocular muscle movement. These symptoms are related to ischemic dysfunction of cranial nerve, mechanical compression of the cranial nerves, and eyeball component due to retrograde blood flow into the superior ophthalmic vein and venous engorgement of the orbital contents. Epistaxis, even fatal epistaxis is not uncommon with Type A, direct high-flow fistula [191]. Intracranial hemorrhage can develop with any type of CSDAVF associated with retrograde cortical venous drainage.

14.4.4 Natural History

Previous studies reported that the natural history of DAVFs depends on the venous drainage pattern. DAVFs without retrograde cortical venous reflux including Borden type I and Cognard type I and IIa usually have a benign natural history and rarely cause intracranial hemorrhage and non-hemorrhagic neurologic deficits. The annual rate of newly developed neurological deterioration related to intracranial hemorrhage and/or non-hemorrhagic neurologic deficits ranges from 0% to 0.6% and the annual mortality rate is 0% in the cases of DAVFs without retrograde cortical venous reflux during conservative management or after only partially palliative endovascular therapy [192–194]. These types of DAVFs may improve spontaneously. A previous study reported that 81% of patients with DAVFs without retrograde cortical venous reflex experienced symptom improvement or complete occlusion [166]. However, DAVFs without retrograde cortical venous reflux can be converted to DAVFs with cortical venous reflux over time [189, 192, 193]. This phenomenon may be caused by the progression of stenosis of venous outlets, increased arterial flow, recruitment of arterial feeder, or extension of the fistulous connection [179]. Shah et al. reported that the annual rate of conversion from DAVFs without retrograde cortical venous reflux to DVAFs with cortical venous reflux after only partial palliative endovascular treatment was 0.8% [193].

DAVFs with cortical venous reflux including Borden type II and III, and Cognard type IIb, III, IV, and V have an unfavorable prognosis and can develop intracranial hemorrhage or non-hemorrhagic neurologic deficit if they are not treated. van Dijk et al. reported their long-term follow-up results of the patients with Borden type II and III dAVFs who did not undergo treatment [195]; excluding events at presentation, the annual risk of intracranial hemorrhage was 8.1% and the annual risk of the non-hemorrhagic neurologic deficit was 6.9%. In addition, they reported an annual mortality rate of 10.4%. Cognard et al. also reported intracranial hemorrhage in 40% of patients with Cognard type III DAVFs and in 65% of patients with Cognard type IV DAVFs [189]. If the patients with Borden type II and III were initially present with intracranial hemorrhage and non-hemorrhagic neurologic deficit, there may be a high probability that these symptoms will occur again.

The annual risk of the new non-hemorrhagic neurologic deficit and annual risk of intracranial hemorrhage were 0.07 and 0.03% in Borden type II and III DAVFs without no previous hemorrhage and were 0 and 0.02% in Borden type II and III DAVFs with asymptomatic or minimal symptomatic but no previous hemorrhage [194]. However, the annual risk of non-hemorrhagic neurologic deficit annual risk of intracranial hemorrhage was 20 and 10% in Borden type II and III DAVFs that initially presented with the non-hemorrhagic neurologic deficit [194]. In addition, the annual rebleeding rate was 46% in Borden type II and III DAVFs with previous intracranial hemorrhage [194]. Another study also reported that natural history of DAVFs with retrograde cortical venous reflux that initially presents with intracranial hemorrhage or non-hemorrhagic neurologic deficit is poor; annual risk of intracranial hemorrhage and non-hemorrhagic neurologic deficit range from 7.4% to 19.0% and the annual mortality rate is 3.8% [196].

DAVFs with venous ectasia (Cognard type IV) are well known to cause more intracranial hemorrhages than DAVFs without venous ectasia. Bulters et al. reported that there was a significant difference in annual risk of intracranial hemorrhage between DAVFs with venous ectasia and without venous ectasia; 19.0 and 1.4% [185]. Gross et al. also reported that the annual bleeding rate of Borden type III without venous ectasia was 10%, but the annual bleeding rate of Borden type III with venous ectasia was 21%.

CSDAVFs also show various natural histories. In some cases, the symptoms and signs, especially ocular symptoms, resolve within several days to several weeks after symptom develops. 20%–50% of CSDAVFs close spontaneously even if the patients had significant congestive orbital signs [197]. However, intracranial hemorrhage can also occur with both direct and indirect CSDAVFs associated with retrograde cortical venous reflux. Especially, direct CSDAVFs that initially presented with intracranial hemorrhage usually have a poor prognosis with a high risk of short-term rebleeding if not treated.

14.4.5 Treatment

DAVFs without retrograde cortical venous reflux can be managed conservatively because the natural history of these DAVFs is usually benign and these DAVF may be occluded spontaneously. However, these DAVFs should be carefully and periodically monitored with neurologic and radiologic examinations because DAVFs without retrograde cortical venous reflux may be converted to DAVFs with cortical venous reflux over time. Advanced DAVFs with retrograde cortical venous reflux should be considered for neurosurgical treatment to prevent intracranial hemorrhage and non-hemorrhagic neurologic deficit.

With the development of endovascular treatment techniques, devices, and materials, endovascular treatments are usually considered as the first-line treatment method of DAVFs for curative purposes. Endovascular treatment is divided into two categories: transarterial embolization and transvenous embolization (Figs. 14.7 and 14.8). The transarterial approach is a technique of embolization of arterial feeders and fistula using liquid embolic agents (NBCA or ONYX) via microcatheterization of arterial feeders. The transvenous approach is a technique of embolization of the fistula, cortical venous drainage and sinus itself using liquid embolic materials and/or detachable coils. This approach is particularly effective in the treatment of CSDAVF [179].

Microsurgery with craniotomy is often necessary when lesions are very difficult to be obliterated successfully or safely using endovascular treatments. DAVFs of anterior cranial fossa can be treated safely and effectively using microsurgery [166, 179]. In cases of DAVFs located in anterior cranial fossa, the primary arterial feeders are ethmoidal branches of the ophthalmic artery (Fig. 14.9). During endovascular treatments, arterial and/or venous access of DAVFs located anterior cranial fossa is very difficult and these techniques may result in unintentional injury or occlusion of the ophthalmic artery and central retinal artery that cause visual loss. For DAVFs that located superior sagittal sinus, microsurgical disconnection of the fistula is useful in the cases of difficulties with endovascular access to the fistula and/or cases of impossibility to safely sacrifice of the sinus. Microsurgery with craniotomy may be also considered for other sites of DAVFs in cases of high-risk of complications associated with the endovascular procedures, incomplete treatment or failure to access during endovascular treatment (Fig. 14.10).

Radiosurgery is also a viable alternative for treatment of DAVFs. However, the usefulness and effectiveness of radiosurgery for DAVFs remain controversial, because there is a lack of large case-control studies to support the routine used of radiosurgery for DAVFs. In addition, it is estimated that it would take 1–3 years for symptom resolution and obliteration of the fistula after radiosurgery [166, 179]. Therefore, it is not recommended to treat DAVFs using radiosurgery as the first-line treatment, especially for DAVFs with retrograde cortical venous reflux, intracranial hemorrhage, and non-hemorrhagic neurologic deficit.

Radiosurgery can be used as an adjuvant treatment method for complex DAVFs that preclude endovascular or microsurgical treatment.

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Part VI

Brain Hemodynamics

Brain Hemodynamics

15

Nathan Gaines and David S. Liebeskind

Abstract

Revision of the fundamental pathophysiology of cerebral ischemia may seem unwarranted, yet advances in stroke imaging and therapeutics over the last 30 years have revolutionized our understanding of basic tenets in the field. Brain hemodynamics remains a poorly understood area of basic pathophysiology with tremendous implications for the clinical management of cerebrovascular disease. Early descriptions by Astrup et al. in the 1980s of thresholds for cerebral ischemia and the ischemic penumbra (Astrup et al., Stroke 12(6):723–725, 1981) in stroke remain the predominant framework for acute stroke pathophysiology. This idealized model captures the basic principles of ischemia well: there are thresholds of cerebral blood flow (CBF) through which cells progress stepwise from dysfunctional but viable to irreversibly damaged and, ischemic stroke typically has a core region of irreversibly infarcted tissue with a surrounding region of salvageable tissue known as the penumbra. In the intervening decades, however, advances in neuroimaging and clinical management of stroke have forced reconsideration of the greater complexities of CBF and cerebral ischemia. While this earlier model presents a fairly static situation, in practice, clinicians encounter a dynamic process, with numerous variables affecting the clinical outcome, perhaps most notably, the option for therapeutic revascularization that was developed after the model was published. The major ongoing challenge for acute stroke management is that current therapies, i.e., intravenous tissue plasminogen activator (tPA) and endovascular thrombectomy, risk not only futility if administered too late, but may cause additional harm through reperfusion injury and hemorrhagic conversion in a subset of cases. Better understanding of the complex interactions between patient-specific variables affecting CBF is therefore essential for effective and safe precision medicine in stroke.

Rather than emphasizing the more theoretically straightforward models of cerebral hemodynamics and stroke, this chapter will focus on advanced multimodal neuroimaging and emerging understanding of the complexities of CBF pathophysiology such as collaterals, microcirculation, and venous hemodynamics that underlie the wide variance encountered in clinical practice. While there are numerous clinical situations that deserve careful discussion of brain hemodynamics, for clarity this chapter will primarily focus on cerebral blood flow as it relates to ischemic stroke.

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15.1 Hemodynamics of Cerebral Blood Flow

15.1.1 Normal Hemodynamics and Autoregulation

Cerebral hemodynamics remain an unsolved area of investigation; traditional laboratory thresholds for both normal values and for cellular dysfunction and ischemic infarction are complicated by numerous factors encountered in clinical practice. The influence of age, time, blood pressure, medical comorbidities, therapeutic interventions, and other variables on the complex processes of autoregulation, collaterals, microcirculation, venous outflow, and cellular dysfunction versus cell death remains a work in progress. Genuine understanding of cerebral hemodynamics will require an integrated model for these complex interactions; at present, no such model exists.

Cerebral blood flow (CBF) is defined as the cerebral perfusion pressure (CPP) divided by the cerebrovascular resistance (CVR):

$$\mathrm{CBF} = \mathrm{CPP} / \mathrm{CVR}$$

CPP is the difference between mean arterial pressure (MAP) and intracranial pressure (ICP):

$$\mathrm{CPP} = \mathrm{MAP} - \mathrm{ICP}.$$

Apart from circumstances with elevated ICP or extremes of MAP, CBF is determined by CVR, which is a product of vessel radius, vessel length, and blood viscosity. Since the cerebral vasculature lacks the precapillary sphincters that primarily regulate vascular resistance in the peripheral vasculature, the dominant mechanism for regulating CBF is through changing the intraluminal diameter of the arteries and arterioles [1].

The major physiologic drivers of change in CVR are carbon dioxide, oxygen [2, 3], as well as myogenic, neurogenic, and endothelial mechanisms (e.g., nitrous oxide) [4]. Changes in carbon dioxide are more potent than those of oxygen. CBF does not change significantly until pO_2 falls to about 30–50 mmHg [5], while voluntary hyperventilation to drive down pCO_2 produces vasoconstriction with CBF reductions of 30–35% and inhaling CO_2 results in vasodilation and increased CBF by up to 75% [2, 3].

Under normal circumstances, autoregulation is highly effective in maintaining stable CBF over a wide range of CPP; at least 70–150 mm Hg [6]. The autoregulatory curve can shift based on chronic illness, acute disease states, and acute CNS insults, among other factors. For example, chronic hypertension shifts the entire curve to the right such that higher CPP is tolerated before CBF increases but CBF can begin to fall at typically normotensive MAP levels that would be tolerated in non-hypertensive individuals [7]. The shape of the curve can also be changed in certain disease states with shrinking of the normal autoregulatory zone (e.g., subarachnoid hemorrhage, bacterial meningitis, critically elevated intracranial pressure). In extreme circumstances of complete autoregulatory failure the curve may even behave in a linear fashion such that changes in CPP and CBF are matched (Fig. 15.1).

Early investigations produced the common wisdom that autoregulation is regionally impaired following stroke; however, the findings of subsequent studies are more nuanced. Two forms of cerebral autoregulation are recognized: dynamic and static. Dynamic autoregulation refers to rapid changes in blood pressure over seconds. Static autoregulation involves the response to more prolonged, steady-state changes in blood pressure. In stroke, dynamic autoregulation is impaired throughout the acute and subacute period, with changes affecting ipsilateral and contralateral brain hemispheres and present even in small strokes [4]. The clinical implications of reduced dynamic autoregulation are unclear. However, preservation of static autoregulation has been demonstrated in several small studies by introducing antihypertensive medications to reduce MAP in the acute and subacute period after stroke, with no significant impairment of regional autoregulation being observed [8–10]. One explanation for discrepancies in the data is that earlier studies focused on vasomotor reactivity to agents such as inhaled CO_2 and acetazolamide as a surrogate measure of autoregulation. While vasomotor reactivity is impaired or even absent following

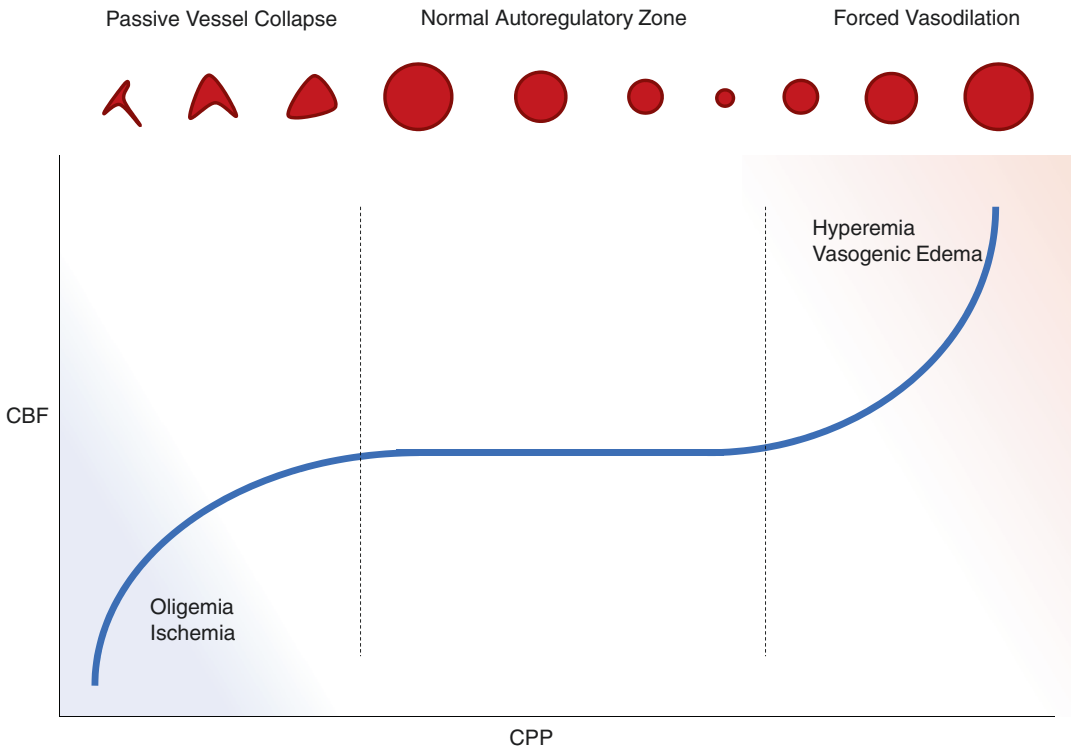

Fig. 15.1 Autoregulatory curve

stroke, subsequent studies have demonstrated that vasomotor reactivity and autoregulation are in fact distinct processes [4, 11]. It appears from these data that steady reductions in MAP affecting static autoregulation may not directly result in impaired CBF in cerebral tissue at risk, at least for some patients, but the findings are not definitive.

It is clinically important to recognize, however, that several circumstances common to stroke patients do impair autoregulation. The rightward shift of the autoregulatory curve in chronically hypertensive patients as well as impaired regional CPP due to persistent arterial occlusion or locally elevated ICP are two common situations in which reduction in MAP could lead to progressive ischemia. It is also important to recognize that the limits of autoregulation are absolute. For example, hypercapnia cannot produce additional vasodilation if it has already been maximized by decreased CPP and vice versa. Consequently, underlying anemia, hypercapnia, or hypoxemia may exhaust the autoregulatory potential [12, 13].

15.1.2 Hemodynamic Failure in Cerebrovascular Disease

There are several models of hemodynamic failure but none capture the complexities of clinical practice. One such model uses a three-stage classification system to describe hemodynamic failure in arterial occlusion or stenosis [14]. Stage 0 applies when CPP remains normal, CBF is preserved, and responses to arteriolar vasodilatory stimuli are intact. Cerebral blood volume (CBV), mean transit time (MTT) are preserved (see the following section for definitions). Stage I, hemodynamic compromise, describes decreased CPP and increased MTT with CBF maintained through compensatory arteriolar vasodilation resulting in increased CBV; oxygen extraction fraction remains normal. Stage II, known as

"misery perfusion" or hemodynamic failure, results when CPP falls below the autoregulatory range and increased oxygen extraction is required to maintain a relatively preserved cerebral metabolism. The utility of this model is limited as there are too many exceptions to the imaging findings it predicts.

More generally, traditional observational studies of hemodynamic failure in stroke describe a fall in CBF that is offset metabolically by a compensatory increase in the oxygen extraction fraction, paired with decreased cerebral oxygen metabolism [15]. Dynamic variations in CBF occur in the initial hours following stroke [16], but eventually some areas of high oxygen extraction will infarct while other survive [17, 18]. A state of "luxury perfusion" may result after reperfusion that describes the subsequent rise in CBF through abnormally dilated vessels due to elevated pCO_2 in the area of infarction, but with persistently low cerebral metabolism and oxygen extraction. In the absence of therapeutic recanalization, the timing of spontaneous reperfusion is variable but peaks around 14 days [19]. In chronic infarction, CBF gradually declines to match the low levels of cerebral metabolism [20].

Typical thresholds for CBF corresponding to neuronal dysfunction (<20 ml/100 g/min) and cell death (<10 ml/100 g/min) have been described in animal models [21], but standard values and clinical outcomes vary in numerous ways, rendering such measures more theoretical than clinically applicable. CBF ischemic thresholds in humans are more variable, ranging from 4.8 to 8.4 ml/100 g/min [22]. Different cell types are more susceptible to ischemic infarction with gray matter being more vulnerable [23, 24] as is seen in typical infarction patterns from global cerebral hypoperfusion, which preferentially affects the basal ganglia, thalami, cerebral cortex, cerebellum, and hippocampi. Cellular dysfunction and cell death are a product of both the degree and duration of ischemia; i.e., brief severe ischemia may cause no lasting damage while persistent moderate CBF impairment can result in infarction. Various factors appear to modify the severity of stroke: observational studies suggest modest improvement in outcomes related to statin use prior to stroke [25], remote ischemic preconditioning [26], body temperature, and even smoking [27] among many other factors, further highlighting the complex variability of tissue outcomes.

Disruption of neurologic function in viable brain tissue due to cerebral hypoperfusion is recognized in the penumbral area of acute ischemic stroke, but clinical dysfunction can also result from chronic sub-ischemic impairment in CBF. One prominent example is the finding that cognitive dysfunction in moyamoya disease correlates with hypoperfusion to frontal and parietal lobes similar to patients with frontal and parietal lesions [28]. In another study, revascularization with burr hole surgery improved cerebral perfusion markers on MRI, leading to complete resolution of cognitive impairments in adults with moyamoya disease [29].

15.1.3 Collateral Circulation

The collateral circulation plays a pivotal role in the pathophysiology of cerebral ischemia, but knowledge of how this complex and highly variable system functions remains limited. During arterial insufficiency, collateral flow pathways can be recruited to compensate for reduced CBF through primary and secondary pathways. The primary pathways are those in the circle of Willis, but it is complete in only a minority of cases. Common variants include absence or hypoplasia of a posterior communicating artery in 30%, anterior cerebral artery in 10%, and anterior communicating artery in 1% (see Fig. 15.2). The major secondary pathways include reversal of flow in the ophthalmic artery, dural and leptomeningeal or pial arteriolar connections to cortical vessels, and anastomoses of distal segments of the major intracranial vessels. These anastomoses are most robust between the anterior cerebral arteries (ACA) and middle cerebral arteries (MCA), less prominent between the MCAs and posterior cerebral arteries (PCA), and sparse between the PCAs and ACAs. Analogous anastomoses exist in the vertebrobasilar and cerebellar circulation [30].

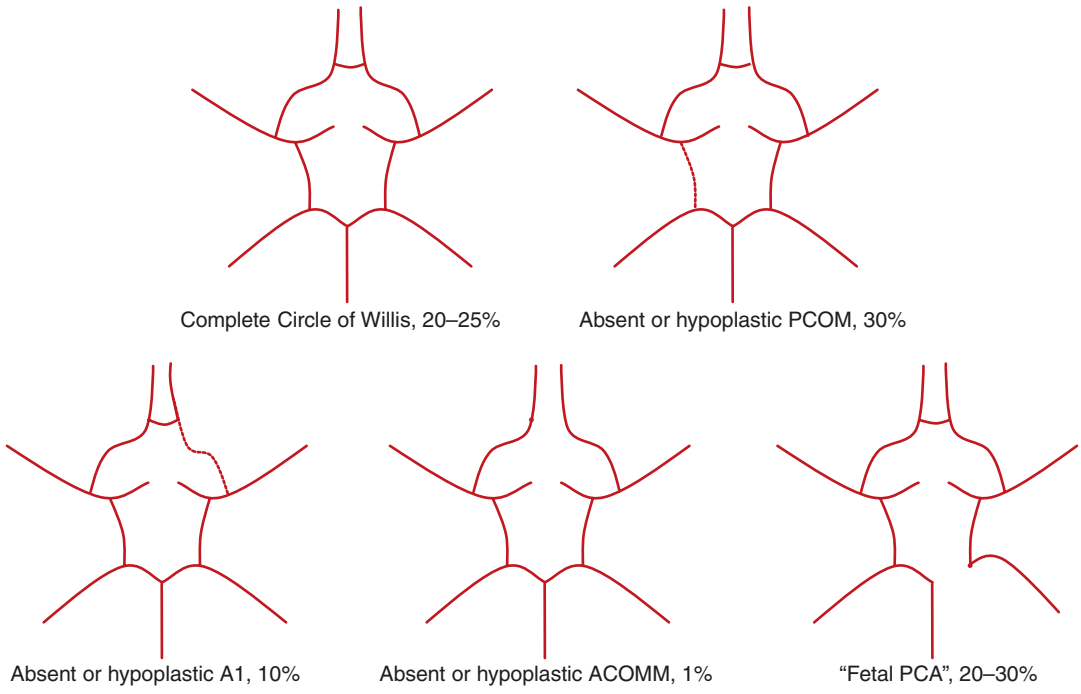

Fig. 15.2 Common circle of Willis variants

While large caliber primary collaterals are able to provide immediate supplementary blood flow, the smaller caliber secondary collateral vasculature may take time to develop sufficient capacity to make a clinically meaningful contribution to tissue at threat of infarction. The exact factors leading to collateral recruitment are poorly understood and likely depend on a combination of hemodynamic, metabolic, and neural mechanisms [30]. Angiogenesis may stimulate collateral growth in the periphery of an ischemic region [31], though these vessels may be recruited for removal of necrotic debris rather than augmenting CBF [32]. Development of collaterals does not guarantee their persistence, and efficacy of collaterals likely depends on patient age, duration of ischemia (i.e., chronic or acute), and comorbid medical illnesses, though exact relationships with these parameters are not yet defined [30] (Figs. 15.3, 15.4, and 15.5).

In acute ischemia, collaterals are important for augmenting CBF, spontaneously clearing thromboemboli, and enhancing access of thrombolytics [33]. The presence of leptomeningeal collaterals

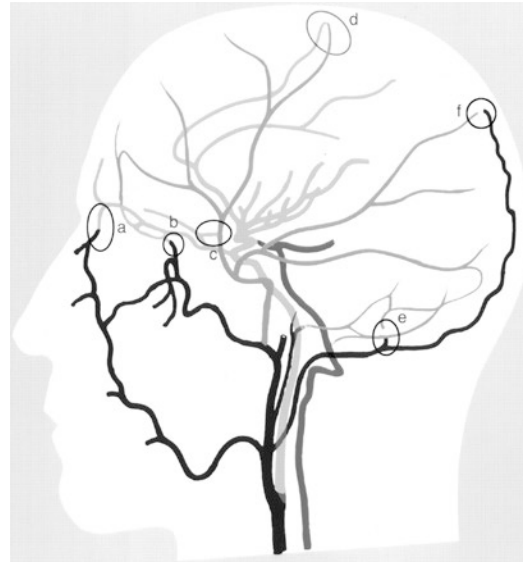

Fig. 15.3 Extracranial arterial collateral circulation. Shown are anastomoses from the facial (a), maxillary (b), and middle meningeal (c) arteries to the ophthalmic artery and dural arteriolar anastomoses from the middle meningeal artery (d) and occipital artery through the mastoid foramen (e) and parietal foramen (f). Stroke 2003;34:2279–2284 [30]

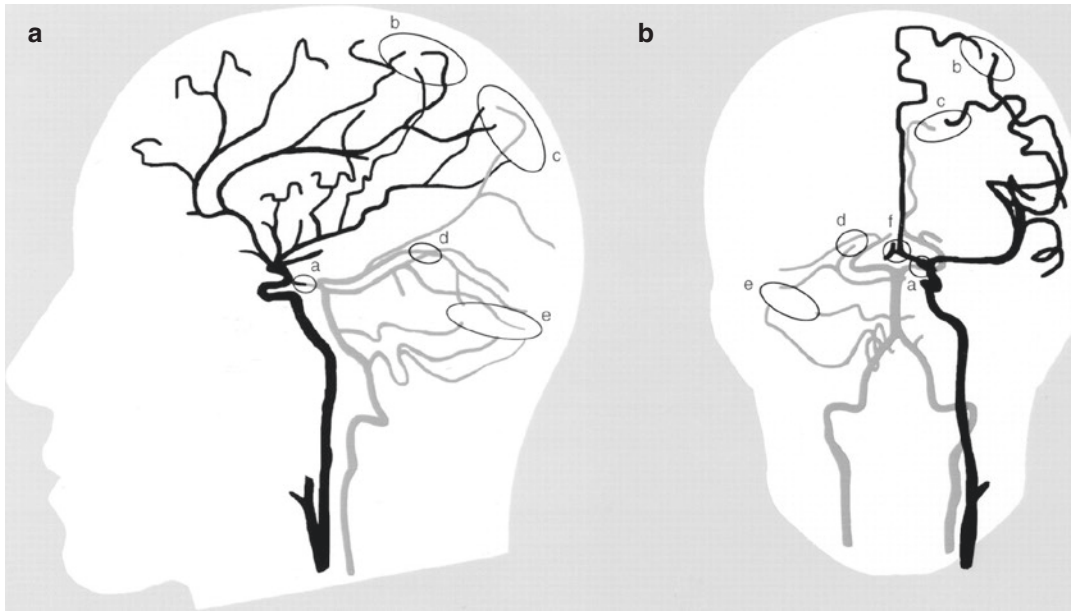

Fig. 15.4 Intracranial arterial collateral circulation in lateral (**A**) and frontal (**B**) views. Shown are posterior communicating artery (a); leptomeningeal anastomoses between anterior and middle cerebral arteries (b) and between posterior and middle cerebral arteries (c); tectal plexus between posterior cerebral and superior cerebellar arteries (d); anastomoses of distal cerebellar arteries (e); and anterior communicating artery (f). Stroke 2003;34:2279–2284 [30]

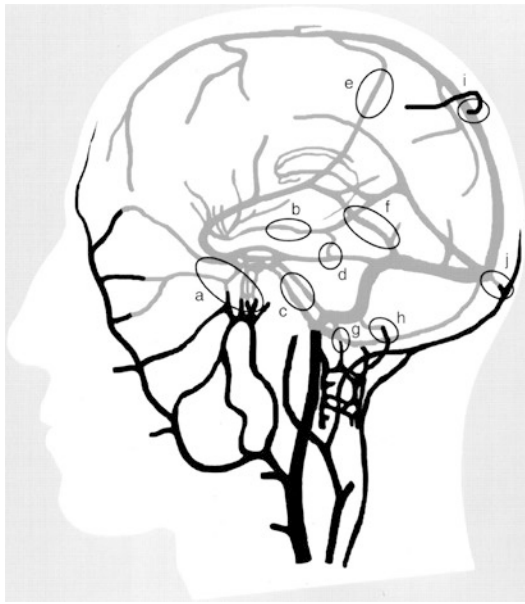

Fig. 15.5 Venous collateral circulation. Shown are pterygoid plexus (a), deep middle cerebral vein (b), inferior petrosal sinus and basilar plexus (c), superior petrosal sinus (d), anastomotic vein of Trolard (e), anastomotic vein of Labbé (f), condyloid emissary vein (g), mastoid emissary vein (h), parietal emissary vein (i), and occipital emissary vein (j). Stroke 2003;34:2279–2284 [30]

predict improved clinical outcomes in MCA occlusion whether or not thrombolytics are given [34]. Therapeutic approaches to enhance collateral formation in acute cerebral ischemia remain unproven at this time, including hypervolemic therapy and permissive or induced hypertension.

Chronic hypoperfusion, such as in progressive carotid artery disease or moyamoya syndrome, has been a major focus of research on collateral development. However, attempts to correlate collateral patterns with hemodynamic and metabolic parameters have so far led to conflicting data. Primary collaterals are assumed to compensate initially with secondary collateral formation gradually occurring as primary collaterals fail; increased secondary collaterals are typically considered a marker of impaired cerebral hemodynamics [30]. The clinical status of patients with disorders causing chronic hypoperfusion (e.g., carotid stenosis) is determined not only by the degree of the primary stenotic lesions, but by the quality of collateral formation. Chronic hypertension has been shown to have an inverse relationship with development of preformed

intracranial collaterals in chronic carotid occlusive disease [35] but the underlying mechanisms for this relationship are unknown. Therapeutic enhancement of collateral circulation is possible in select patients through encephaloduroarteriosynangiosis (EDAS) procedures and has been shown to improve outcomes in pediatric moyamoya disease [36].

15.1.4 Venous Hemodynamics

Despite accounting for about 70% of the cerebral blood volume, the cerebral venous circulation is seldom included in discussions of cerebral hemodynamics, likely because the arterial circulation is both better understood and the site of primary injury in the majority of vascular neurology. Venous pathology likely plays a larger role than previously suspected in cerebrovascular disease. Primary venous pathology is increasingly being recognized thanks to improvements in neuroimaging and higher clinical index of suspicion.

In cases of direct venous dysfunction, such as cerebral venous thromboses, there is even more variation in clinical presentation, baseline anatomy, collateral pathways, and prognosis seen with arterial occlusive disease. Symptoms range from asymptomatic, to mild and nonspecific, to severe neurologic dysfunction and life-threatening disease. As with arterial disease, differentiating patients who warrant aggressive management while avoiding unnecessary therapeutic risk in well compensated patients requires understanding the underlying pathophysiology that informs individualized treatment strategies.

The mechanisms of hemodynamic failure in cerebral venous ischemia differ significantly from arterial disease and are less well understood. Whereas arterial obstruction limits CBF directly, venous congestion underlies impairment of CBF in cerebral vein thrombosis leading to an outflow, rather than inflow problem. Additionally, impairment of CSF drainage via the arachnoid granulations can lead to elevated intracranial pressure. Cerebral dysfunction is the result of a progressive process, starting with increased venous capillary pressure, subsequent impaired drainage and capillary dilation that disrupts the blood–brain barrier and results in extravasation of plasma, and, in severe cases, eventually results in capillary rupture and hemorrhage [37]. Venous infarction results when the combined effect of these changes impairs regional CBF below the regional ischemic threshold. The process may halt and recover spontaneously at any stage, and reversibility of neurologic dysfunction is common due to robust collaterals in the venous system [38, 39]. Cytotoxic and vasogenic edema are seen but in contrast to typical arterial ischemia, structural brain imaging often appears visually worse than the neurologic exam [40]. In a study using time-resolved MRV to evaluate CVT hemodynamics, venous drainage in patients without brain lesions showed sufficient collateral recruitment, while those with brain lesions depended more on drainage through partially occluded outflow tracts [41]. It is also worth noting that venous flow varies by body position: drainage through the internal jugular veins predominate in the supine position (as seen in most angiography studies) but in the upright position the deep venous plexuses such as the vertebral plexus take over [42]—an observation that may have implications both for the interpretation of diagnostic studies and the optimal head positioning of patients with CVT.

15.2 Measurement of Cerebral Blood Flow: Brain SPECT, PET, MRI, and CT

Perfusion imaging represents a major set of tools for precision medicine by helping characterize the state of cerebral blood flow beyond merely identifying occlusions. The various modalities differ significantly and their correct application requires a thorough understanding of the unique advantages and limitations of each technique. There are two major classes of cerebral perfusion imaging techniques: those that use diffusible tracers including positron emission tomography (PET) and single-photon emission computed tomography (SPECT), and those that use nondif-

fusible tracers including CT perfusion (CTP) and magnetic resonance imaging perfusion (MRP).

Each of these attempt to quantify CBF, which, confusingly, also refers to a specific perfusion imaging output parameter in addition to the general concept that is the topic of this chapter. Cerebral blood flow in perfusion imaging is a measure of cerebral blood volume (CBV) over time; CBF = CBV/*t*. Methods for measuring time parameters differ between the imaging modalities, and understanding these differences is necessary for interpreting the results.

15.2.1 SPECT and PET

SPECT and PET are the gold standards for CBF measurement but are too time intensive for acute stroke care and not widely available enough for routine clinical application. These modalities measure absolute CBF by recording regional concentration of radioactive tracers. PET is more reliable for measures of CBF and can also quantify oxygen extraction fraction and cerebral metabolic rate [43]. These modalities are more often used in the research setting and have significantly advanced our understanding of cerebral hemodynamics in stroke and helped identify and define differences between infarcted tissue and dysfunctional tissue at threat, i.e., core and penumbra.

PET and SPECT also uncovered the phenomenon of remote tissue deactivation, or diaschisis, in stroke [43]. This refers to reductions of CBF and cerebral metabolism in brain regions not directly damaged by stroke but functionally related to the involved site. One prominent example is crossed cerebellar diaschisis, seen in lesions involving the corticopontocerebellar pathways; reversibility has been demonstrated following reperfusion therapy [44, 45]. Better understanding of these network phenomena may help explain occasional deviations in the neurologic exam from that expected by "textbook" neuroanatomy in hyperacute neurologic injury.

The ability to measure cerebral metabolism also allows for longitudinal studies showing the patterns of recruitment and compensation in functional networks following stroke [46]. These findings have had implications for stroke rehabilitation, such as the discovery that the unaffected hemisphere may inhibit movement of a paretic limb [47] or language function in patients with aphasia [48], both of which may respond to inhibition of the unaffected hemisphere using transcranial magnetic stimulation [49, 50].

15.2.2 Perfusion MRI and CT

CTP and MRP record the transit of intravascular contrast material through the cerebral vasculature. The primary measures of time used in these modalities are mean transit time (MTT), time to peak (TTP), and time to maximum concentration of the contrast marker (T_{max}). Automated software programs use deconvolution to generate these measures from tissue concentration curves as demonstrated in Fig. 15.6. CBV is derived from the area under the normalized curve. CBF is derived from the CBV and MTT.

MRP can also be performed without the use of an injected contrast material by using the arterial spin labeling technique (ASL). ASL magnetically labels endogenous water molecules in the incoming blood vessels and calculates CBF from changes in labeled blood flowing into the cerebral tissue. Another major advantage of MRI-based perfusion imaging is the ability to pair it with multimodal structural sequences such as diffusion weighted imaging (DWI), susceptibility weighted imaging (e.g., GRE or SWI), and fluid inversion recovery (FLAIR). These structural images aid in understanding the stage of infarction and hemodynamics, in addition to identifying stroke mimics. FLAIR vascular hyperintensities can be another indicator of slow flow through vessels.

15.2.3 Measuring Core and Penumbra

The major clinical application for multimodal neuroimaging in acute stroke management is in identifying clinical-to-imaging mismatch by calculating the amount of irreparably infarcted tis-

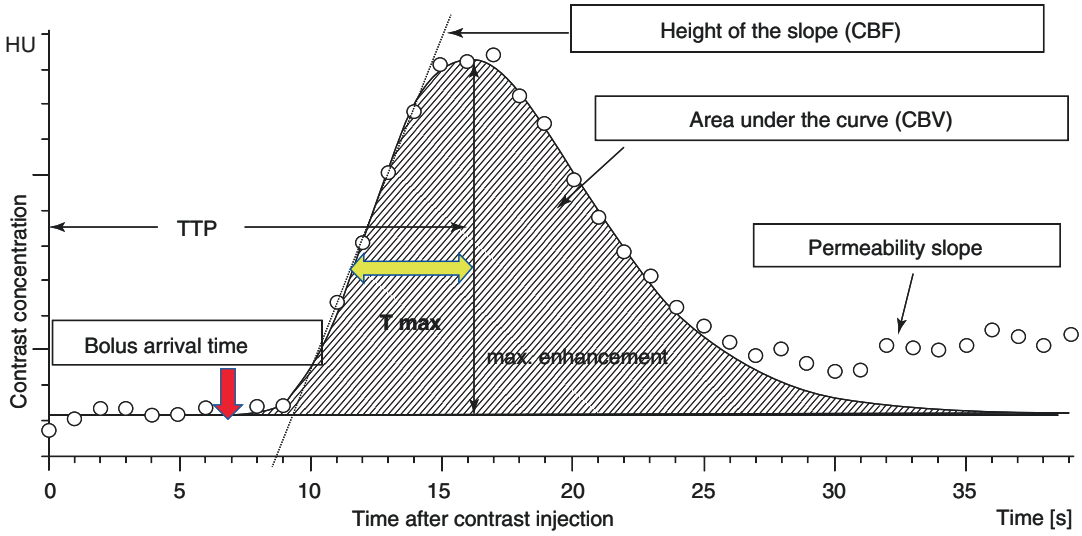

Fig. 15.6 CT perfusion and MRI perfusion tissue concentration curves and CBF parameter derivations. The time to peak (TTP) is measured from the onset of contrast injection to the peak of the deconvolved tissue curve. T_{max} is calculated from the onset to the peak of the deconvolved tissue curve. The cerebral blood flow (CBF) and cerebral blood volume (CBV) are calculated from the height of the curve and the area under the curve, respectively. The presence of "permeability slope" indicates blood–brain barrier disruption. Neuropharmacology. 2018 May;134(B): 249–258 [51]

sue from salvageable tissue at risk and comparing to the clinical exam; i.e., to determine the "core and penumbra." Since brain tissue in the penumbra is dysfunctional, the neurologic exam should reveal impairment in those regions but imaging parameters should suggest viability. Ideally, prompt reperfusion could salvage those tissues and restore neurologic function. Structural imaging, particularly MRI, is extremely valuable, but in the hyperacute setting non-contrast CT may underestimate infarcted tissue since early ischemic changes may take several hours to develop. While DWI is generally considered to reflect the core, it can overestimate infarcted tissue at times due either to heterogeneity of the apparent lesion volume [52] or, rarely through DWI reversal following successful recanalization has been observed [53] (Figs. 15.7 and 15.8).

Commonly accepted thresholds for core infarct and tissue at risk should be treated with skepticism. The relative CBF (rCBF) threshold for the ischemic core is generally recognized as <30% on CTP [55], but a poor signal-to-noise ratio can result in unreliable measure of core infarct volume [56]. Decreased CBF can also be seen in the penumbra so cannot be used in isolation to measure core. Low CBV (<40% of normal) is also used as a measure of core infarct through CBF measures may perform better [53]. Increased time domain parameters (TTP, MTT, T_{max}) can also be used to predict tissue fate, but they are complicated by variability across imaging modalities. Additionally, the route of blood to the ischemic area cannot be determined using these methods, so prolonged time parameters may simply reflect delayed flow through small collaterals to regions with adequate CBF and salvageable tissue.

Among time parameters for penumbra, T_{max} is the most studied, with different cutoffs resulting in higher or lower sensitivity and specificity. Time parameters need to be paired with other measures, such as CBV, for proper interpretation. High T_{max} and low CBV likely represent core infarct while high T_{max} and normal or elevated CBV suggest penumbra. Elevated CBV in the context of prolonged T_{max} is likely a result of autoregulatory vasodilation and increased collateral flow [57]. In chronic occlusive conditions such as intracranial atherosclerotic disease or

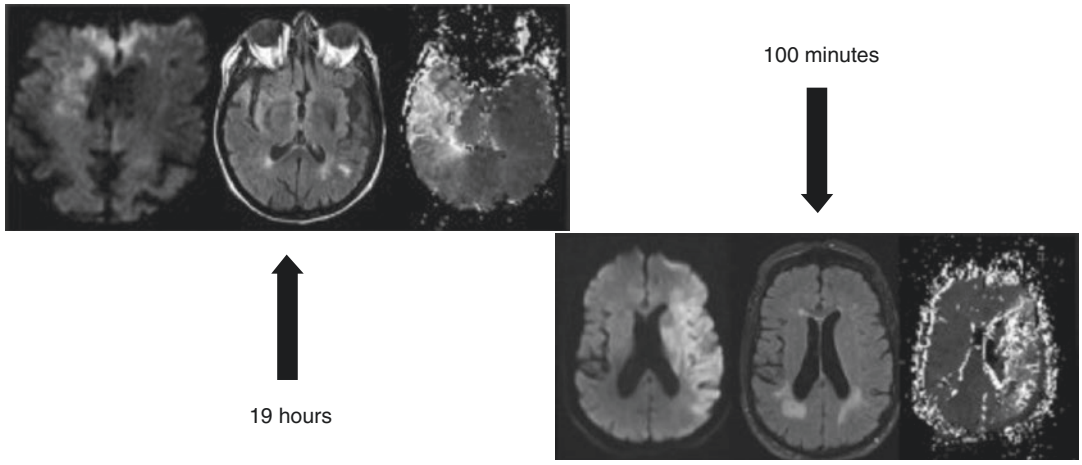

Fig. 15.7 DWI lesion poorly correlates with time of onset. Detailed imaging of acute middle cerebral artery stroke (left to right: diffusion-weighted imaging, fluid-attenuated inversion recovery, time-to-peak perfusion magnetic resonance imaging) shows that one cannot tell time from images. Ann Neurol. 2009 Nov; 66(5):574–590 [54]

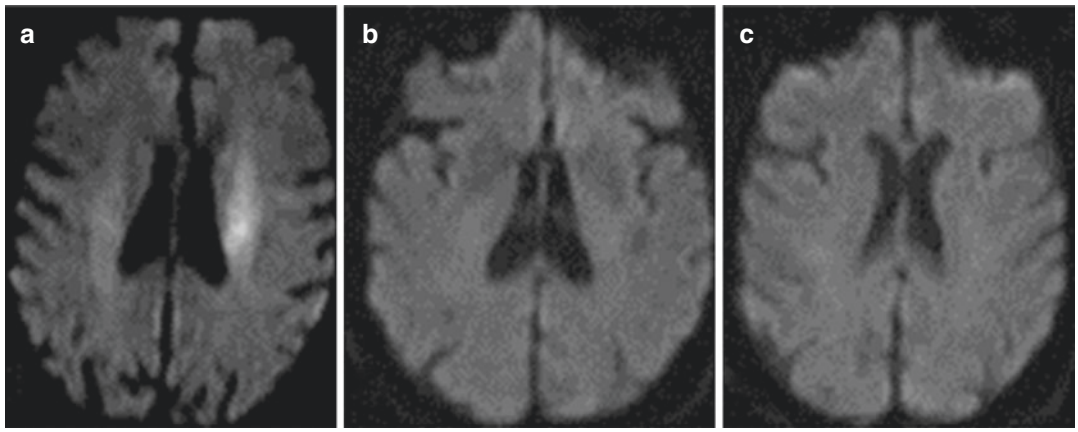

Fig. 15.8 DWI Reversal. Serial diffusion-weighted imaging of acute left middle cerebral artery occlusion shows an initial subcortical abnormality (**a**) and complete reversal (**b**, **c**) 5 days after treatment with intravenous thrombolysis. Ann Neurol. 2009 Nov;66(5):574–590 [54]

moyamoya syndrome, time parameters may be very prolonged without imaging evidence of infarction or with reperfusion outcomes that are better than would be expected based on criteria used in delayed endovascular intervention trials such as DEFUSE [58, 59] (Fig. 15.9).

Beyond the intricacies of the imaging sequences, there are also practical limitations to consider. Inaccurate or misleading perfusion maps can result from numerous scenarios such as poor cardiac output, atrial fibrillation, proximal arterial stenosis, seizures, suboptimal placement of arterial and venous density regions of interest, and other case-specific confounders.

In short, imaging techniques for measuring core and penumbra are not yet sophisticated enough for complete automation and require careful interpretation by clinicians with knowledge of the clinical situation. They also represent a single snapshot in time of a complex and dynamic process that is subject to change, both spontaneously and through medical intervention (Fig. 15.10).

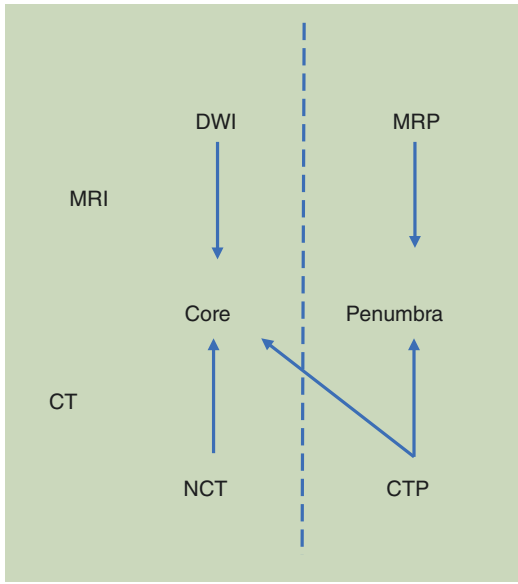

Fig. 15.9 Prediction of core from CT and MRI. MRI predicts core using structural imaging (DWI) and perfusion using MRP. In contrast, CTP uses both structural and perfusion imaging to predict core

15.3 Core and Penumbra

The concept of core and penumbra attempts to model the evolution of acute ischemic stroke and identify individuals who would—or would not—benefit from recanalization therapies. The model is useful for conceptualizing stroke, but in its simplest form relies on a number of assumptions that are rare in clinical practice—for instance, that the lesion is ovoid, homogenous, static, and predictably progressive. The model prompted attempts to develop universally applicable, quantifiable measures and discrete cutoffs for key structural and perfusion imaging variables that have resulted in conflicting results, uncovering the model's shortcomings. The stages of hemodynamic failure introduced previously do not unfold stepwise in clinical practice; the trajectory of hemodynamic compromise is nonlinear and difficult to predict.

IMAGING	CORE	TISSUE AT RISK (PENUMBRA)	ADVANTAGES	DISADVANTAGES
MRI	DWI ADC < 650 FLAIR	FLAIR vascular hyperintensity (slow flow) GRE susceptibility artifact in leptomeningeal vessels	High sensitivity of DWI and good correlation with final infarct volume Clues to time of stroke onset Assessment of stroke mechanism	Occasional overestimation of infarct core with reversibility of initial DWI lesion Rare DWI negative stroke more common in hyperacute phase
CT	ASPECTS	None	Easy to use Widely available	Low inter-rater reliability Radiation +/- contrast
CTA	CT ASPECTS	Collateral status	More direct assessment of LMF Time-resolved multiphase and dynamic CTA has higher interrater agreement	Requires post-processing and whole-brain perfusion CT for dynamic CTA Radiation +/- contrast
CTP & MRP	CT: ASPECTS, Low CBV, rCBF<30% MRI: DWI	Tmax elevated CBV preserved or elevated	Quantitative	Requries contrast Requires post-processing CBF poor indicator of core Limited use in posterior fossa
Nuclear scans: PET, SPECT	CBF below 10 ml/100gr/min	CBF between 10-17 ml/100gr/min OEF elevated CMRO2 preserved or diminished	Gold standard for penumbral imaging Quantitative	Needs nuclear radiotracer subjective measurements Not readily available
DSA	None	Time of maximal opacification Collateral status	Real-time collateral imaging Direct visualization of site of occlusion	Invasive Radiation Contrast dye

Fig. 15.10 Summary of imaging modalities for predicting core and penumbra

When arterial occlusion or clinically significant stenosis occurs, regional CBF transiently decreases. Even in cases of radiographically complete occlusion diminutive flow routes may persist, allowing for thrombolytic access to the clot [54]. The initial fall in CBF is followed rapidly by a compensatory increase in CBV with restoration of CBF, predominantly through the collateral circulation. Collateral circulation may be sufficient to prevent infarction but in many cases of acute stroke the collaterals eventually fail for reasons that are poorly understood. Tissue infarction is a product of both the degree and duration of ischemia, and the magnitude of infarction is modified by patient-level variables, as described above (e.g., age, prior status of cerebral vasculature and tissue, comorbidities, medications, etc.). The "core" is likely better understood as heterogeneous, discontinuous, evolving tissue regions that are most susceptible to ischemia at a given time and fail to recover even if reperfusion occurs. The penumbra regions are similarly heterogeneous and dynamic but are relatively less susceptible to infarction and potentially salvageable, either through intrinsic compensation or therapeutic intervention. A third region of "benign oligemia" with altered CBF but low likelihood for infarction has been proposed. However, it is not strictly oligemic, since CBV may be normal or even elevated, nor is it benign. The third region is best conceptualized as a reflection of the abnormal regional hemodynamics induced by stroke [59].

Tissue changes, venous hemodynamics, and microcirculation also contribute to the evolution of an ischemic stroke. Impaired arterial flow and increased tissue pressure from cytotoxic edema can lead to venous collapse around the area of a stroke [60–62], further exacerbating impairment of blood flow, increasing edema, and potentially raising the risk of hemorrhagic conversion. Increased tissue pressure in the areas of core infarction leads to redirected blood flow to the surrounding tissues with lower tissue pressure, a process known as the cerebral venous steal phenomenon. This process may be a cause of secondary brain injury in stroke and expansion of the ischemic lesion [63]. Poor venous outflow around infarcted tissue correlates with poor arterial collateral flow, demonstrating the important interaction between collaterals, venous congestion, and microcirculation. Whether the driving mechanism is increased tissue pressure and impaired venous outflow, poor collaterals, or, more likely, a combination, is difficult to delineate but the relationship appears clinically significant. In primate models of MCA ischemic stroke, the presence of flow in draining cortical veins was associated with smaller infarct volumes [64]. Increasing venous pressure to avoid collapse in areas at risk for infarction, perhaps by enhancing collaterals, may reduce flow diversion by maintaining patency of outflow tracts, though with the risk of increasing cerebral edema [62] (Fig. 15.11).

Alterations in the capillaries also play a role in stroke evolution [65]. Capillary flow in the brain is heterogeneous but can become more homogenous, leading to greater oxygen extraction efficiency in response to increased oxygen demands. In stroke, dysfunctional or constricted capillaries, if widespread, may lead to greater tissue resistance and persistent ischemia even after arterial reperfusion; one possible cause of the "no reflow" phenomenon after tPA or mechanical thrombectomy. However, decreased flow from higher resistance through these narrowed capillaries may be partially compensated for by increased time for oxygen extraction [66]. Alternately, reactive vasodilation and hyperemia increase abnormal high velocity flow through open capillaries and lead to functional shunting and paradoxical reduction in tissue oxygenation akin to luxury perfusion. It thus appears that capillary dysfunction is of two sorts and can worsen ischemic stroke either by further impairing regional CBF or, paradoxically, by regionally excessive increase of CBF with deleterious reduction in oxygen extraction. Common risk factors for stroke, such as aging, hypertension, diabetes mellitus, Alzheimer's disease, and nicotine use, etc. impair capillary reactivity. Absence of chronic microvascular changes due to these comorbidities in animal models may explain some of the differences between animal models of stroke and clinical

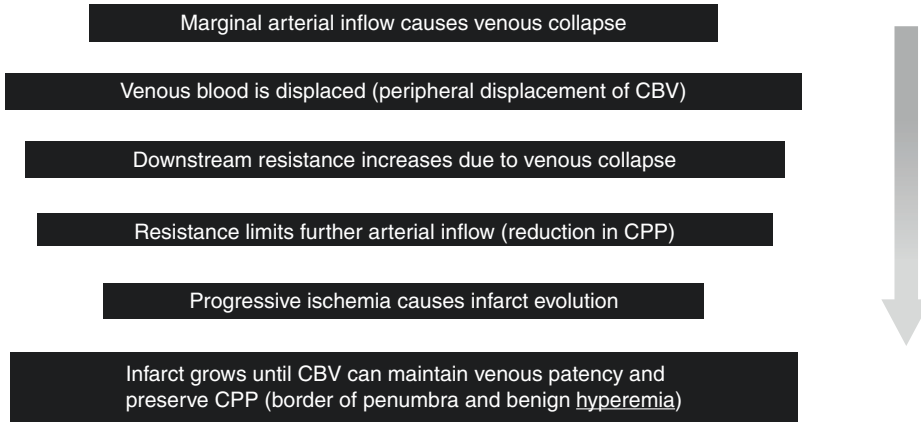

Fig. 15.11 Hypothetical model of infarct progression. Progressive changes in ischemic pathophysiology (arrow from top to bottom), including venous factors that affect cerebral blood volume (CBV) and cerebral perfusion pressure (CPP). Peripheral zones are spared from infarction because of benign hyperemia, characterized by increased CBV. Ann Neurol. 2009 Nov;66(5):574–590 [54]

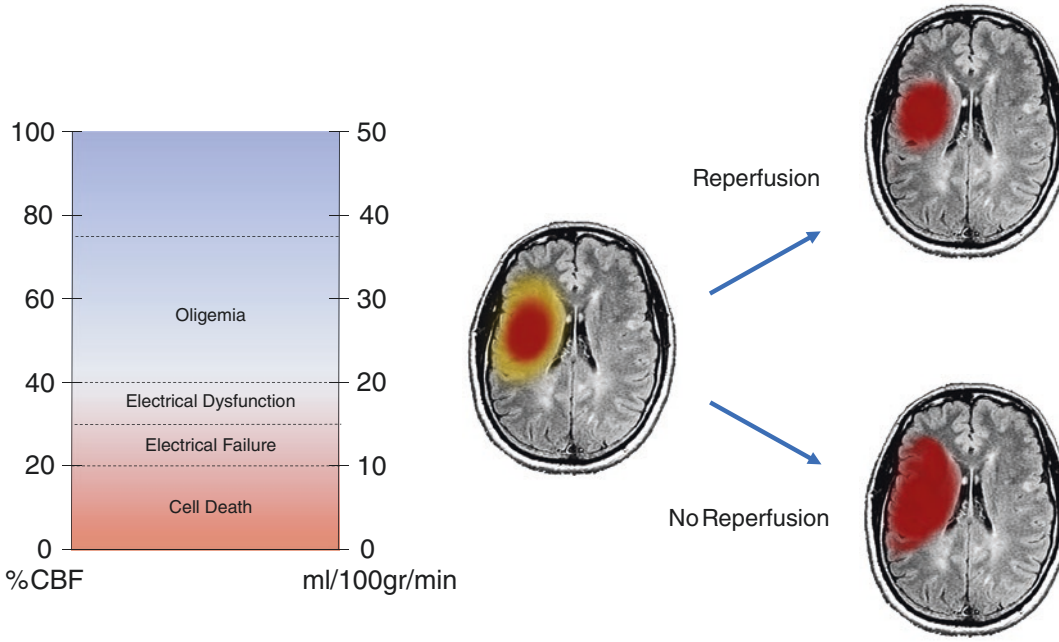

Fig. 15.12 Traditional model of simplified core and penumbra and fixed ischemic thresholds. In this model, the ischemic lesion is assumed to be ovoid, homogenous, static and predictably progressive. Ischemic thresholds are assumed to be fixed. Red shade represents predicted core infarct area. Yellow shade predicts penumbra which behaves reliably by recovering if reperfused or fully infracting without reperfusion

experience; in many cases, stroke in humans may be more accurately described as an acute decompensation of a chronic process [64] (Figs. 15.12 and 15.13).

The dynamic nature of core and penumbra is further illustrated by the subset of patients with fluctuating symptoms. Spontaneous improvement or worsening can result from a variety of

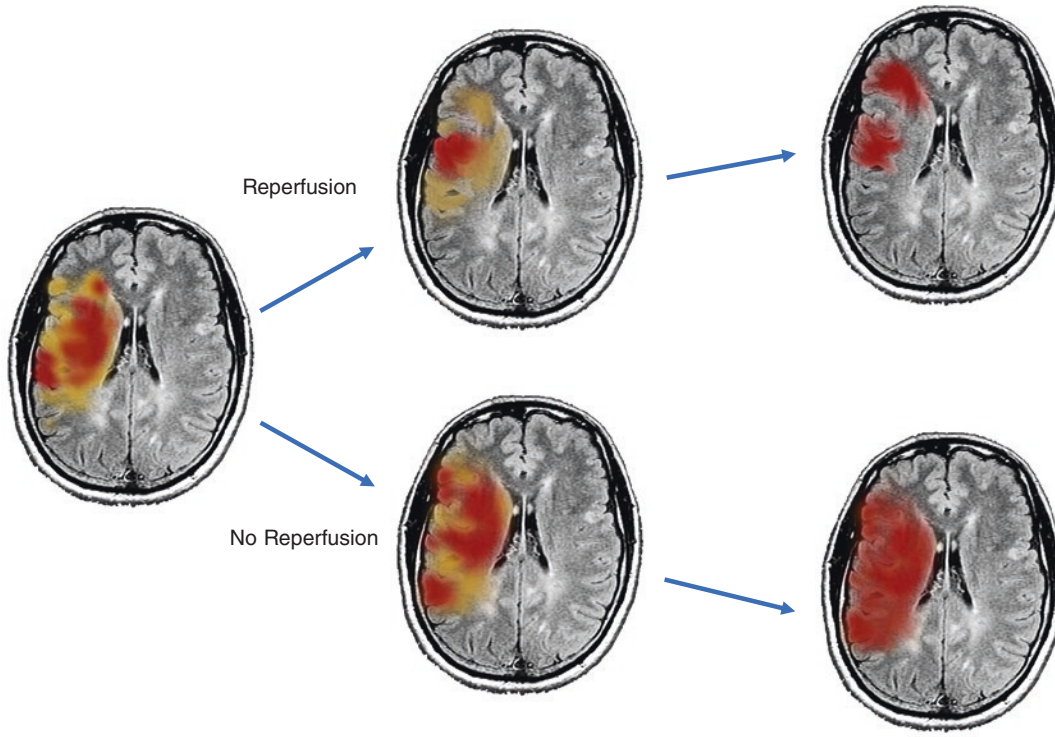

Fig. 15.13 Proposed model of complex core and penumbra. Yellow shade represents predicted penumbra and red shade represents predicted core. Both core and penumbra in this model are discontinuous, heterogenous, and variable. Early predictions of both cores and penumbras can be incorrect and evolve with time. Hazy shading for preliminary and final predicted core areas depict heterogeneous tissue fates within regions of infarction

factors that alter CBF, including spontaneous recanalization, distal embolization or thrombus propagation, reocclusion, and fluctuations in collateral flow. In a subset of patients this can even be affected by upright versus supine head positioning; presumably with patients who have borderline collateral compensation [67].

The mantra "time is brain," like core and penumbra, may apply at the population level, but there is significant variability at the patient level. For one, true time of onset of vessel occlusion should be considered an unknown since in many cases symptoms likely start only when, or if, collaterals fail, rather than at the moment of obstruction. Mechanism of stroke, status of collaterals, premorbid conditions that affect vessel physiology and microcirculation, as well as individual patient factors will influence how quickly or slowly strokes progress. Diffusion lesion size has been shown to correlate poorly with time from stroke onset (see Fig. 15.7) [68]. In a review of patients who underwent thrombectomy, more rapid time to reperfusion increased the odds of a favorable outcome in patients with poor collaterals but was not significantly associated with favorable outcomes in patients with robust collaterals [69]. This suggests that many patients with large vessel occlusion and robust collaterals appear to have a period of relative stability in infarct volume during the initial hours following symptom onset; without recanalization these patients would likely worsen as collateral compensation fails. In contrast, patients with poor collaterals on imaging tend to progress rapidly (Fig. 15.14).

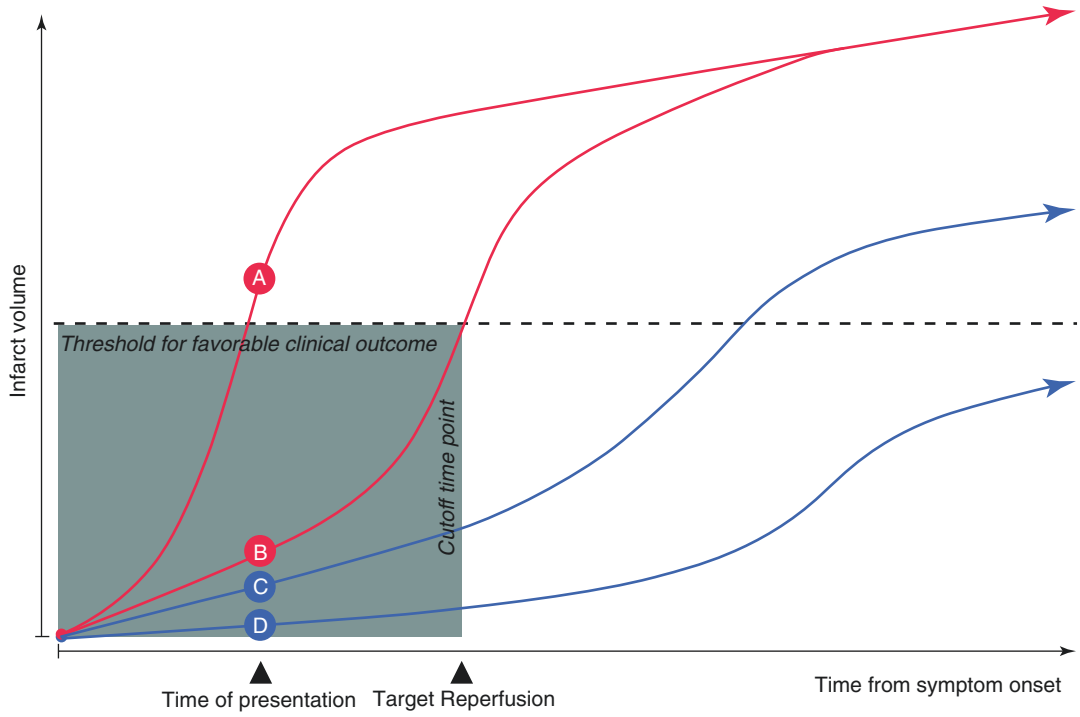

Fig. 15.14 Time is brain but relativity applies. Simplified illustration, which represents the unique effect of time-to-reperfusion on clinical outcome based on proposed collateral scenarios. (A) Universally poor collaterals, which may show large infarcts and severe neurologic deficits at the time of presentation. (B) Rapidly failing collaterals, which may show small-to-medium infarcts and severe neurologic deficits at the time of presentation. (C) Slowly failing collaterals, which may show small infarcts and moderate-to-severe neurologic deficits at the time of presentation. (D) Universally good collaterals, which may show tiny-to-small infarcts and mild-to-moderate neurologic deficits at the time of presentation. In real clinical practice, patients in scenarios B and C can be ideal candidates for endovascular reperfusion. However, the clinical outcome is limited by time-to-reperfusion in scenario B. AJNR 2015;36:495–500 [69]

15.4 Conclusions

Attempts to quantify cerebral blood flow in terms of ischemic thresholds have resulted in overly simplistic models with limited real-world applicability. Unfortunately, core and penumbra cannot yet be reduced to single numerical values. Prior and current attempts to quantify stroke imaging parameters highlight the disconnect between traditional models of ischemia that emphasize arterial occlusion and the more complicated factors that ultimately determine the subsequent perfusion delays and tissue fate. Collateral flow, venous hemodynamics, and microcirculation are major determinants of core and penumbra but are frankly too complicated to be incorporated routinely in acute stroke decision-making algorithms using current imaging modalities.

Spatial and temporal features of stroke have not been properly considered. Current CBF measures provide only a snapshot of a highly dynamic process; they offer only hint at past and future hemodynamic failure or compensation. Structural and perfusion imaging also fail to capture the heterogeneity of both core and penumbra. Definitions of core and penumbra need to take into account whether intervention will be pursued or not since that drastically changes how the lesions will evolve.

Multimodal stroke imaging with structural and CBF measures provides a set of diagnostic tools to offer valuable guidance in acute hemodynamic compromise but major limitations persist. Predicted core and penumbra are far from certain and should not be viewed as a sealed fate. The current automated processes still require real-time expert interpretation. More sophisticated models are needed to move stroke care beyond simplistic models of sequential cascade, rigid thresholds, and linear time course of ischemia in the brain. Until then, delivering optimal precision medicine for acute stroke patients requires clinical acumen, in-depth understanding of the underlying pathophysiology including the complexities of cerebral hemodynamics, and the ability to formulate nuanced interpretations of complex neuroimaging.

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Part VII

Basic Aspect: Cell Death and Neurorepair

Pathophysiology of Neuronal Cell Death After Stroke

16

Toru Yamashita and Koji Abe

Abstract

Stroke is a leading cause of death around the world and results in a drastic reduction in the quality of life. Thus, molecular mechanisms underlying stroke-related neuronal cell death such as necrosis, necroptosis, apoptosis, and autophagy have been extensively investigated in the past 30 years. In the ischemic stroke brain, depletion of ischemic energy leads to increased cytosolic Ca^{2+} through pump failure and cell depolarization, activating phospholipase A2. Phospholipases liberate arachidonate, causing a burst of free radicals in the peri-infarcted lesion. Free radicals lead to apoptotic cell death, and play an important role in the pathological process of ischemic stroke. Concurrently, the free radical scavenger, edaravone, was developed from translational research, mainly using the animal stroke model, and was approved in April of 2001 in Japan for the treatment of acute cerebral infarction, as a neuro-brain protection drug.

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In this chapter, we review the molecular mechanisms underlying neuronal cell death in strokes and the development of edaravone and its application to clinical settings, while incorporating our recent related findings.

16.1 General Principles of Cell Death Mechanisms: Necrosis, Necroptosis, Apoptosis, and Autophagy

Necrosis is the term currently used to describe non-programmed cell death or accidental cell death [1, 2], and is generally considered to be a passive process because it does not require new protein synthesis, with minimal energy requirements. This accidental and passive cell death, necrosis, is morphologically characterized by cell and organelle swelling, as well as membrane rupture, followed by the uncontrolled loss of intracellular contents (Table 16.1, Fig. 16.1). Necrosis is usually induced by noxious stimuli including infectious agents, hypoxia, and extreme environmental conditions, including heat and radiation. After exposure to noxious stimuli, the depletion of energy leads to an increase in cytosolic Ca^{2+} through pump failure and cell depolarization. An acute increase in the intracellular calcium concentration activates a calcium-dependent cysteine protease, calpain, that leads

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Table 16.1 Characteristics of necrosis, necroptosis, and apoptosis

		Necrosis	Necroptosis	Apoptosis
Morphological change	Swelling of organelles	+	+	–
	Cell swelling	+	+	–
	Cell membrane rupture	+	+	–
	Release of cell content	+	+	–
	Membrane blebbing	–	–	+
	Cell shrinkage	–	–	+
	Nuclear fragmentation	–	–	+
	Chromatin condensation	–	–	+
Molecular biological change	Phosphatidylserine (PS) exposure on the cell membrane	–	–	+
	Caspase activation	–	–	+
	RIPK1/RIPK3 activation	–	+	–

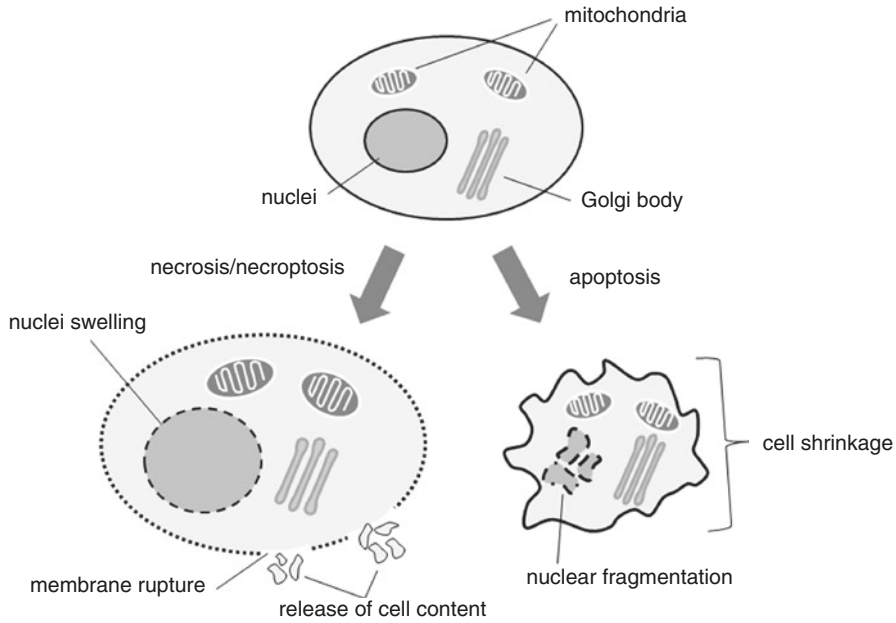

Fig. 16.1 Comparison of morphological changes between necrosis/necroptosis and apoptosis. In necrosis/necroptosis, the cell swells, becomes leaky and the cell membrane is disrupted. Finally, the cell releases its contents into the surrounding tissue resulting in inflammation. On the other hand, apoptotic cells shrink, chromatin condenses and cells are phagocytosed without triggering inflammatory processes

to cleavage of the cytoskeletal protein. Finally, extracellular fluid enters into cells through the ruptured cell membrane, causing cell swelling and cell death [3].

As mentioned above, necrosis has historically been regarded as unregulated cell death that is induced by nonphysiological stress. However, accumulating evidence suggests that several types of programmed necrosis, including necroptosis [2], ferroptosis [4], parthanatos [5], pyroptosis [6], NETosis [7], and transcriptional repression-induced atypical death (TRIAD) [8], can be executed by a regulated mechanism. In TRIAD, general transcriptional repression

induces slowly progressive atypical cell death associated with a shift in the balance between YAPdeltaCs as prosurvival factors and activated p73, which promotes cell death. Our lab and other labs found that TRIAD occurs and takes part in pathological processes in neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and Huntington's disease [8, 9]. As a type of programmed necrosis, necroptosis was originally defined as cell death by necrotic cell death morphology and dependency on the function of receptor-interacting serine/threonine-protein kinase 1 (PIPK1) [2, 10] (Table 16.1). Necroptosis occurs following the activation of PIPK1, in response to the ligation of tumor necrosis factor-receptor (TNF-R). PIPK1 activates PIPK3, which gains the ability to phosphorylate and activates mixed lineage kinase domain-like protein (MLKL), leading to cell death (Table 16.1).

Apoptosis is currently considered as caspase-mediated programmed cell death [11, 12] and is morphologically characterized by plasma membrane blebbing, cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation (Table 16.1, Fig. 16.1). Apoptotic cells also exhibit biochemical changes such as the exposure of phosphatidyl-l-serine on the plasma membrane [13]. These apoptosis-related morphologic features result from the activation of caspases by either death receptor ligation or the release of apoptotic mediators from the mitochondria. In other words, apoptosis involves a complex cascade of reactions that are regulated by specific protease termed caspases. Dying by apoptosis requires energy in the form of ATP. Finally, apoptotic bodies are recognized and removed by phagocytic cells, thus apoptosis basically does not induce inflammation around dying cells.

Autophagy is a self-degradative process in response to various stresses, especially nutrient deficiency. In other words, autophagy is regarded as the process by which a cell consumes itself during periods of starvation. The process of autophagy involves four steps including initiation, nucleation, fusion of the authophagosome and lysosome, and hydrolyzation [14] (Fig. 16.2). Firstly, a double membrane vesicle forms in the cytosol encapsulating whole organelles and bulk cytoplasm, and these vesicles are referred to as autophagosomes. Autophagosomes then fuse with the lysosome, where the contents are degraded to be recycled. The formation of an autophagosome is induced by class 3 phosphoinositide-3-kinase, Atg6 and ubiquitin or ubiquitin-like modifications of the target proteins. Autophagy plays a degradative role during which cells degrade dysfunctional and unnecessary cellular components for the turnover of both damaged organelles and long-lived proteins.

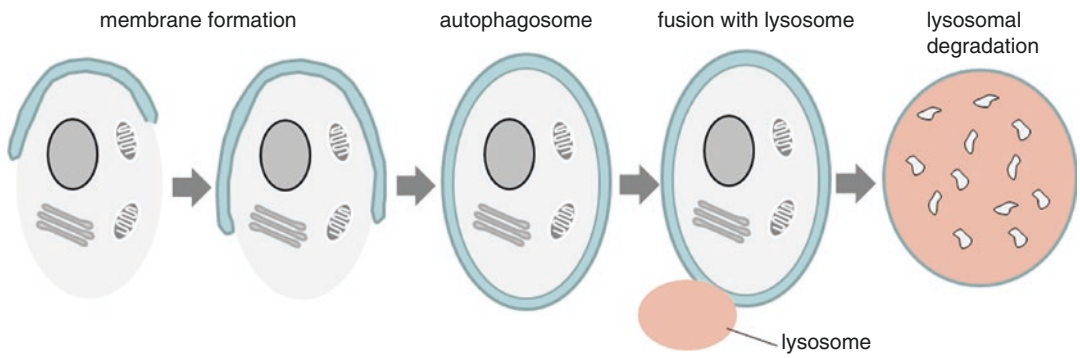

Fig. 16.2 Schematic diagram of autophagy. Autophagy initially begins with the formation of an isolation membrane. Secondly, expansion of the membrane forms an autophagosome. Thirdly, the outer membrane of the autophagosome fuses with a lysosome. Finally, the sequestered material is degraded and recycled

16.2 Mechanism of Cell Death Caused by Ischemic Stroke Versus Hemorrhagic Stroke

In the ischemic stroke brain, depletion of ischemic energy leads to increased cytosolic Ca^{2+} through pump failure and cell depolarization, activating phospholipase A2. Phospholipases liberate free fatty acids, particularly arachidonate, from cell membranes. This freed arachidonate causes a burst of free radicals in the ischemic penumbra, which is a therapeutic target area, and free radicals are drastically increased after reperfusion [15]. The free radicals directly or indirectly lead to apoptotic cell death, and play an important role in the pathological process of ischemic stroke (Fig. 16.3a).

On the other hand, in a hemorrhagic stroke, the intracerebral hematoma is a key component of pathological processes. This parenchymal accumulation of blood causes tissue disruption causing a mass effect such as primary brain injury. With large hematomas, the mass effect may increase intracranial pressure, and decrease cerebral blood flow resulting in peri-hematomal ischemia. However, the extent to which the peri-hematomal ischemia takes place remains controversial [16]. In secondary brain injury of a hemorrhagic stroke, thrombin is the main player. Thrombin is essential for blood coagulation and becomes activated within 1 hour after intracerebral hemorrhage. The activated thrombin breaks down the blood–brain barrier (BBB), leading to brain edema, and directly induces neuronal damage. The lysis of hematoma within the first day after intracerebral hemorrhage causes the release of hemoglobin, which is then converted into neurotoxic components such as heme and iron. Heme and iron are major contributors to secondary brain injury as a result of abundant free radical production (Fig. 16.3b) [17]. Of note, free radicals are a common key player and common therapeutic target both in ischemic and in hemorrhagic strokes.

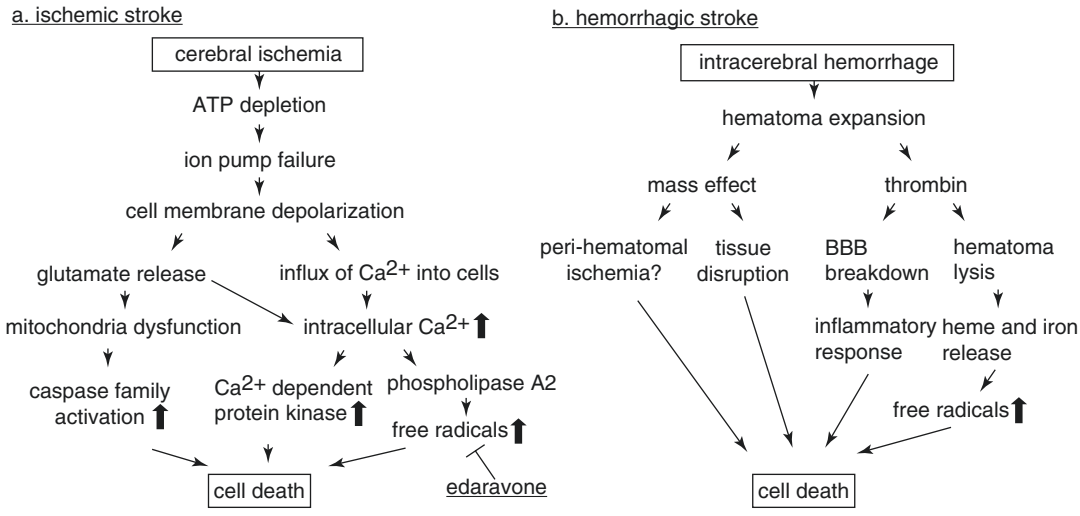

Fig. 16.3 Comparison of pathological mechanism of cell death between ischemic stroke (**a**) and hemorrhagic stroke (**b**). Free radicals are a common key player and common therapeutic target both in ischemic stroke and in hemorrhagic stroke

16.3 Excitotoxic Cell Death

Excitotoxic cell death is triggered by the release of glutamate or related excitatory amino acids under certain conditions, for example, cerebral ischemia. Glutamate is a major excitatory neurotransmitter in the central nervous system, acting through both 1) ligand gated ion channels such as the N-methyl-D-aspartate (NMDA) receptor, the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, and the kainate receptor, and 2) G-protein coupled (metabotropic) receptors. Cerebral ischemia increased the extracellular concentrations of glutamate, which are mainly released from acidemic glial cells [18]. This results in widespread stimulation of both synaptic and extra-synaptic NMDA receptors, causing a massive influx of calcium into cells, and activation of intracellular enzymes, causing cell death (Fig. 16.3a). Therefore, glutamate receptor antagonists have attracted much attention as potential neuroprotective agents, but randomized clinical trials have failed to show any beneficial effect of those drugs in acute ischemic stroke patients [19].

16.4 Apoptosis Induced by Stroke

Neurons in the ischemic core die through necrosis whereas apoptosis is the main contributor to neuronal cell death in peri-infarct lesions called the penumbra. Numerous studies have shown that excessive intracellular calcium increases via the activation of the glutamate receptor, especially the NMDA receptor, and can cause alterations to the mitochondrial structure and calcium-dependent opening of the mitochondrial permeability transition (MPT) pore, allowing the release of soluble proteins such as apoptosis-inducing factor and cytochrome c [20, 21]. Cytochrome c combines with Apaf-1 to promote caspase-9 activation, which in turn activates effector caspase to trigger an ensuing cascade of proteolytic events, leading to cell death [22].

16.5 Free Radicals as a Therapeutic Target

As described above, arachidonate causes a burst of free radicals in the ischemic penumbra, and free radicals are drastically increased after reperfusion [15]. Many researchers have tried to discover a free radical scavenger without side-effects such as narcotizing or suppressing cerebral metabolism [23]. In the early stages of investigations, edaravone was found to have a promising effect by quenching the hydroxyl radical (OH) and by inhibiting both OH-dependent and OH-independent lipid peroxidation. To evaluate the effect of edaravone on brain edema in the post-stroke brain, we administered edaravone in the transient middle cerebral artery occlusion (tMCAO) rat model. In this model, water content, which reflects disruption of the BBB, significantly increased after 3 and 6 hours of ischemia, and a further increase was found after 3 hours of ischemia following 3 hours of reperfusion. Therefore, we concluded that edaravone markedly suppressed ischemic and post-ischemic brain swelling [24] (Fig. 16.4). In addition, post-ischemic treatment with edaravone significantly decreased the size of cerebral infarcts and improved neurological deficits 1 day after tMCAO [25]. Another research group reported that edaravone markedly suppressed the accumulation of a product of nucleic acid oxidation, 8-oxo-2′-deoxyguanosine (8-oxodG), and sequential inflammatory responses at the peri-infarct lesion in the mouse stroke model [26]. In addition, we recently reported that edaravone showed strong neuroprotection after cerebral ischemia, which was confirmed by in vivo and ex vivo optical imaging for the apoptosis marker, annexin V, while also reducing cerebral infarct (Fig. 16.5) [27]. In a clinical trial, edaravone attenuated the resulting disability in humans 90 days after acute ischemic stroke without serious adverse effects [28] and it has been used clinically in Japan as a neuroprotective agent for acute stroke patients since 2001.

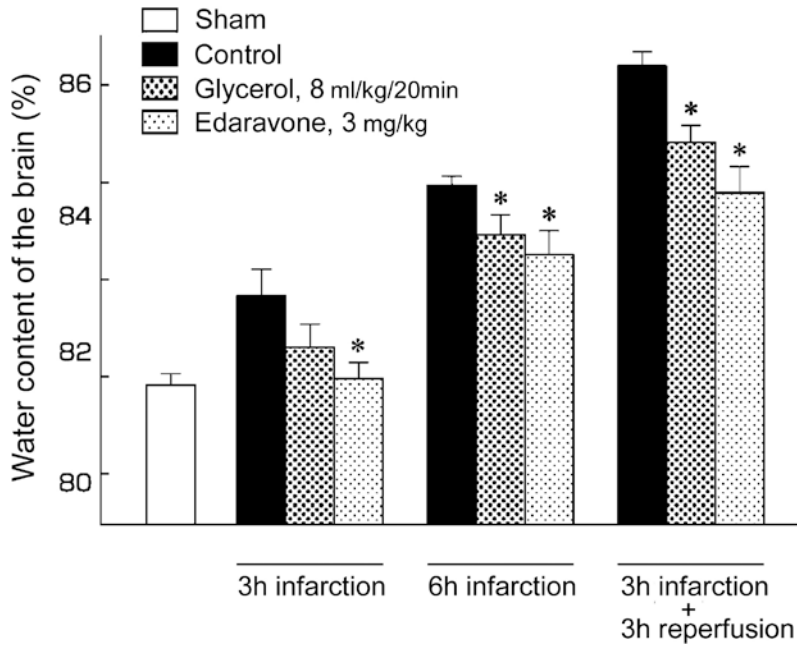

Fig. 16.4 Effects on brain edema in the rat MCA occlusion or occlusion–recirculation model (revised from Abe et al. 1988). Rat MCA occlusion or recirculation was obtained by insertion or removal of a nylon thread, respectively. MCA: middle cerebral artery. $*p<0.05$ vs. control (by Dunn's multiple comparison test) [24]

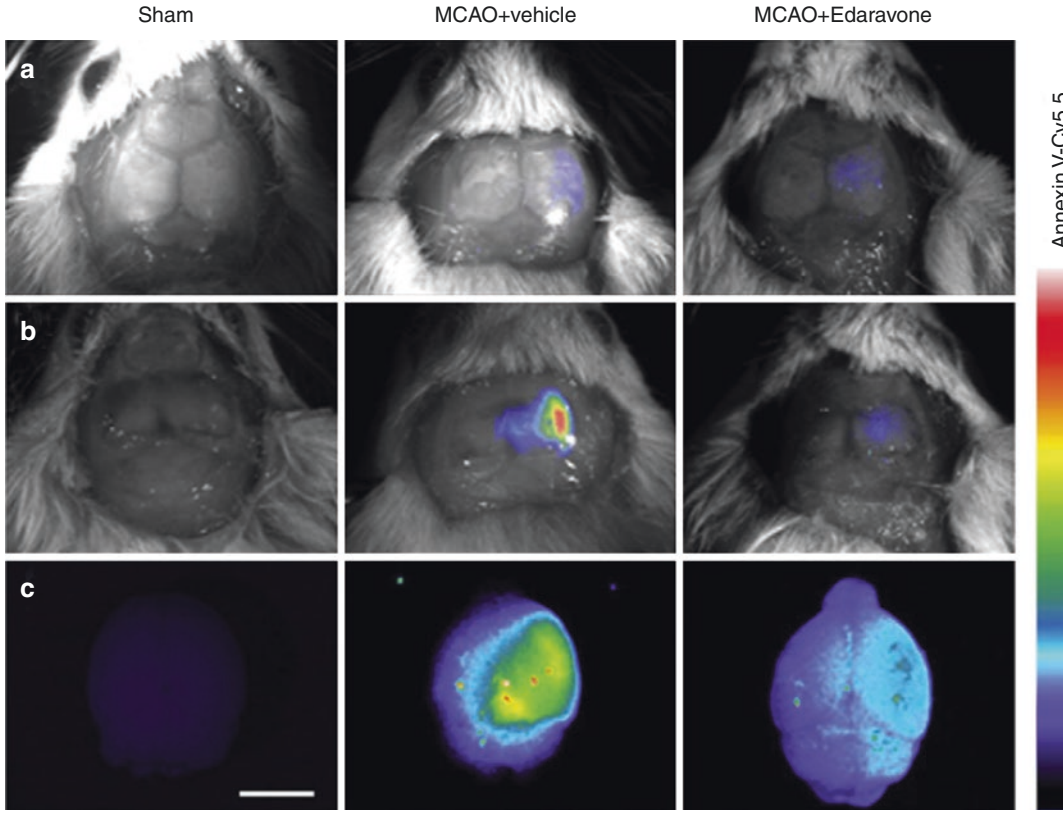

Fig. 16.5 In vivo imaging of Annexin V-Cy5.5 (**a**) with removal of head skin, (**b**) removal of the scull bone, and (**c**) ex vivo imaging of the brain (revised from Liu et al. 2011). This optical imaging method successfully demonstrated that edaravone treatment suppressed apoptosis in post-stroke mice brains 48 hours after tMCAO [27]

16.6 Conclusion

In this chapter, we briefly highlighted the pathophysiological mechanism of neuronal cell death in the ischemic and hemorrhagic strokes. From the results of basic research, free radicals are regarded as a key regulator of disease progression in not only the ischemic stroke but also in the hemorrhagic stroke. Therefore, in the near future, the free radical scavenger edaravone may be widely applied to the therapy of various kinds of diseases.

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17 Emerging Mechanism of Cell Death Caused by Stroke: A Role of Neurovascular Unit

Ryo Ohtomo and Ken Arai

Abstract

Stroke is one of the leading causes of death and even the survivors suffer from severe aftereffects. Although effective treatments have long been awaited, early therapeutic approaches focused on neuronal death had been insufficient due to the heterogeneous etiology of stroke. From the fact that brain function along with dysfunction arise from integrated interactions between a network of cellular components, conceptual structural unit, so-called "neurovascular unit" was proposed as a new paradigm for the investigation of stroke. Since then, variety of cell–cell and cell–extracellular matrix interactions have been discovered, which lead us to profound understanding of the pathophysiology of stroke. Besides neuronal damage, pathophysiology of stroke also consists of glial activation and transformation, vascular and blood–brain barrier alteration, and inflammatory reactions. Recent investigation shows that mediators of these reactions are not only detrimental but also could turn out to be beneficial for neurovascular repair in the chronic phase of the disease. In this chapter, we briefly overview the mechanisms of cell–cell interactions within the neurovascular unit under the normal conditions, and then discuss the crosstalk between different cell types during the acute and chronic phases of stroke.

17.1 Introduction

Stroke is one of the leading causes of death around the world. Even if stroke patients survive, they often suffer from devastating neurological deficits needing sufficient rehabilitation and medication for secondary prevention. For this reason, increasing number of stroke patients has been one of the main reasons of swelling medical expenses in developed countries for decades.

Until the late 1990s, various experiments had been carried out for the breakthrough of this situation, and their results brought us profound understanding of the pathophysiology of stroke. However, neuroprotective drugs that were developed based on the findings of these

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studies came up empty-handed in human trials. Under such circumstance, first meeting of Stroke Progress Review Group was convened by National Institute of Neurological Disorders and Stroke in 2001. In this workshop, based on the complex pathophysiology of stroke which involves multiple cell–cell interactions, failure of clinical trials was attributed to the narrowness of therapeutic target limited to neuronal death. Scientists emphasized that purely focusing on neurons is not sufficient, since brain function along with dysfunction arise from integrated interactions between a network of cellular components such as neurons, glia, and cerebral endothelium. This conceptual structural unit as a new paradigm for investigation of the central nervous system (CNS) was proposed as "neurovascular unit (NVU)" [1] (Fig. 17.1).

17.2 The Neurovascular Unit (NVU) and Its Components

The NVU is responsible for the regulation of blood flow through the vascular system. Large arteries on the surface of the brain separate into smaller arteries and arterioles known as pial arteries. Pial arteries are innervated by nerves from autonomic and sensory ganglia sending signals for constriction and dilation. These signals are considered to mediate global changes in cerebral blood flow (CBF).

In the parenchyma, the arterioles become closely associated with astrocytes, which play an important role in regulating diameter of the arterioles. As vessels continue to run deeper into the brain, they lose their smooth muscle cell and pia mater coverage, and gain pericytes between the vascular endothelial cells and astrocyte end-feet.

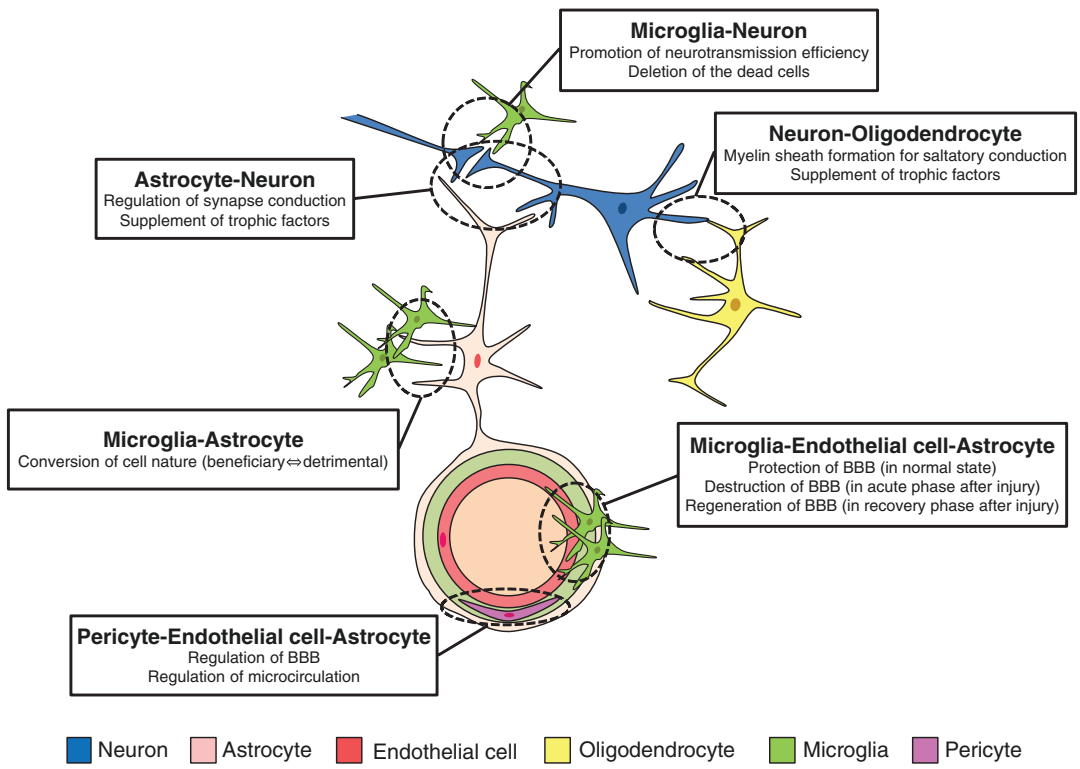

Fig. 17.1 Schematic of the neurovascular unit: Neuron, astrocyte, cerebral endothelium, oligodendrocyte, microglia, and pericyte compose the neurovascular unit. Cell–cell interactions between the NVU components are critical to maintain the brain function

Astrocytic end-feet occupy a larger surface area of the vasculature than neural processes at this depth, consistent with the major role of astrocytes in the regulation of vessel diameter. Along the length of the vasculature, neuronal and astrocyte processes contact with other NVU components, which regulate the function of the whole unit. In this section, we briefly describe individual components of the NVU and their roles inside the NVU.

17.2.1 Neurons

Neuronal processes physically contact with the vasculature, and mediate a local increase in CBF in response to the increased metabolic demand of the neurons. This mechanism is known as functional hyperemia. Vasoconstriction and dilation are thought to be conducted by the contractility of smooth muscle cells of the arterioles, and capillary pericytes responding to vasoactive substances released by neurons and astrocytes during synaptic activity such as metabolites of cyclooxygenase-2 [2], cytochrome P450 epoxygenases [3], acetylcholine [4], corticotropin-releasing factor [5], neuropeptide Y [6] nitric oxide [7], somatostatin [8], and vasoactive intestinal polypeptide [9]. Neurons are assumed to regulate regional CBF depending on the area of the brain and populations of neurons nourished by the vasculature, the presence of glial cells that mediate local stimuli, the magnitude and duration of neuronal activity, and the effects of brain insult that may influence any of the above factors. Association of neuronal processes with vasculature of the brain is crucial for the nascent stage of blood–brain barrier (BBB) as well as its maintenance. Vascular endothelial growth factor (VEGF) signaling is thought to regulate vascular patterning during development [10], and neural progenitor cells contribute to stabilizing the incipient vascular network [11]. It is speculated that neuronal activities continue to maintain the vascular network even after the developmental stage by supporting astrocytes which are the main regulators of cerebrovascular permeability [12].

17.2.2 Vascular Endothelial Cells

Vascular endothelial cells are the core anatomical component of the BBB, protecting the brain by limiting transcellular and paracellular transportation of pathogens and deleterious factors from cerebral vessels. No fenestrae are seen in vascular endothelial cells of the brain and transcytosis occurs at very low rate [13]. Tight junctions and adherens junctions formed between adjacent endothelial cells build a physical barrier that blocks paracellular diffusion of ions and molecules. Tight junctions are composed of combinations of integral membrane proteins such as claudins and occludins and cytoplasmic accessory proteins including ZO-1, ZO-2, ZO3, and cingulin that link these transmembrane proteins to the cytoskeleton of actin [14]. This builds up tight inter-endothelial seal with maximum of 1800 ohms/cm^2 trans-endothelial electrical resistance in vivo [15]. Besides physical barrier, vascular endothelial cells form a transport interface between the blood and the brain. The luminal as well as abluminal membranes of endothelial cells contain polarized transporters, receptors, ion channels, and metabolite-degrading enzymes, so that molecules such as amino acids, electrolytes, glucose, and nucleosides can be delivered to the brain from the blood, and efflux metabolite waste products and solutes to the opposite direction [16]. Endothelial cells nourish neighboring neurons by supporting the development of axons [17], by protecting them from stress, and by providing niche for supporting neural stem cells. This cell–cell signaling called "neurovascular niche," between the endothelial cells and neuronal precursor cells mediate and sustain ongoing neurogenesis and angiogenesis in adult brains [18]. Endothelial cells are also known to be supportive for oligodendrocyte lineage cells. Endothelial cells and oligodendrocyte precursor cells (OPCs) are speculated to provide an "oligovascular niche," wherein endothelium-derived growth factors facilitate the proliferation of OPCs [19]. This support is attenuated under certain pathologic conditions such as cerebral ischemia and traumatic brain injuries [20].

17.2.3 Astrocytes

Astrocytes are found throughout the brain constituting nearly half of brain cell population. They exhibit heterogeneous morphology that varies depending on cell populations they interact with. Traditionally, astrocytes have been considered to physically, biochemically, and metabolically support cells of the CNS. However, recent studies have revealed variety of its functions regarding the regulation of NVU. Individual astrocytes play an important role on the formation, function, and elimination of the synapses. They extend numerous processes to several neurons which can result in the formation of 140,000 synapses [21]. Synaptic formations and pre-/postsynaptic functions are promoted by transmitters secreted from astrocytes. Astrocytes possess many receptors like neurons. This enables neurotransmitters to activate calcium-based signaling cascades in astrocytes to release active substances which act back to neurons to regulate their activities. Each astrocyte has its own spatial domain which will not overlap with other astrocytes. However, they are closely interconnected with neighboring astrocytes by gap junctions for the promotion of long ranged signaling [22]. In the context of the NVU, astrocytes tune vascular tone and CBF through their fine processes that form close liaison with blood vessels and synapses [23]. When neuronal activity is enhanced, nearby astrocytes send signals about the need for a regional increase of CBF to blood vessels, directly through gap junctions or indirectly by releasing soluble factors. As mentioned previously, astrocytes regulate BBB. Scar-forming astrocytes play a pivotal role when the sealing of BBB injury is necessary. Historically, reactive astrocytes after brain injury were considered as detrimental, but can become beneficial under certain conditions. Reactive astrocytes produce pro-inflammatory cytokines and astroglial scar that are likely to inhibit axon regeneration. However, they can also support neurons through upregulation of the genes that induces synaptogenesis [24] or by the secretion of trophic factors. When reactive astrocytes were conditionally knocked down in mice, enlargement of the lesion with more inflammatory responses were observed after brain trauma [25]. Additionally, reactive astrocytes are reported release tissue-type plasminogen activator which promoted neuronal dendrite formation [26]. The dual function of reactive astrocytes after brain injury remains mostly unknown and awaits elucidation. As they are highly secretory in nature, astrocytes are also known to influence oligodendrocyte linage cells either positively or negatively by releasing multiple trophic factors. End-feet of the astrocytes cover 99% of the abluminal vessels, and express high levels of water channel proteins (aquaporin-4), which are assumed to play pivotal role for perivascular clearance mechanism called the “glymphatic system” [27].

17.2.4 Pericytes

Pericytes are mural cells buried within the basement membrane which surrounds the vessels. They extend thin processes along the (precapillary) arterioles, capillaries, and (postcapillary) venules [28]. Morphology of the pericytes is known to change according to their position in the vascular bed. They show diverse functions such as formation and maintenance of the vessels, clearance of cellular debris, and CBF regulation. Density of pericytes and population of the pericyte-covered endothelial cells are also known to vary among the organs. CNS has higher coverage of pericytes compared to other organs, covering approximately 30% of the abluminal surface. In areas without basement membrane, pericytes are able to communicate directly with endothelial cells through gap junctions and with other pericytes through peg-and-socket contacts [29]. Transduction cascades that include angiopoietin, Notch, PDGF-B, sphingosine-1 phosphate, and transforming growth factor (TGF)-β, are responsible for the functional coupling between pericytes and endothelial cells [30]. Angiogenic actions of pericytes are triggered by the expression of several matrix metalloproteinases (MMPs) and urokinase plasminogen activator receptor that enhance extracellular matrix degradation. These reactions remove mechanical inhibition of endothelial cell migration, and facilitate

the release of matrix-sequestered angiogenic factors [31]. Pericytes are known to secrete tissue inhibitor of metalloproteinase 3, which protects basement membrane proteins from degradation during the vessel stabilization phase. Maintenance of BBB is also one of their important roles. In vivo experiment which used mice with PDGFRβ signaling deficiency (shows deficits in embryonic pericyte recruitment) showed that loss of pericytes resulted in the increased permeability of BBB [32].

17.2.5 Microglia

Microglia are the resident immune cells of the brain which constitute nearly 10% of CNS glia. Unlike astrocytes, ependymal cells, and oligodendrocytes, microglial cells are mesodermal in origin. During early development, myeloid precursors are seeded throughout the brain and develop into cells with high plasticity and mobile capability. In contrast to other glial cells, microglia are not electronically coupled with syncytial network and retain their own surveillance territory [33]. During their native resting state, microglia have small cell bodies with numerous long and highly branching processes. Random scanning by their processes rapidly leads them even to tiny ruptures in the blood vessels. When microglia transform into amoeboid morphology under pathological condition, they become highly phagocytic, and start producing and secreting numbers of cytokines with soluble factors. These processes are thought to be assisted by neighboring astrocytes which release purinoreceptor ligands [34]. Activated microglia have heterogenic phenotypes. Two famous phenotypes would be M1 and M2 microglia. When microglia are challenged by the invasion of pathogens, M1 phenotype releases inflammatory mediators such as interferon (IFN)-γ, interleukin (IL)-1β and tumor necrosis factor (TNF)-α along with phagocytosis. On the other hand, M2 phenotype releases anti-inflammatory factors such as insulin-like growth factor (IGF)-1, IL-4, and IL-10 to remove apoptotic cells or myelin debris. However, in vivo, there is a broad range of activated microglial phenotypes that reflect the specific stimulus and the status of the surrounding cells that compose the NVU. For example, it is known that expression of CD4, FcγRII, and TNF-α mRNA in hippocampal microglia is higher than those from the cerebellum, cerebral cortex, diencephalon, and tegmentum [35]. Expression of Neurotrophin-3 is known to localize in microglia within the cerebral cortex, globus pallidus, and medulla. Recent studies showed that while microglia associated with inflammation attenuate neurogenesis, microglia activated by certain T cell-derived cytokines may promote neurogenesis [36]. Modulation of microglial polarization, which presumably could serve as an effective therapeutic tool for stroke, is currently under investigation.

In the NVU, there are also perivascular microglia/macrophages that originate from residing microglia of the CNS and monocytes from bone marrow circulating the vessels. Perivascular microglia couple with tip cells on sprouting vessels to facilitate angiogenesis during developmental stage. In the adult brain, perivascular macrophages are known to derive from circulating monocytes, and fight against pathogens in the very front line [37]. Perivascular macrophages maintain contact with other types of cells composing the NVU, and the crosstalk between these cells presumably contributes to the NVU function and dysfunction. Recent studies utilizing two-photon laser scanning microscopy showed that under certain pathological condition, parenchymal microglia could migrate to form perivascular cuffs that lead to vascular degradation and progression of the disease [38].

17.2.6 Oligodendrocytes

Although the NVU is relatively a well-accepted conceptual model for profound understanding of the phenomena occurring during brain injuries in the gray matter, cell–cell interactions are very important for white matter as well. Oligodendrocyte is one of the major types of cell found in the white matter. Lipid-rich myelin produced by oligodendrocytes enwraps axons and

enable saltatory conduction of electrical impulses. Myelin-forming oligodendrocytes are derived from OPCs which originate from subventricular neuronal stem/progenitor cells [39]. In the adult brain, OPCs can be found within the whole brain, comprising 5–8% of all cell components. It is known that most of the myelination process occurs early in life, and continues at least into late adolescence. In certain regions of the CNS, ongoing myelination may also be seen in adults. Experiments indicate that myelin in adult CNS may show some plasticity when stimulated by alternations in neural activities. For example, successful learning of juggling in human was shown to be correlated with an increased fractional anisotropy within the white matter underneath the intraparietal sulcus, suggesting that increase in myelination could occur in adult brains [40]. Rat experiment has also shown that environment modification could result in a detectable increase of myelin in adulthood [41].

Since axons are myelinated by matured oligodendrocytes, interactions between oligodendrocytes and neurons have been broadly examined. Oligodendrocytes are known to send signal to neurons through myelin–axon interactions. However, axon loss without severe demyelination was observed in mouse models with dysfunctional oligodendrocyte, implicating that oligodendrocytes could also support axon survival without through myelin sheath [42, 43]. It has been recently demonstrated that oligodendrocytes may serve as a principal supplier of lactate, which is indispensable for energy support of the axons [44]. Additionally, trophic factors such as IGF-1 and glial cell-derived neurotrophic factor (GDNF) released from oligodendrocytes have been shown to facilitate survival of neurons and outgrowth of axons in vitro [45]. Meanwhile, axonal activities, axon-secreted molecules, and axonal surface ligands have been proposed to regulate differentiation and maturation processes of oligodendrocytes. Examples are: (1) Jagged ligands expressed in axons that send signal to OPCs through Notch pathway inhibiting their differentiation [46], and (2) PSA-NCAM or LINGO-1 which are also known as molecules that inhibit myelination [47, 48]. There is an experimental evidence that myelination is partly triggered by electrical activities of the axons in developmental stage. Study using a mouse model of remyelination has shown that OPCs derived from the subventricular zone were observed to receive synaptic input of remyelination [49]. This result suggests possible involvement of neuronal activity in remyelination process as well.

As mentioned above, interaction between the endothelial cells and oligodendrocytes in the "oligovascular niche" after brain injury presumably triggers angiogenesis and oligodendrogenesis in the white matter of adult brain. MMP-9 released from oligodendrocytes is proposed to promote vascular remodeling during the chronic phase after white matter injury [50]. Also in demyelinating diseases such as vascular dementia, leukodystrophy, and multiple sclerosis, OPCs are speculated to attempt remyelination in degenerated areas during the chronic phase [51]. Although ability of endothelial cells to promote oligodendrogenesis remains unknown, they have shown potential to facilitate migration and proliferation of OPCs in cell culture studies.

17.2.7 Basement Membranes

A specialized extracellular matrix is made up from secreted proteins to form the basement membrane between endothelial cells and pericytes, and between astrocytes and pericytes. Since pericytes cover the vasculature discontinuously, astrocytes and endothelial cells share single basement membrane in the discontinued area. Proteomic studies of rodents show that composition of extracellular protein in brain vasculature differs from those found in the peripheral vessels. Basement membrane protein composition varies even between the large and small vessels within the brain, indicating functional heterogeneity of NVU throughout the brain [52]. Major proteins of the basement membranes include numbers isoforms of extracellular matrix proteins such as collagens, fibrillins, fibronectins, laminins, and vitronectin. Cytokines, growth factors, enzymes responsible for the degradation and processing of MMPs, and proteins like lectins that bind to

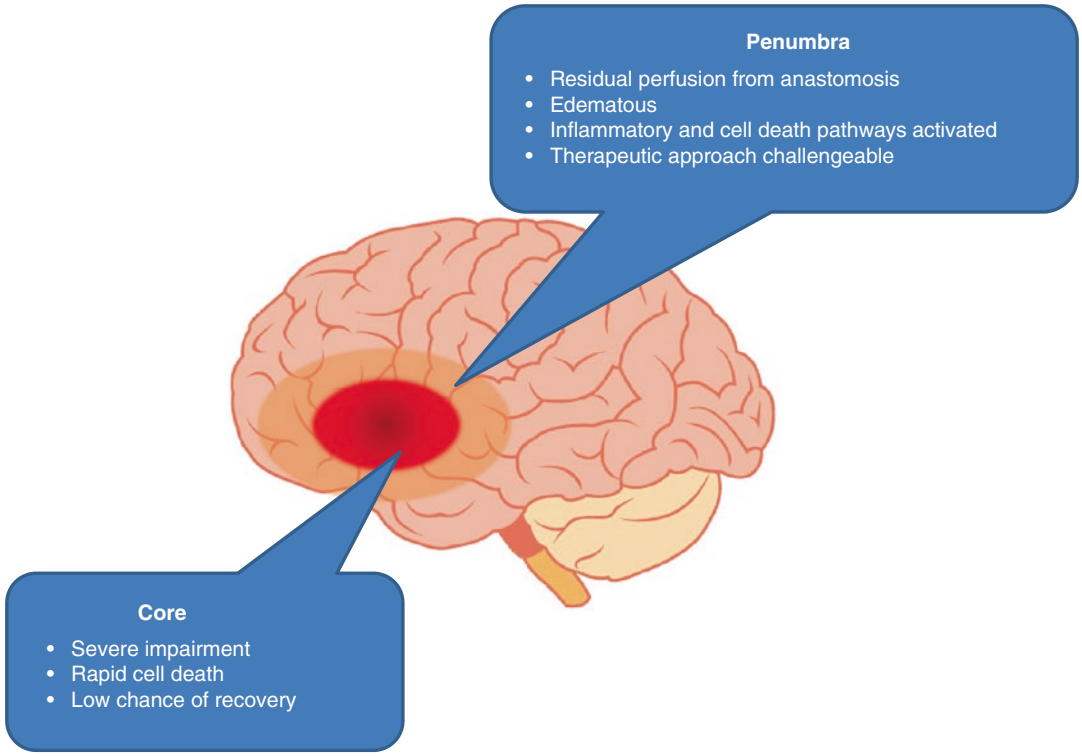

Fig. 17.2 Schematic of ischemic infarction: In the central core areas of stroke, blood flow deficits and/or hemorrhagic lesions are severe and brain cells die rapidly. On the other hand, in the peripheral areas (penumbra), it has been proposed that cell death, inflammation, and neurovascular perturbations proceed at a slower pace. Hence, theoretically the penumbra region can be a therapeutic target

extracellular matrix are also included. Extracellular matrix and protein components that support basement membrane are essential for the proper operation of NVU as they directly regulate signals from many activated receptors found on the cellular components of NVU.

17.3 Stroke Pathophysiology and NVU

Among the CNS diseases which have been studied in relation to the NVU, stroke is the most investigated type of disease, since its pathophysiology consists of fairly significant biphasic reactions of chemical mediators. In the acute phase after the onset of stroke, severe decline of CBF causes abrupt deprivation of nutrient supplies that leads to irreversible damage in the "core" of the affected area. During chronic phase, remodeling signal may occur within the semi-preserved area surrounding the "core" called "penumbra" (Fig. 17.2). Although precise mechanisms of post-stroke biphasic pathophysiology remain to be elucidated, in this section we will discuss some of the key phenomena that were identified to modulate the responses of NVU in acute and chronic phases of stroke.

17.3.1 NVU Dysfunction in Acute Phase of Stroke

In ischemic stroke, cells in the "core" of the lesion are exposed to rapid loss of adenosine triphosphate and energy stores due to severe decline of blood flow. As neuronal cell death within the "core" occurs within a few minutes, it is usually impossible to protect those neurons by medication. In hemorrhagic stroke, area surrounding the hema-

toma may also suffer from expanding edema and progressive inflammation, although molecular mechanisms are not well defined in comparison with ischemic stroke. Fundamental mechanism of neuronal death in the acute phase of stroke is complex. However, results of the experiments over the past three decades have implicated presumable involvement of excitotoxicity, oxidative stress, and, in some occasions, apoptotic-like pathways [53]. When the brain fails to generate sufficient adenosine triphosphate by reduction of CBF, energy failure and loss of ionic gradient occurs. Consequently, glutamate reuptake processes are impaired and excessive calcium entry and release are promoted by accumulation of glutamate. Degradation of cytoskeletal and enzymatic proteins by calcium-dependent proteases and synthases contribute to neuronal death. Calcium homeostasis abnormality also affects the neighboring cells by generating nitric oxide and peroxynitrite, which directly attack cells. When dysfunction of oxidative phosphorylation occurs in mitochondria, reactive oxygen free radicals are discharged to further eliminate cells by attacking nucleic acids, lipids, and proteins. Along with these pathways related to ions and free radicals, deleterious molecules such as caspases also accelerate cell death via apoptosis. Besides these mechanisms related to cell death, inflammatory cascade is triggered by upregulation of damage-associated molecular patterns (DAMPs) within few hours after the onset of stroke. HMGB1, heat shock proteins, and hyaluronic acid are included in DAMPs [54]. After being released from dead cells (passive pathway) and activated microglia and astrocytes (active pathway), DAMPs are captured by Toll-like receptors and other scavenger receptors which are broadly expressed in NVU component cells such as endothelial cells, microglia, and perivascular macrophages. Once this signaling is activated, mediators such as chemokines, cytokines, nitric oxide, and reactive oxygen species (ROS) are excreted from cells mentioned above leading to breakdown in BBB function [55]. DAMPs also upregulate adhesion molecules lining the endothelial cells such as ICAM-1, VCAM-1, and E-selectin, making it possible for circulating leukocytes to enter into brain parenchyma through loosened BBB. Homeostasis of BBB largely depends on interaction between endothelial cells, astrocyte, and extracellular matrix. Disruption of fibronectin, heparin sulfate proteoglycan, laminin, and type IV collagen break down signals between cells and extracellular matrix, and even between the cells that is needed for the function of NVU. Dysregulation of proteinases that contribute to proteolysis of extracellular matrix, and extracellular proteases occurs during the disease. Particularly, the MMP family has been known to cause neurovascular damage following stroke. Increased levels of MMPs were confirmed in both animal stroke models and stroke patients [56–60]. When excessive, MMPs take on deleterious activities by degradation of the extracellular matrix comprising the basal lamina, which damages the BBB directly. Inhibition of MMPs is found to reduce volume of infarction and edema in experimental models of stroke [61]. MMPs cause dysfunction of NVU also by inducing proteolysis of the extracellular matrix. This detaches cells from the extracellular matrix and leads to induction of anoikis [62]. These perturbations could be captured as failure of crosstalk between the NVU components. Lacking normal endothelial-astrocyte signaling may result in leakage of BBB. Signaling error between neurons and endothelium may interrupt hemodynamic coupling needed for active brain function. Improper neuron–glia signaling may affect release–reuptake kinetics of neurotransmitter and its transmission along the axons. Thus, focusing only on neuronal death will not be enough when thinking about therapeutic target for stroke. A truly effective therapy would be, if any, to protect all the functional interactions between the multiple types of cells which are the constituent of NVU. It is a disappointing fact that none of previous convincing discoveries toward the mechanisms of neuronal death during the acute phase of stroke have successfully provided benefits to stroke patients. Among all the translational barriers, heterogeneity of patients and very rapid cell–cell interaction after the onset of stroke make it difficult to suppress acute reactions efficiently. Therefore, recent studies have gradually shifted their focus to promoting recovery of the NVU in the chronic phase of stroke.

17.3.2 NVU Remodeling in Chronic Phase of Stroke

After the acute phase of stroke, patients present temporal recovery to some extent. Functional magnetic resonance imaging studies show that peri-infarcted regions retain plasticity [63], although cellular mechanisms underlying processes for recovery remain to be clearly elucidated.

Primary neurovascular responses during the recovery phase of stroke involve angiogenesis and neurogenesis. Since their molecular mechanisms are evolutionarily conserved, both phenomena share similar mediators and pathways. It is now a well-accepted fact that in adult brains, cell–cell signaling between the endothelium and neuronal precursor cells serves to mediate and to sustain pockets of active angiogenesis and neurogenesis. These interactions compose the "neurovascular niche," where soluble signals mediate crosstalk between the vascular and neuronal compartments. Endothelial cells in the brain release trophic factors to partly mediate this phenomenon. In subgranular and subventricular zones of the normal brain where neurogenesis is known to occur, the neurovascular niche mediates the complicated cell–cell signaling mechanism that takes place between endothelial cells and neural precursor cells. Maintenance of close relationship between angiogenesis and neurogenesis as mentioned above is essential for post-stroke recovery. When neuroblasts migrate through perivascular routes, along with the enhancement of vascular regeneration by promotion of neurogenesis, angiogenic stimulation adversely facilitates neurogenesis [64]. As rodent stroke model and human stroke samples show active angiogenesis within the peri-infarct regions [65, 66], recovery mechanism in the chronic phase of stroke is built on plasticity and remodeling processes controlled by mutually dependent neurovascular coupling that assemble various mediators and signals. Hence, our immediate goal for the treatment of stroke would be to discover medical therapies that can uplift endogenous signals and substrates needed for neurovascular remodeling, although how such approaches could be applied in daily clinical settings remains unclear. Notably, most of the candidate target molecules for stroke therapy act in biphasic manner during the course of stroke. As previously mentioned, in the early phase of stroke, MMPs trigger neurovascular dysfunction by breaking down BBB and inducing anoikis-like cell death. However, during the chronic recovery phase, the same mediators may become beneficial to neurovascular remodeling which includes angiogenesis and neurogenesis. In an experiment using mouse model of stroke, endothelial cells and glial cells were shown to proliferate in peri-infarcted areas secondary to MMP-9 elevation. What is more interesting is that mice with inhibited MMPs during the delayed phase resulted in worse outcomes [67]. Additionally, there was a co-localization of secondary MMP-9 signals with neuroblasts migrating from the subventricular zone, and here, inhibition of MMPs also blocked the transference of the neuroblasts toward the legion as well [68]. Mediators such as VEGF and HMGB1 can also play dual roles in neurovascular responses following stroke. While VEGF increases permeability of BBB in the acute phase, it facilitates angiogenesis and neurogenesis in the delayed recovery phase of stroke. HMBG1, which is normally present in the nucleus, is released in extracellular space under ischemic insult. As previously described, HMBG1 induces necrosis and accelerates the migration of destructive inflammatory cells during the acute phase of stroke. Conversely, during the delayed chronic phase, it mediates beneficial plasticity needed for recovery of the NVU. Dual role is also found in TNF-α, released from activated glial cells upon stimulation by the DAMP molecules. However, its dual mechanisms do not necessarily depend on timeline, and are thought to be affected by its target and secondary signals after the binding to corresponding receptors. Reactive oxygen species could be another example. Contrary to harmful events it may cause in the acute setting of stroke, it has been shown to mediate migra-

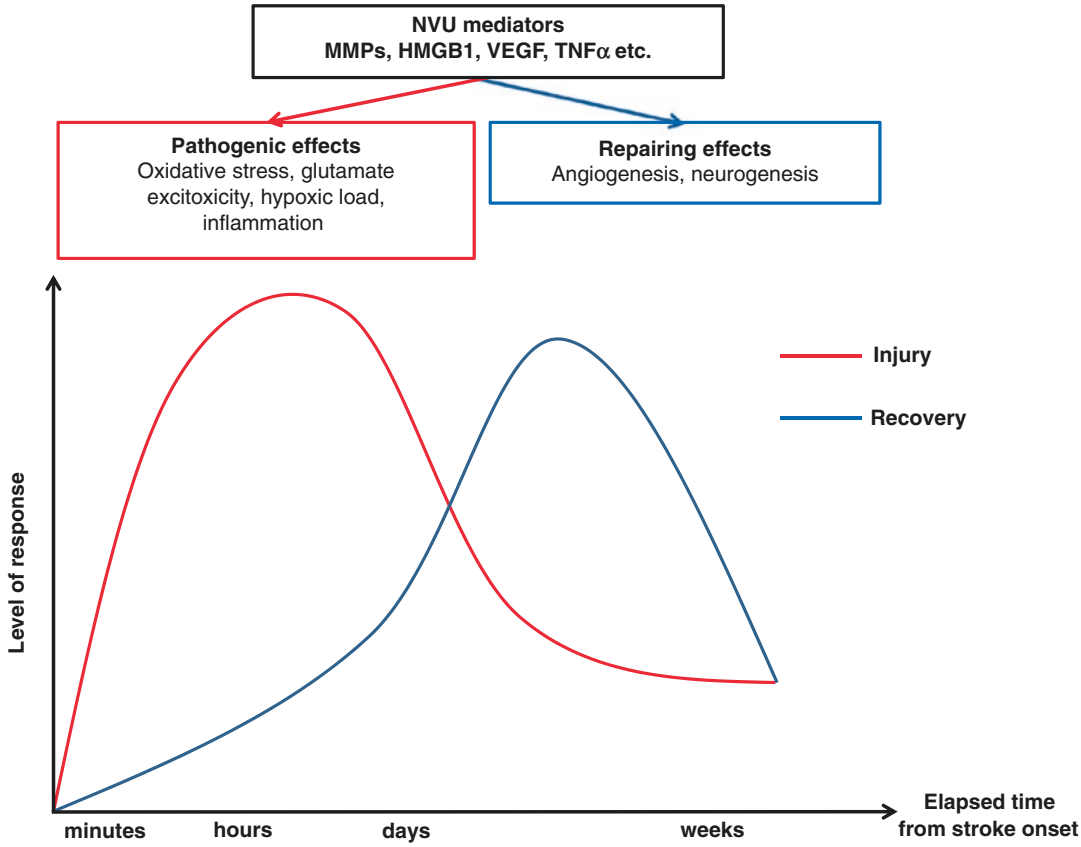

Fig. 17.3 Schematic to summarize the biphasic responses after stroke onset: In the acute phase, deleterious responses lead to NVU damage. On the other hand, remodeling signaling may emerge at the later time point. NVU mediators such as MMPs and VEGF would work in both phases, with opposite actions

tion of the OPCs essential for oligodendrogenesis [69]. Likewise, there are various mediators in the NVU with detrimental effects in the acute phase that turn out to be beneficial in the chronic phase (Fig. 17.3). Therefore, if we are to succeed in neurovascular protection of stroke patients, it is essential for us to consider when the acute phase of deleterious responses turns into recovering phase.

17.4 White Matter Injury

The concept of NVU has been mainly utilized for investigations of stroke pathophysiology occurring in the gray matter. However, since lacunar infarction is the most common type of ischemic stroke, knowledge about white matter damage is also clinically important for stroke treatment. In comparison with the cellular mechanisms of neurovascular coupling in the gray matter, pathophysiology of the white matter stroke still remains relatively unknown. As oligodendrocytes are one of the major component cells of the white matter, protection of oligodendrocyte lineage cells is of paramount importance when thinking about the treatment of stroke involving the white matter. From the notion that cell–cell trophic interactions are functioning in the white matter as well, the idea of NVU is now being applied to research of the white matter stroke. Neuronal axon, oligodendrocyte lineage cells (including myelinating oligodendrocytes and OPCs), endothelial cell, and astrocyte are the main component of the white matter. Astrocytes and endothelial cells collaborate to maintain BBB in white matter

as seen in the gray matter. Astrocytes are in close apposition to oligodendrocytes within the white matter, and interact directly via gap junctions for the maintenance of their functions [70, 71]. Soluble factors secreted from astrocytes are also reported to protect oligodendrocyte lineage cells from ischemic stress [72]. Needless to say, interaction between myelin and axon is critical for homeostasis of the white matter. Oligodendrocytes also maintain functional integrity and survival of axons through a myelin-independent manner by releasing trophic factors such as IGF-1 and GDNF. Just like the gray matter, activation of several deleterious factors and pathways takes place during the acute phase of stroke. Survival and normal functions of oligodendrocytes are affected by direct attack of MMPs to myelin components. Even if cells could avoid immediate death, metabolic dysfunction triggered by the assault would result in abnormal myelin replenishment and synthesis of myelin-related proteins, ultimately leading to impairment of myelin–axon coupling. Biphasic reactions of endogenous mediators are also known to occur in the course of white matter stroke, and several molecules are shown to work for repairing in the chronic phase. OPCs, which migrate from the subventricular zone to form myelin sheaths during development, are also distributed in the adult brain. It has been proved that some of these cells are guided to the lesion where remyelination is needed after the white matter injury [73]. Although precise molecular mechanism of migration after white matter stroke remains to be elucidated, oligovascular niche (corresponding to neurovascular niche within the gray matter) is speculated to play a crucial role in sustaining trophic interactions between the OPCs and vascular endothelial cells.

17.5 Conclusions

Ever since its birth, the concept of NVU has provided us with novel frameworks for the research of CNS diseases including stroke. Therapeutic target has shifted from "neuron-centric" to "neurons + surrounding atmosphere" where dynamic interactions of different cell types take part in function and dysfunction of the brain. Besides neuronal damage, pathophysiology of stroke also consists of: (1) glial activation and transformation, (2) vascular and BBB alteration, and (3) inflammatory reactions. These responses are detrimental in the acute phase, and sometimes turn out to be beneficial for neurovascular repair in the chronic phase, leading to the biphasic course of clinical manifestation. Investigating cellular mechanisms within the transitional zone between these two phases may give us a new hint for the development of effective treatments for stroke.

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Basic Aspect: Neurorepair After Stroke

18

Margherita Zamboni, Jens Magnusson, and Jonas Frisén

Abstract

This chapter discusses the scientific premise of stem cell-based therapies aimed at repairing damage produced by cerebrovascular insults in the adult human brain. Understanding the principles that govern stem cell biology will be of crucial importance to help designing treatment strategies for regenerative medicine. For this reason, the chapter is divided in two sections. The first part will touch upon pivotal basic research that has paved the way to a fuller comprehension of neurogenesis in the developing and adult brain. Interestingly, many molecular mechanisms that play roles in neurogenesis are shared between brain development and adulthood. Therefore, studies that have focused on brain formation have also guided investigations around homeostatic neurogenesis, as well as regenerative repair of the adult brain. The second section of this chapter will introduce recent biomedical investigations around the possibilities of initiating ectopic neuroregenerative programmes, or boosting physiological cell turnover rates for regenerative repair. In this context, we will discuss opportunities for promoting endogenous neurogenesis that may be generated from actual or potential stem cells residing throughout the brain. Finally, we will discuss experimental approaches aiming to replace lost neurons using endogenous sources.

18.1 Stem Cell Biology and Endogenous Neurogenesis in Brain

18.1.1 Stem Cell Biology: General Principles

Stem cells are cells that can proliferate to maintain their own population, often referred to as self-renewal, and give rise to different cell types through a process of differentiation. In the embryo, they allow formation of all organs in the body. They are still present in adulthood, although decimated in numbers and limited in their potency to organ-specific cell types. In the adult organism, stem cells are continuously active for homeostatic turnover of cell populations in dynamic organs, such as skin and blood, or they contribute to regenerative repair after injury. Maintenance of adult stem cell pools is ensured through tissue-specific stem cell niches, in which dividing cells may give rise to other stem cells, as well as progeny destined for differentiation into postmitotic cells. Stem cells can exist in dormant or activated states, which depend on their

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metabolism, transcriptional and epigenetic profile, as well as spatio-temporal orientation. Thanks to their capacity for self-renewal and multipotency, stem cells have been proposed for therapeutic strategies. For instance, transplantation of haematopoietic stem cells obtained from the bone marrow has been successful in remitting diseases of the blood, such as leukaemia and plasma cell myeloma.

18.1.1.1 Tracking Cell Generation

A challenge in regenerative medicine is the ability to trace self-renewing cells, quantifying their turnover rates, and characterizing their maturation in different postmitotic cell types. Researchers have taken advantage of a wide variety of methods that allow them to follow the life of stem cells. For instance, Ki67 is a protein that is transiently expressed during the cell cycle, and is commonly adopted to measure numbers of dividing cells in immunohistochemical staining or in flow cytometry [1]. Labeled thymidine analogues, such as BrdU and EdU, are another means of tracking dividing cells [2]. The advantage of using these over Ki67 expression is that cells stably integrate the analogues into their genome. Thus, one could quantify newly created cells even past their mitotic phase. Using these analogues, however, carries a risk of overestimating cell division, because BrdU and EdU can be detected even in the progeny of cells that have previously been labeled. Finally, experiments employing thymidine analogues are only suitable for short-term, preclinical studies due to dangerous side effects associated with their administration.

A novel approach has been devised to measure cell renewal rates in human individuals. This method takes advantage of a dramatic surge in environmental Carbon^{14} (^{14}C) levels, which increased due to nuclear bomb testing over the past century [3]. The concentration of ^{14}C rapidly increased up until the early 1960s, and has been decreasing through uptake by the biotope through photosynthesis since 1963 when an international test ban treaty was agreed to and over-ground nuclear bomb tests were discontinued. Atoms of carbon (incl. isotopes) present in the environment are incorporated into cells during DNA synthesis and the amount of integrated ^{14}C reflects the isotope concentrations at the time of cell division [4]. Thus, measuring the ^{14}C concentration in genomic DNA of a cell population enables the determination of that population's turnover dynamics. By means of ^{14}C dating, researchers in our lab have been able to infer turnover rates of various cellular populations, including those of the heart and central nervous system [5–7].

18.1.2 Endogenous Neurogenesis

18.1.2.1 Stem Cells in Brain Development and Adulthood

During neurodevelopment, neurons and macroglia (i.e. astrocytes and oligodendrocytes), arise from various regions around the ventricles, hollow structures filled with cerebrospinal fluid (CSF) [8]. Lineage-tracing technologies have allowed stable expression of fluorescent protein reporters into progenitors of neural stem cells (NSCs) and have enabled appreciation of the neurogenic process. Thanks to experimental designs that track differentiation of NSCs, researchers have, for instance, established that pyramidal neurons of the neocortex and astrocytes both originate from radial glia that span their processes between the ventricular zone, on the basal side, and the pial surface, on the apical side [8, 9]. In contrast, interneurons are formed in subpallidal regions and tangentially migrate to populate cortex [8].

Historically, the brain has been considered to be an organ where no neuronal replacement takes place. The earliest reports of adult neurogenesis date back to Altman's "Are new neurons formed in the brains of adult mammals?" in 1962 [10]. The author used thymidine-based methods to record addition of new neurons to the dentate gyrus and olfactory bulb of rodents. Sadly, his work was either ignored or harshly criticized by contemporary scientists. A decade later, Kaplan also tried to persuade, though without success, the scientific community of the existence of neurogenesis in the adult rodent and cat hippocampus, olfactory bulb and cortex

[11]. Rakic strongly opposed this idea, with his publication "Limits of Neurogenesis in Primates" [12]. It was not until the 1990s that research in neurogenesis finally started thriving, largely because of advances in available methodology. Several groups now reported that NSCs could be isolated from the adult rodent brain [13, 14] and also that neurogenesis takes place in vivo in both experimental animals [15] and humans [16]. In addition, it was during this time found that adult neurogenesis is positively regulated by factors such as exercise and enriched environment [17, 18].

It is now widely accepted that the mammalian brain retains neurogenic capacity in a few small regions throughout the lifespan of an individual. New neurons originate in neurogenic niches that contain NSCs, which display proliferative and multipotent properties, even during physiological conditions. In the adult mammalian brain, the germinal niches are found in the subventricular zone (SVZ), which is a narrow band flanking the lateral walls of the lateral ventricles, as well as in the subgranular zone of the hippocampal dentate gyrus (Fig. 18.1). More than a thousand new neurons are generated

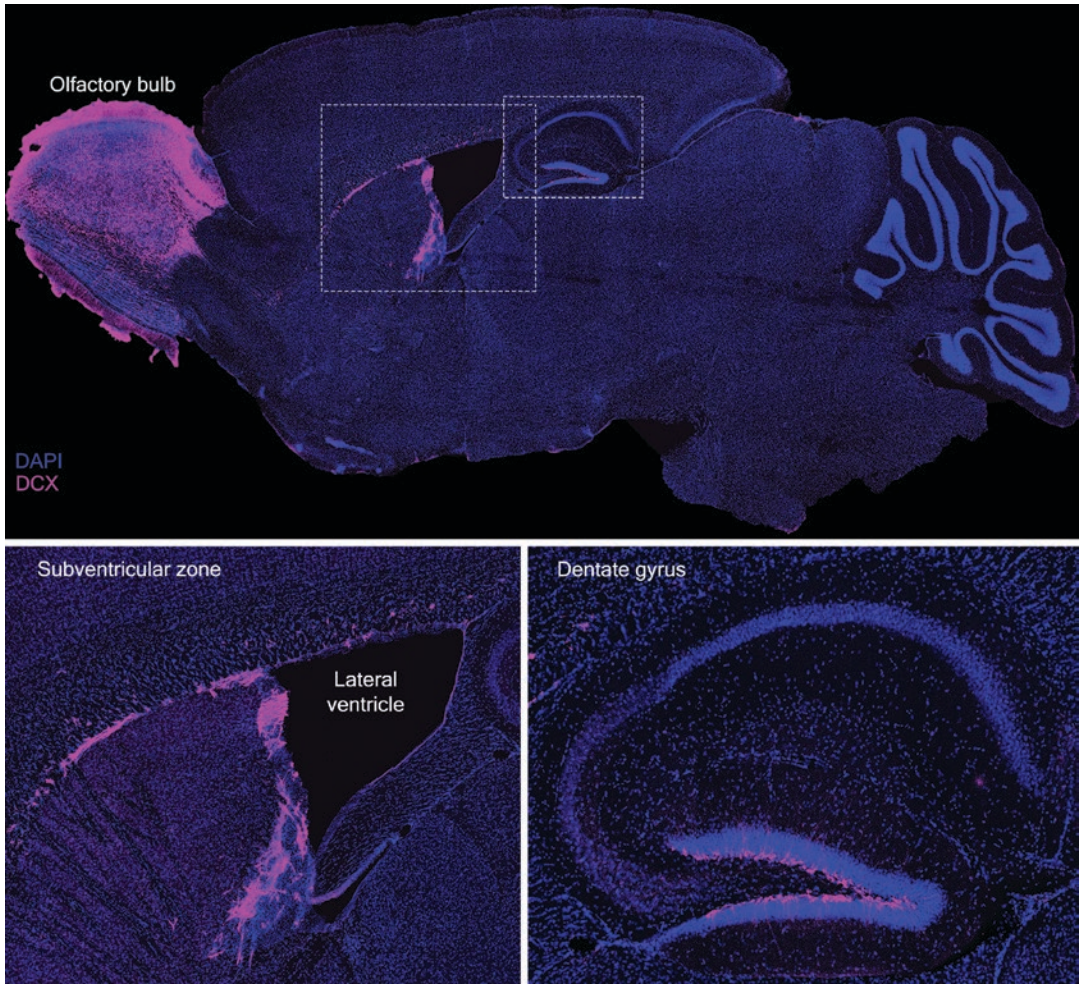

Fig. 18.1 Neurogenic regions in the adult mouse brain. An immunohistochemical staining against the neuroblast-specific protein Dcx was performed on a sagittal tissue section through an adult mouse brain. This shows that new neurons are generated in two regions: the subventricular zone, from which newly generated neuroblasts migrate to the olfactory bulb, and the hippocampal dentate gyrus

every day throughout adulthood [5, 19]. Newborn neurons display a transient, hyper-excitable electrophysiological profile [20], which may give them a special role in information processing. For example, they may be important for storing similar experiences as distinct memories [21]. The functional relevance of adult-born neurons is demonstrated in instances of impaired neurogenic activity, whether in the context of experimental manipulation, or due to neurological conditions. Animal models of impaired hippocampal neurogenesis display difficulties in learning and memory abilities, such as contextual learning and retention of spatial information [22]. Additionally, several human diseases have been suggested to be associated with altered neurogenic behavior in the hippocampus. These include both psychiatric diseases, such as schizophrenia and depression, as well as neurodegenerative conditions, such as Alzheimer's disease [22]. In the SVZ of most mammals, new immature neurons migrate to the olfactory bulb where they are important for certain aspects of odor discrimination [23]. Thus, neurogenesis appears to be important for neural circuit function in the brain regions where it occurs. On the whole, however, adult neurogenesis is extremely limited: it only occurs in such small, specialized niches; the vast majority of neurons in the brain cannot be replaced if they are lost.

There are species-specific differences in neurogenesis. Interestingly, humans do not have any olfactory bulb neurogenesis [6]. This may be because humans, unlike rodents, rely very little on their sense of smell for survival. Hippocampal neurogenesis, on the other hand, is very active in adult humans [5]. In addition, retrospective birth dating and IdU labeling of neural cells using ^{14}C have allowed scientists to identify an additional and unique site of adult neurogenesis in the human brain. It appears that interneurons are continuously added in the human striatum, a structure that lies adjacent to the SVZ [24] (Fig. 18.2). To this date, the origin of these cells remains unclear, although it is tempting to specu-

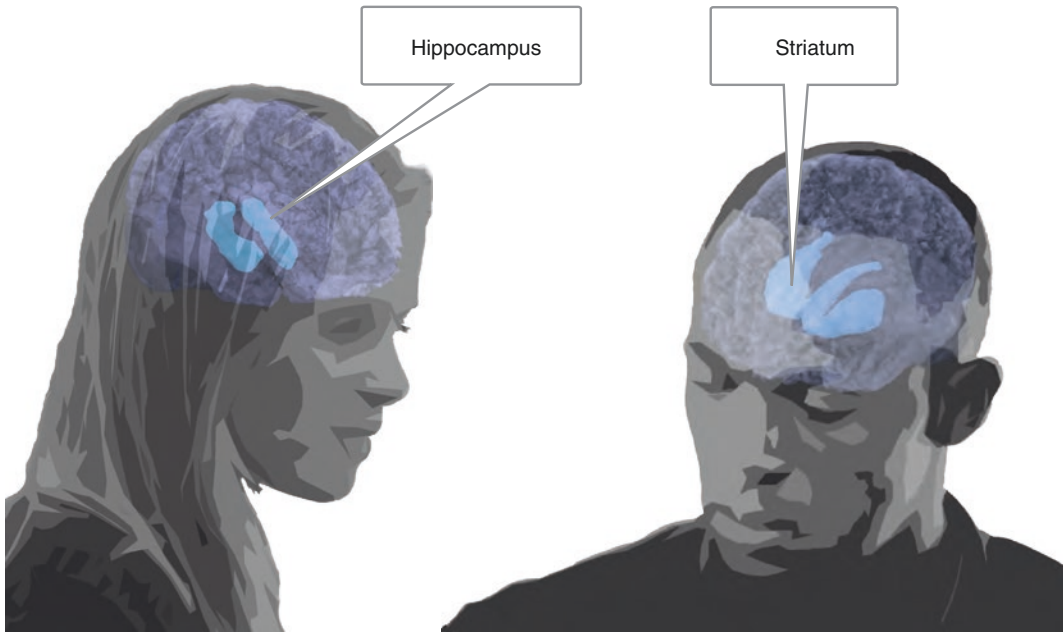

Fig. 18.2 Regions in the healthy adult human brain where new neurons are added throughout adulthood. As in most mammals, adult neurogenesis takes place in the dentate gyrus of adult humans. However, in contrast to most other mammals, adult neurogenesis does not occur in the human olfactory bulb. Instead, new neurons are continuously being added to the striatum

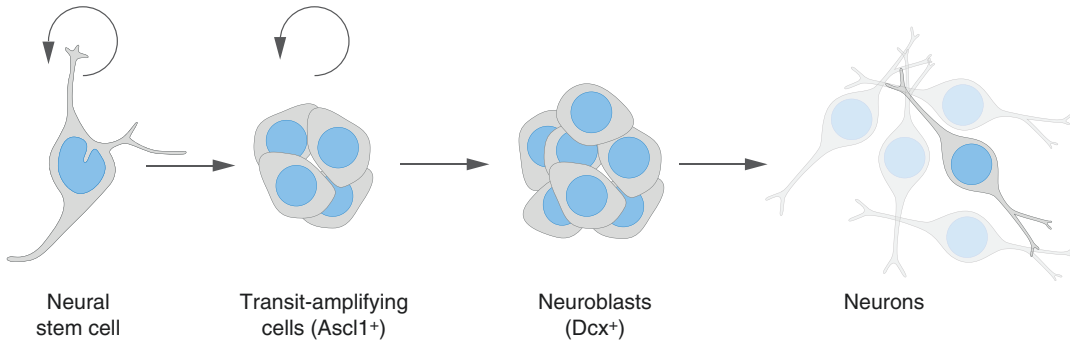

Fig. 18.3 Mechanism by which neural stem cells generate neurons in the adult neurogenic niches. Neural stem cells divide to give rise to transit-amplifying cells. These, in turn, divide a few times in rapid succession to generate neuroblasts, which mature into neurons

late that neuroblasts may be migrating from the neurogenic niche at the SVZ.

Cell types that differ along stages of differentiation can be found in the neurogenic niches. Specifically, astrocyte-like cells are adult NSCs [25]. They share several molecular and functional properties with parenchymal astrocytes, such as expression of many astrocyte genes. Recent studies have suggested that the NSC population may be heterogeneous in the progeny it gives rise to, as well as its cell turnover rates. Indeed, NSCs residing in different locations around the lateral ventricles seem to be predetermined in the type of olfactory bulb interneurons they will give rise to [26]. Additionally, Llorens-Bobadilla and colleagues took advantage of state of the art single-cell RNA sequencing technologies to segregate several subpopulations, based on their self-renewal rate, along the quiescent-to-activated axis [27]. They have shown that recruitment of dormant NSCs into the cell cycle is accompanied by diminished glycolytic and lipid metabolism and a simultaneous surge in transcriptional activity of lineage-primed transcription factors (i.e. pro-neuronal or glial) and genes implicated in protein synthesis. NSCs develop into transit amplifying cells that can be identified through immunohistochemical staining of Ascl1 (Achaete-scute homolog 1) (Fig. 18.3). These cells are short-lived and go through brief rounds of division before generating neural progenitors. Finally, neuroblasts expressing doublecortin (DCX) and PSA-NCAM are formed in the neurogenic niche. These give rise to proliferative clusters and become committed to the neuronal lineage, being identified as immature neurons. Following another cell division phase, neuroblasts depart for a migratory journey that will take them to their final destination in the brain [28].

The germinal niche is also characterized by a specific microenvironment and ultrastructure that is crucial for stem cell behavior [29, 30]. In particular, studies have shown that NSCs extend a process into the lateral ventricle, thus gaining a privileged access to growth factors contained in the CSF [29, 31]. Subsequently, Tavazoie and colleagues have proposed that the proximity of NSCs and transit amplifying cells to the cerebral vasculature supports their proliferation [32].

18.1.2.2 Molecular Basis for Self-Renewal and Fate Determination of NSCs

Cell turnover rates and lineage commitment are dictated by molecular mechanisms that are highly regulated in a spatio-temporal manner. Numerous studies have identified many of the molecular cues that instruct NSCs towards expansion, or differentiation into neurons and glia. Additionally, researchers have been able to interfere with the neurogenic process using transgenic animal models, viral vectors, and small molecules that enhance or inhibit molecular signaling activity. As a result, they have determined ways for boosting proliferation or favoring differentiation.

Interestingly, the signaling pathways implicated in neurogenesis are conserved through development and into adulthood. Examples of these include Sonic Hedgehog (Shh), Notch, and BMP (bone morphogenetic protein). Knocking out Shh during corticogenesis severely impairs patterning of the cortical lamina and fate determination of neural progenitors [33]. Notably, Shh is also required to regulate adult neurogenesis, and acts as a mitogen in concert with epidermal growth factor (EGF) to control proliferation of astrocyte-like NSCs and their progeny in the SVZ [34]. Likewise, Notch has been implicated in both developmental and adult neurogenesis, where it plays roles in regulating stem cell quiescence and lineage fate determination, favoring astroglia differentiation over neuronal maturation [35]. In addition, developmentally active BMP signalling contributes to morphogenesis of the nervous system and participates in the switch between neuro- and astrogenesis. It is, furthermore, implicated in adult neurogenesis, where its activity halts proliferation and maturation of neuroblasts, while imposing quiescence of stem cells or glial differentiation [36]. Interestingly, ectopically infused Noggin, a natural inhibitor of BMP signaling, alters fate determination preferences at the germinal niche, favoring production of neurons [36].

18.1.2.3 Neurogenesis in the Injured Brain

Investigations on the regenerative potential of mammalian brains principally comes from preclinical studies employing animal models that aim at mimicking mechanisms and symptoms of human pathologies. Importantly, species may diverge significantly in their cell turnover capacity. For instance, great differences in regenerative capabilities are seen between mammals and certain amphibian species, which show superior reparative potential after brain insults. Considering in what ways brains differ in their reaction to injury may help shaping more effective therapies that mimic dynamics of regeneration as seen in more permissive species, such as the salamander. The amphibian brain is quickly and efficiently repopulated with cells after neuronal loss, at least if the neuronal loss is limited. This is apparent in the midbrain of salamanders subjected to chemical ablation of dopaminergic neurons. In this context, the neuronal population is completely regenerated through a process of proliferation and differentiation of ependymoglia stem cells that is finely regulated through dopaminergic signaling [37]. Neurons can be replaced even if as much as a third of one brain hemisphere is removed [38], and all neuronal subtypes are apparently replaced in their correct proportions [39]. However, even in salamanders, these neurons fail to reestablish long-range neuronal connections (millimeters) [39].

In contrast to the relatively effective brain repair of salamanders, injury-induced production of neurons in quiescent regions is very restricted in the mammalian brain. This poses great limitations to the possibility of achieving satisfactory functional recovery. Mammals and amphibians also diverge in the context of scar formation. Shortly after damage to the mammalian, but not the amphibian, central nervous system, astrocytes and pericytes are recruited to build a scar that seals the site of damage, and separates it from the remaining, viable tissue. Astrocytes undergo a process of reactive gliosis, during which they become hypertrophic and extend their processes to form a physical and chemical barrier between lesioned and intact tissue [40]. Pericytes are responsible for extracellular matrix deposition and formation of connective tissue, which further encapsulates the lesion [41]. In the acute phase after a brain insult, the scarring process seems to prevent spreading of damage. However, it may, in the long run, hinder formation of new connections, and eventually restoration of functional neural networks. Interestingly, when salamander organs are subjected to insults, they do not form scars that segregate damaged regions from the intact tissue [42]. Thus, absence of scarring processes may partly explain the greater regenerative potential seen in amphibian brains.

One additional limitation to successful neuronal replacement is that axons regrow very poorly in the central nervous system. This is in part because many neuronal subtypes in the central nervous system form poor growth cones at the tip

of their regrowing axons, which hampers their successful outgrowth [43]. But in addition to such neuron-intrinsic limitations, poor axonal regrowth is also a product of the environment of the central nervous system. The scar that forms around an injury constitutes a chemical barrier that inhibits axonal regrowth [44]. But even in the healthy central nervous system, axonal regrowth is poor, as demonstrated by observations of peripheral neurons attempting to grow their axons into the spinal cord [45]. In the peripheral nervous system, severed axons regrow much more effectively. One explanation for poor axonal growth in the central nervous system is that axons here are not myelinated by Schwann cells, as they are in the periphery. Schwann cells have an important role in guiding regrowing axons [46]. In the central nervous system, axons are myelinated by oligodendrocytes, which do not have this guiding role. In fact, central nervous system neurons whose axons project into the periphery, such as lower motor neurons, can regrow their Schwann cell-ensheathed axons if they are severed in the periphery [47].

Injury-induced neurogenesis has been recorded, though limited, in a few regions of the adult mammalian brain, including the striatum and the hypothalamus [48, 49]. Reports have suggested that neurogenesis may also occur in the rodent neocortex, though findings remain, to this date, controversial [50]. The regenerative process may involve actual stem cells resident in the neurogenic niche, which migrate towards sites of damage. It may also call into play cells that are not normally identified as self-renewing, multipotent cells. These are defined as potential stem cells, which play other, unrelated roles in the healthy brain, but start proliferating and generating neurons following injury. Parenchymal astrocytes have been identified as a source of quiescent stem cells, which support neuronal functioning during tissue homeostasis, but can engage in neurogenic programs following damage [48].

18.1.2.4 Stimulating Endogenous Neurogenesis After Stroke

Reactive neurogenic activity has been recorded by several research groups following ischemic insults (Fig. 18.4). Studies have, for instance, implicated cells from the germinal niche, which engage in proliferative programs and migrate towards sites of damage. Astrocyte-like NSCs from the SVZ have been shown to undertake a regenerative response after an ischemic injury in rodents [51]. This mainly occurs in the striatum, a region that in humans is commonly afflicted by stroke. Additionally, ependymal cells, which are co-inhabiting the SVZ but do

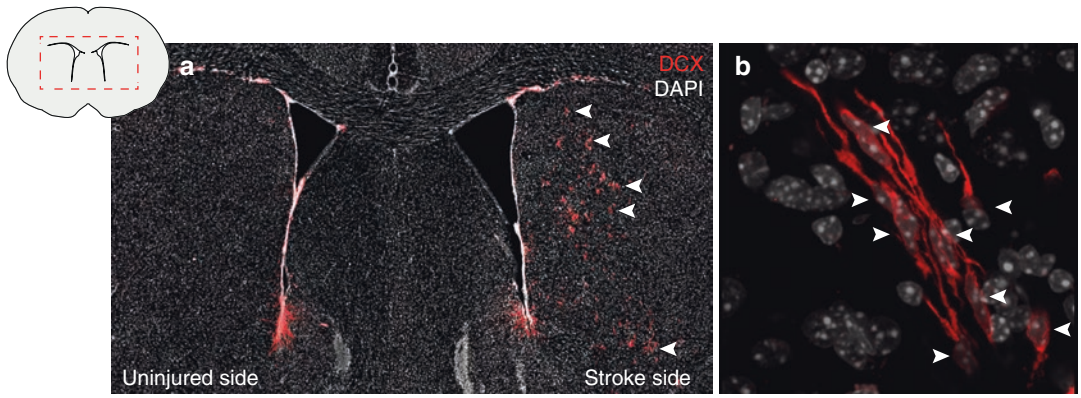

Fig. 18.4 Stroke-induced neurogenesis in the mouse striatum. A coronal section from a stroke-injured mouse brain was imaged 7 weeks after the experimental stroke, which was inflicted using transient middle cerebral artery occlusion. Neuroblasts have appeared in the ischemic striatum (**a**; arrowheads highlight examples of neuroblasts). The panel in (**b**) shows a magnification of migrating striatal neuroblasts (arrowheads highlight individual neuroblasts). Such stroke-induced striatal neuroblasts derive from both the nearby subventricular zone and from local striatal astrocytes

not normally display neurogenic activity, seem to give rise to astrocytes and neuroblasts after stroke in mice [52].

Interestingly, neurogenic responses may become evident outside of the canonical germinal niches. There, parenchymal astrocytes that are conventionally busy coordinating neuronal communication and other homeostatic processes, may reveal an intrinsic, otherwise quiescent potential for neurogenesis [48]. Similar to NSCs of the neurogenic niches, striatal astrocytes undergo a proliferative phase, during which they upregulate the proneural transcription factor Ascl1. Transit amplifying cells expressing Ascl1, subsequently, turn into clusters of DCX^+ neuroblasts. With the end of cell division, astrocyte-originated neuroblasts assume the form of migrating cells that translocate to sites in the tissue where they complete maturation into neurons. Further research will elucidate whether addition of astrocyte-derived neurons may be sufficient for neural networks to repair themselves and achieve detectable functional recovery. Additionally, future investigations will help understanding whether human astrocytes can also be forced towards neuronal lineages and, thus be considered for development of stem cell-based therapies. In support of this view, both Arsenijevic and colleagues [53] and Palmer and Gage [54], have identified a population of progenitors in the human cortex, which displayed potential for multilineage differentiation in cultures. The study, however, did not detect the identity of these progenitor cells, nor were the findings confirmed by other reports [55, 56].

While stroke-induced striatal neurogenesis has been demonstrated in a series of independent studies, it remains to be clarified whether neuronal replacement also occurs in other regions of the injured mammalian brain. Recent investigations have proposed that a cortical lesion may redirect migration of NSCs from the SVZ towards sites of damage [57]. Once in the cortex, however, the neural progenitors show propensity for an astroglial lineage fate. Similar to striatal glia, parenchymal astrocytes residing in the cortex may also harbor neurogenic potential, which may be revealed following injury. In line with this perspective, Sirko and colleagues [42] showed that astrocytes isolated from cortical regions subjected to stab wound injury, are able to form neurospheres, which are indicative of their multilineage potential in vitro. The authors, however, did not see the same response in vivo, perhaps demonstrating a hostile cortical microenvironment that prevails over intrinsic neurogenic capabilities of astrocytes. Other investigations have proposed the occurrence of neuronal turnover in the cortex, following an ischemic insult [58], although findings remain, to this day, controversial. Most importantly, while histological analysis and ^{14}C dating could demonstrate occurrence of striatal neurogenesis in healthy human brains [24], neuronal turnover in cortical regions could not be detected, neither in healthy subjects [7] nor in patients afflicted by stroke [59].

18.1.2.5 Therapeutic Implications of Endogenous Neurogenesis

Stroke is one of the major causes of death and long-lasting adult disability in the world. Cognitive and motor impairments derive from extensive neuronal death, associated with loss of cerebral blood flow. This underscores the importance of developing therapeutic strategies that are aimed at replacing neurons lost to injury to allow recovery of function. In fact, an advantage of treatments that focus on promoting endogenous neurogenesis concerns their extended therapeutic window. Indeed, thrombolytic treatments, which can be used in a subset of patients afflicted by stroke, will only be effective if administered within hours after an ischemic episode has occurred. In reality, a small portion of victims of a cerebrovascular insult qualifies for this therapeutic option. By contrast, stimulation of endogenous regenerative processes may still be effective throughout the chronic phase after stroke, which is mostly associated with remodeling and reorganization of surviving cells. Indeed, while proliferation of SVZ cells occurs in the first 2 weeks after stroke in rodents, migration of neuroblasts into the ischemic region has been recorded for as long as 16 weeks later [60]. Notably, approaches that rely on regeneration of

affected regions of the brain may also involve transplantation of neuronal progenitors, obtained for instance from embryonic sources or reprogramming of the patient's own cells. These therapeutic strategies are discussed in the next chapter.

Several preclinical investigations have, so far, supported the idea that the adult mammalian brain remains capable of stroke-induced remodeling and regeneration, at least to some extent. Clinical evidence, however, suggests that processes of reactive neurogenesis possibly occurring in the brains of patients afflicted by an ischemic insult are still not sufficient to achieve satisfactory recovery. The limited impact that endogenous neurogenesis has on functional recovery may derive from several issues. On the one hand, it is possible that contribution of actual (and potential) stem cells is too restricted, at least in terms of numbers of newly generated neurons. On the other hand, it remains to be clarified whether young neurons can effectively integrate in the pre-existing circuits and, in fact, recover function of cells lost to injury. Therapeutic strategies that focus on promoting repair based on endogenous neurogenic processes may thus try to tackle and improve these aspects of injury-induced regeneration.

A significant portion of neural progenitors generated by NSCs after stroke dies before achieving full neuronal maturation. Arvidsson and colleagues estimated that new neurons had replaced only 0.2% of dead neurons 6 weeks after stroke in rats [51]. However, in a follow-up study, the authors found that the neurogenic response still continued 1 year after stroke [61], making it possible that neuronal replacement had become about an order of magnitude higher at this time point. Although it remains unclear to what extent lost neurons should be replaced in order to achieve significant neural circuit restoration, new therapies may focus on boosting proliferation, differentiation, and survival of newly created progenitors. For this purpose, one may target molecular cues that have been implicated in the regulation of endogenous neurogenesis, such as Notch and BMP signaling [62]. Alternatively, ectopic manipulation of mitogens and neurotrophic factors, such as EGF and BDNF, have shown to enhance proliferation of progenitors, as well as survival of neuronal cells in the striatum [63]. In order to achieve recovery of function, proliferating neural progenitors may also need to give rise to region-appropriate neuronal cell types that are depleted after stroke. Interestingly, Arvidsson and colleagues [51] have shown in rats that neuroblasts originating from the SVZ migrate to striatal injury sites, where they mature into medium spiny neurons, the most commonly affected neuronal population. Studies in mice, on the other hand, have shown that stroke-induced neurogenesis primarily replenishes calretinin-expressing interneurons, rather than the neuronal subtypes that were lost [64].

For effective functional integration to occur, one also needs to consider the complex network of connections established among neurons in a circuit. Communication between neurons wired together occurs through spreading of electrical stimulation that travels from one cell to the next. This electrical activity makes up behavior. Newly generated neurons need, therefore, to find their place in the circuitry and properly connect to neighboring cells, in order to compensate for the loss of activity that follows stroke-induced neuronal death. The first experimental evidence of functional integration of newly generated striatal neurons comes from studies carried out by Hou and colleagues [65]. The authors could demonstrate that new neurons form synaptic structures reminiscent of pre-existing connections. They furthermore showed that neurons generated after stroke are integrated in the surrounding circuitry, being able to collect input from presynaptic cells, and fire action potentials to the neighboring neuron. Notably, the process of scar formation may be relevant to further enhancing this aspect of regeneration: Certain aspects of the scarring processes, such as the formation of a physical barrier and deposition of extracellular matrix, may indeed prevent axons of new cells from sprouting and reorganizing into the lesioned tissue [66]. Taken together, preclinical investigations are promising and have repeatedly demonstrated that there are ways of boosting endogenous neurogenic processes to

improve cell replacement after ischemic injuries, which may become feasible to employ as therapeutic strategies in the future.

It may sound self-evident that new neurons could mediate improved brain repair after injury. However, the mechanism by which such improvement would occur is not obvious. There are several ways in which new neurons could have an impact on spared neuronal circuits. Perhaps the most straightforward way is that each lost neuron would be replaced with a new one of exactly the same subtype—that the neuronal replacement strategy is so perfect that all lost neuronal subtypes are regenerated in their correct proportions. It is indeed possible to imagine future scenarios where stem cell differentiation protocols are refined to the extent that it is possible to generate all types of neurons required. However, this on its own will not be enough to restore the brain to its pre-injury state, because of two reasons. The first is that neuronal function is dependent on neuronal connections. Perfect replacement of neurons therefore requires perfect replacement of all their connections. This will likely be very difficult to achieve because the patterning signals that guided neural connectivity during brain development are largely absent in the adult brain. For this reason, neuronal connections—particularly long-range connections—are likely difficult for new neurons to reestablish. The second reason why neuronal replacement will not be enough to perfectly restore brain function is that brain injury leads to extensive scarring and tissue remodelling. To restore a chronic stroke lesion to its former state would therefore require biological tissue engineering on an altogether different scale than what seems realistic today. For these reasons, neuronal replacement is more likely to have beneficial effects through other mechanisms than direct replacement:

One possibility is that new neurons improve circuit function through the neurotransmitters they secrete. For example, in transplantation strategies to treat Parkinson's disease, dopaminergic neurons are grafted to the striatum, where dopamine is needed—even though dopaminergic neurons are normally located in the substantia nigra, far from the striatum [67]. The important thing with this neural transplantation strategy is that dopamine levels are restored in the striatum, even though pre-existing neuronal connections are not recreated. The same strategy may be applicable for other damaged circuits.

Another possibility is that new neurons act like relays that indirectly reconnect two spared neurons that used to be directly connected to each other. This has been shown to occur in a rat model of spinal cord injury, where transplanted NSCs developed into neurons that received synaptic connections from cortical motor neurons, and themselves developed projections that targeted neurons distal to the lesion [68].

A third possibility is that regeneration strategies focus only on generating interneurons. Although interneurons constitute only 10–15% of all neurons in the rodent brain [69], they are capable of modulating the output of surrounding neurons [70], such that their impact on neural circuits is large compared to their small numbers. This suggests that it might only be necessary to generate a small number of interneurons to achieve a significant functional impact on brain function. As described above, the few neurons generated in the rodent striatum in response to lesions are primarily interneurons [48, 64], which suggests that this is the strategy actually employed by the healing striatum. One study estimated that a few hundred interneurons had been generated 7 weeks after stroke in mice [48]. In another study, a similar number of transplanted interneurons were shown to have a beneficial effect on functional recovery in a mouse model of Parkinson's disease [71]. Therefore, even a small number of interneurons may be enough to promote some level of functional recovery after brain injury.

18.2 Conclusion

Today, research on therapeutic neuronal replacement is still in its infancy. New studies need to promote neuronal replacement in regions other than the striatum, either through stimulation of local neurogenic programmes or through redirection of migrating neural progenitors. Neocortical regions are relevant targets for new (pre-)clinical

investigations, due to their common involvement in stroke-related pathology and their implication in long-lasting cognitive deficits and motor impairments. Additionally, the field of regenerative neuroscience needs to develop safe and selective therapies that precisely tackle the process and/or cell population of interest, without unwanted, off-target effects. As our understanding of the molecular mechanisms that regulate NSC behavior improve and strategies for clinical delivery are refined, technologies to restore cognitive and motor function will continue to develop.

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19 Mechanism of Recovery After Stroke

Seong-Ho Koh

Abstract

Stroke is one of the biggest health problems in the world, especially considering the aging global population**.** Stroke causes diverse neurological sequelae, for which there is still no cure. In the clinic, it is not rare to see patients showing improvement in their neurological sequelae several weeks or months after stroke compared with their status in the early post-stroke stages. These phenomena are thought to be associated with the natural recovery process after stroke. The exact mechanisms underlying this recovery process are not yet known, but several plausible mechanisms have been suggested. The first is synaptic plasticity, which occurs through the processes of axonal sprouting and synaptogenesis. These processes occur in the peri-infarct area of the brain, but can sometimes be seen in the contralateral hemisphere. The second mechanism is neurogenesis, which arises from endogenous neural stem cells in the subventricular zone and the dentate gyrus in the hippocampus. In this chapter, the suggested plausible mechanisms underlying the natural recovery process that occurs after stroke will be discussed.

Stroke is one of the most common diseases leading to long-term disability worldwide. As such, many patients suffer from the sequelae of stroke, which are a result of the damage done to a large portion of the brain by stroke. Although uncountable clinical trials have been performed with the aim of enhancing recovery of neurological functions after stroke, almost all of them have failed. As a result, there is currently no definitive treatment for the sequelae associated with stroke. Therefore, we can only prescribe medicine as a secondary prevention after the occurrence of a stroke, but not for the treatment of its sequelae. In many cases, however, patients with stroke show substantial spontaneous improvement in neurological functions at discharge or months after the stroke compared with their functions at admission or days after the stroke (Fig. 19.1). If we can elucidate the exact mechanism of recovery after stroke, it might be possible to design new therapeutic strategies for stroke and its sequelae. In the present chapter, the plausible mechanisms involved in recovery after stroke will be reviewed based on published reports. The two most important mechanisms of recovery after stroke are thought to be plasticity and neurogenesis in the brain (Fig. 19.2).

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19.1 Plasticity of the Brain After Stroke

Plasticity of the brain is considered to be one of the most important mechanisms involved in the recovery process after focal brain injury. The concept of "plasticity" in the brain was initially suggested more than 50 years ago based on the finding that repeated learning led to behavioral adaptation through an increase in synaptic efficacy in animals [1]. Many researchers have confirmed that enriched environments and skill learning enhance synaptogenesis via growth of dendrites and increase in the number of dendritic spines, and that long-term potentiation and long-term depression are directly associated with changing synaptic efficacy [2]. Therefore, plasticity indicates changes in neural networks that often result in behavioral consequences.

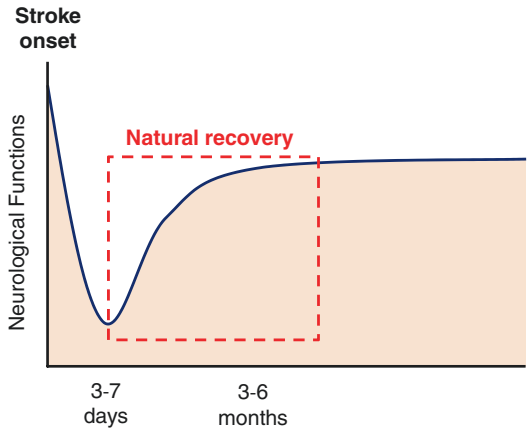

Fig. 19.1 Natural recovery after stroke. Neurological functions usually deteriorate after stroke, and this deterioration is typically maximized within 7 days after stroke. However, neurological functions often improve with time. This phenomenon is called natural recovery

It has been shown that plasticity can occur in the human brain during the recovery period after focal brain injury, as well as during the motor learning process [3]. In detail, recruitment of secondary motor areas was increased after projections from the primary motor cortex to spinal cord motor neurons were damaged by focal brain injury, and a higher level of recruitment was associated with better functional outcome in patients with chronic stroke [4, 5]. It has also been reported that some secondary motor areas can take on new functions during the recovery process after focal brain injury [6]. Especially, the ipsilesional dorsolateral premotor cortex was proposed to behave as an "executive" motor region similar to the primary motor area [6]. Another suggested mechanism to explain the recovery process after stroke is that the injured brain could use other surviving structures and networks that can generate motor signals, other than secondary motor areas, through plasticity [6].

In addition to the role of the ipsilateral hemisphere after stroke, a number of imaging studies

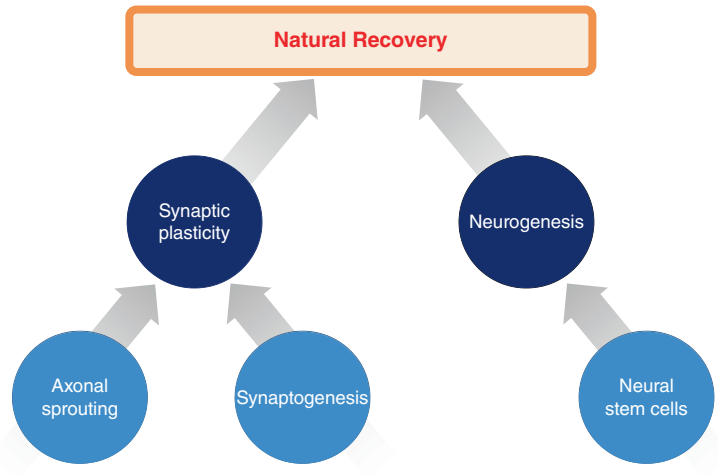

Fig. 19.2 Plausible mechanisms of natural recovery. Natural recovery is thought to occur due to synaptic plasticity and neurogenesis after stroke. Synaptic plasticity is achieved by axonal sprouting and synaptogenesis. Endogenous neural stem cells are thought to contribute to neurogenesis

have demonstrated that bilateral networks are more activated in recovering patients than in healthy controls [7, 8]. This finding suggests that the unaffected hemisphere can help patient recovery after stroke through plasticity, albeit to a limited extent. This suggestion is also supported by longitudinal studies confirming that both hemispheres are involved in recovery from stroke affecting motor and language functions: one study was about strokes that affected motor functioning [9], and the other investigated aphasia associated with subcortical stroke [10]. The studies revealed that increasing performance after stroke is correlated with an increase in activation in the respective networks. For example, chronic aphasic patients with increased activation in Wernicke's homologue showed improved language performance [11]; stronger activation in language-related areas in both hemispheres was correlated with improvement of acute aphasia [10]; and simultaneous electromyography and functional magnetic resonance imaging (fMRI) revealed that bilateral recruitment of premotor and motor areas is related to recovery after acute stroke affecting motor functions [12]. Considering these findings, it seems reasonable to conclude that the unaffected hemisphere positively affects the recovery process after stroke.

On the contrary, however, there are findings against this hypothesis. Some studies have shown that poorer recovery after stroke was markedly correlated with stronger involvement of the unaffected hemisphere [6, 13, 14]. Two explanations for this phenomenon can be proposed. First, patients with lesions to areas of the brain more essential for motor and language might have to depend more highly on contralesional areas to effectively compensate for damaged areas. Second, even if contralesional areas initially positively contribute to the recovery process after stroke, their lasting activation might result in a maladaptive process due to interhemispheric inhibition and could impair more complete recovery. The existence of this negative impact caused by recruitment of the unaffected hemisphere has been supported by several studies using repetitive transcranial magnetic stimulation (rTMS), which can suppress activity in the brain. These studies suggested that suppression of the unaffected hemisphere by rTMS resulted in an improvement in language and motor tasks during the recovery period after stroke [15, 16].

Although there is still some disagreement about the role of the unaffected hemisphere in the recovery process, it seems likely that involvement of the contralesional hemisphere occurs during the recovery process. It has also been reported that the affected and unaffected hemispheres have different recovery time courses. The unaffected hemisphere showed a relatively early upregulation in activity, while the activity of the affected hemisphere was upregulated after the unaffected hemisphere had already normalized [17, 18]. In detail, the entire neural network is depressed just after stroke, and then the activity of the unaffected hemisphere is upregulated and overactivated. Bilateral normalization of activation in most task-related areas follows these phases. During this normalization phase, new network balances in the remaining, non-lesioned portions of the brain seem to be established to recover functions after stroke [17, 18]. However, the precise timing of the events that occur during the recovery period after stroke should be addressed.

Although the exact mechanisms underlying plasticity in the human brain after stroke have not yet been fully elucidated, many studies have suggested that an increase in synaptic efficacy and synaptogenesis could contribute to plasticity and then to recovery after stroke [19]. Here, we outline a diverse number of possible mechanisms thought to underlie plasticity based on numerous studies on the subject.

Cortical plasticity has been observed in many experiments for decades. For a better understanding of cortical plasticity, the development of the brain needs to be further studied. Behavioral experience is the most well-known potent modulator of cortical structure and function [20]. Namely, repetitive behavior and temporal coincidence for skilled motor activities are thought to induce cortical plasticity through axonal sprouting. Repetition of certain behaviors provokes the maturation of thalamocortical connections via two distinct phases. The first phase occurs when

the spontaneous neural activity generated by repetitive behavior increases the expression of axonal guidance molecules, including brain-derived neurotrophic factor (BDNF), so that thalamocortical axons are directed to their cortical targets. The second phase involves continuous cortical activity that causes axonal sprouting within the cerebral cortex [21]. In the past, long-range axonal sprouting was not thought to occur in the adult brain; however, it was recently discovered that injury to the brain can induce axonal sprouting even in adults. For example, axonal sprouting was confirmed to occur after focal cerebral infarction [22]. Now, it is well accepted that the adult brain has a notable capacity to recover following injury through a phenomenon called spontaneous recovery. While spontaneous recovery occurs after injury, behavioral compensation might contribute significantly to the recovery process [23]. For example, when patients have hemiparesis, they use compensatory movements of the trunk during reaching movements [24]. These compensatory movements could change the topography of the brain. For example, the increased use of a proximal limb with impaired digits induces a redistribution of forelimb representation: digit representations are reduced while proximal representations are enlarged [25]. Neural plasticity in the adjacent and intact cortex plays an important role in these processes and in spontaneous recovery after focal stroke. There is a plethora of evidence suggesting that adjacent regions of the cortex compensate for the damaged area. Nudo and Milliken induced focal brain injury to the area of thumb representation in monkeys. After a certain period of spontaneous recovery, it was confirmed that the brains were remapped, and the thumb area reappeared in the adjacent and undamaged cortex [26]. Similar findings have been suggested in humans: the intact, peri-infarct cortex is thought to play a critical role in the recovery process after focal brain injury [27]. Moreover, motor representations in the damaged hemisphere are enlarged after several weeks of rehabilitation [28].

Neuroanatomical alterations are also found in the peri-infarct cortex. In vivo studies using animals with cerebral infarction showed increased GAP-43 immunoreactivity between 3 and 14 days post-infarct [29], and local sprouting and synaptogenesis were elevated between 14 and 60 days post-infarct [30]. With regard to blood supply, arteriolar collateral growth and the number of new capillaries also increased in the peri-infarct area [31]. To date, there have been many suggested mechanisms of axonal sprouting and synaptogenesis. Axonal sprouting and synaptogenesis can occur to help compensate for neuronal loss after stroke. Understanding the mechanisms of synaptic plasticity in the entorhinal/dentate circuit in normal conditions could make it easier to explain the mechanisms regulating axonal sprouting and synaptogenesis in the brain after stroke. Synaptogenesis can naturally occur in the fiber systems of neural circuits through the spatial arrangement of inputs. CA4 synapses extend distally to the granule cell dendritic tree, and septal cholinergic synapses decrease their domain to the entorhinal zone. This synaptogenesis is followed by a sequence of events: [1] CA4 fibers invade the regions controlled by entorhinal inputs, and then [2] the dendritic tree grows outward from the cell body, which causes the migration of CA4 fibers toward the outer molecular layer [32]. When stroke occurs in the mature brain, this growth process starts in a damaged system. The old system is coordinated with the initiation of growth and the formation of new synapses. Neuronal growth requires at least four extrinsic conditions. The normal process underlying neuronal growth occurs as follows: the first step is glial involvement in clearing degenerated tissue; the next step involves an increase in the expression of neurite outgrowth-promoting factors; the third step is establishment of the new composition of the extracellular matrix and expression of cell-adhesion molecules; and the last step is targeting and synapse formation and the expression of molecular systems regulating neurotransmitter release and proper postsynaptic receptors. During this process, the proper expression of neurotrophic factors and cell-adhesion molecules plays critical roles in axon sprouting and regeneration. These diffusible factors are synthesized either by target neurons or by the surrounding glia and

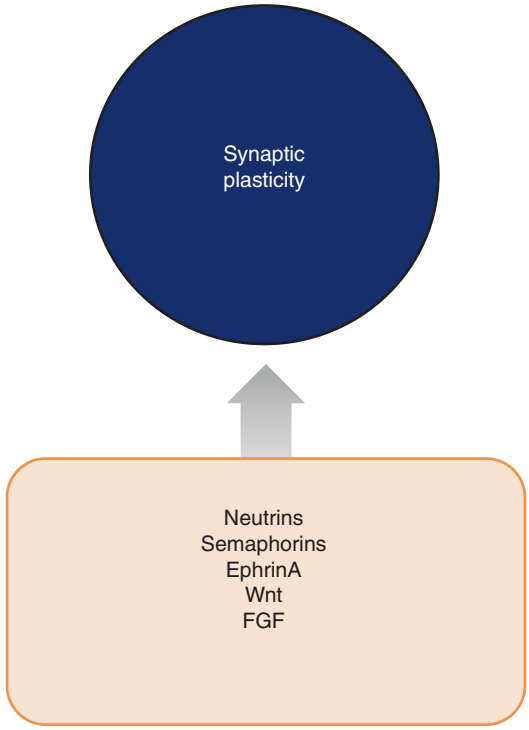

Fig. 19.3 Factors contributing synaptic plasticity. Neutrins, semaphorins, ephrinA, Wnt, and fibroblast growth factor (FGF) are well-known contributors to synaptic plasticity

have a wide range of activities, including the ability to guide axonal projections to their correct targets, promoting neuronal differentiation and maturation, and helping the formation of functional synaptic junctions (Fig. 19.3) [33]. Neutrins, semaphorins, and ephrinA are well-known molecules that can induce axonal sprouting, but their direct functions have not yet been fully established [33]. The Wnt and fibroblast growth factor (FGF) families, which are secreted by neurons and other neuronal cells, are also involved in axonal sprouting and synaptogenesis [33]. Neurotrophins, such as BDNF, can also cause neuronal maturation. BDNF is known to directly control synaptogenesis, so it is considered to be a synaptogenic priming molecule [33]. Other glial cell-derived factors have also been shown to increase axonal sprouting and synaptogenesis. Cell-adhesion molecules (CAMs) are important in guiding synapse specificity. Several classes of CAMs play crucial roles in the formation of synapses via target recognition. Cadherins and protocadherins are the most famous examples: cadherin-6, cadherin-8, and N-cadherin guide subclasses of axons to their targets. In addition, neuronal activity-regulated pentraxin (Narp), Ephrin B1, Syn CAM, and neuroligin can trigger synaptogenesis. All of these molecules enhance axonal sprouting and synaptogenesis through diverse and complicated signaling pathways.

Axonal sprouting occurs through many complex steps. Briefly, two distinct steps have been fully elucidated. First, stroke induces dendritic changes. After stroke, it is well established that dendritic spines undergo remodeling in the peri-infarct area. Both the number of dendritic spines and the spine turnover rate increase within the first 2 weeks after stroke in the peri-infarct area, and these changes are known to contribute to rapid synaptogenesis. Second, neurons located in the peri-infarct area extend branches and form new connections after stroke. Sometimes, this axonal sprouting can occur in long descending pathways and give rise to the formation of new local circuits, long-distance intracortical connections, and long, descending projections to the spinal cord [34]. Synaptogenesis occurs at the same time as axonal sprouting, but does not occur separately from this process. The mechanisms underlying synaptogenesis after stroke are as follows: membrane trafficking associated with presynaptic assembly starts in the presynaptic neurons in the peri-infarct area after stroke; membrane trafficking associated with postsynaptic assembly follows; and the new synapses mature [33].

19.2 Regeneration of the Brain After Stroke

Another possible mechanism for functional recovery after stroke is regeneration of the damaged brain by endogenous neural stem cells, although this contribution might be small. The regeneration of the brain by neural stem cells is a process that was only recently confirmed. As

recently as several decades ago, regeneration of the brain was not considered to be possible. Since it was discovered that there are multipotent, self-renewing progenitor cells and stem cells in the brain [35], many studies have confirmed the existence of neural stem cells in various areas of the brain and of endogenous neurogenesis in the adult brain [36].

Endogenous neural stem cells located in the subventricular zone and the subgranular zone of the hippocampus can be activated by diverse stimuli. Stroke is one of the well-known stimuli that can activate neural stem cells. When stroke occurs in the brain, several types of cytokines are released from damaged neurons and glial cells and induce regeneration of the brain by endogenous neural stem cells. For example, stromal cell-derived factor 1-alpha is a strong activator of stem cells, including neural stem cells. Activated neural stem cells can proliferate and differentiate into various neuronal cells, such as neurons, ependymal cells, astrocytes, and oligodendrocytes, to replace damaged cells. However, neural stem cells can be damaged depending on the severity, size, and location of stroke [37]. In addition, hypoxia and ischemia can result in a change in the differentiation of neural stem cells so that they differentiate into glial cells rather than neurons [38, 39]. This so-called gliosis definitely inhibits functional recovery after stroke, especially at the chronic stage. Damage to neural stem cells might explain the lower functional recovery sometimes seen in patients who experienced a large stroke or damage to the brain that includes the subventricular zone where neural stem cells exist [40]. Therefore, regeneration of the brain by neural stem cells could contribute to the recovery process after stroke if the stroke does not affect the areas where neural stem cells are located.

However, we still do not understand the mechanisms contributing to the regeneration of the brain by neural stem cells after stroke, and only hypothetical suggestions have been proposed (Fig. 19.4). One of the most well-known proposed mechanisms is the phosphatidyl-inositol 3 kinase (PI3K) pathway. The PI3K pathway plays critical roles in cell proliferation, growth, differentiation, motility, survival, and intracellular trafficking. The PI3K family includes three different classes based on the primary structure, role, and in vitro lipid substrate specificity of the molecules. The Class I PI3Ks are the most well-characterized to date and are further divided into two types: Class IA (p110α, p110β, and p110δ) and Class IB (p110γ). The PI3K pathway interacts with the insulin receptor substrate (IRS) and is associated with the tumor suppressor phosphatase and tensin homolog (PTEN), which can inhibit members of the PI3K family. When PI3Ks are activated, they phosphorylate the hydroxyl group in the third position of the inositol ring of phosphatidylinositol (Ptdlns), so that Ptdlns [4, 5] P_2 becomes Ptdlns [3–5] P_3. Ptdlns [3–5] P_3 in

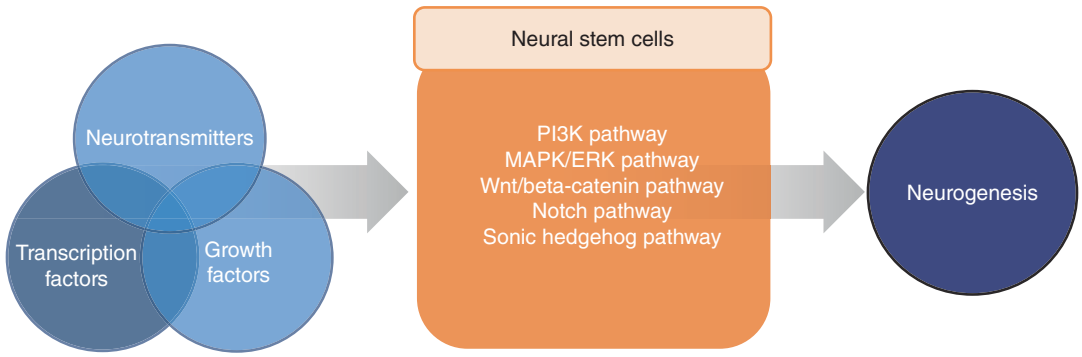

Fig. 19.4 Neurogenesis from neural stem cells. Neural stem cells are activated after stroke, and this activation is affected by diverse growth factors, neurotransmitters, and transcription factors. These molecules induce neurogenesis through the activation of various pathways, such as the PI3K pathway, the MAPK/ERK pathway, the Wnt/beta-catenin pathway, the Notch pathway, and the Sonic hedgehog pathway

turn phosphorylates many downstream effectors, including Akt. Phosphorylated (activated) Akt controls glycogen synthase kinase (GSK)-3β and mammalian target of rapamycin (mTOR), nuclear factor kappa–light-chain-enhancer of activated B cells (NF-kB), endothelial nitric oxide synthase (eNOS), S6 kinase, forkhead box O (FOXO)s, and BAD. These downstream effectors are involved in cell growth, DNA translation, cell-cycle regulation, glucose metabolism, DNA repair, and inhibition of apoptosis [41]. Because of the importance of the PI3K pathway, chemicals affecting this pathway are under a high amount of scrutiny. IRS-1 substrate and platelet-derived growth factor receptor^{740}Y-P (PDGFR^{740}Y-P) activate this pathway and enhance neuronal cell survival and differentiation of NSCs. The role of the PI3K pathway in cerebral infarction has been well established. Ischemia can affect this pathway depending on its duration. The PI3K pathway is activated just after ischemia, but becomes inhibited as the duration of ischemia increases [41]. As described above, the inhibition of the PI3K pathway means PI3Ks cannot control critical signaling proteins that contribute to cell survival, proliferation, differentiation, and so on. Therefore, there has been much effort to develop PI3K activators for the treatment of stroke [41]. The role of the PI3K pathway in the regulation of NSCs is important. The PI3K pathway directly controls the proliferation, differentiation, and migration of endogenous NSCs. BDNF, FGF, SDF-1a, and many other neurotrophic factors can activate the PI3K pathway in NSCs. The activated PI3Ks strongly increase the survival, proliferation, and migration of NSCs. It is well known that many neurotrophic factors are released in the infarct and peri-infarct areas. Therefore, it is likely that the neurotrophic factors released after stroke activate NSCs, and the activated NSCs can contribute to the regeneration of the brain and the recovery process after stroke.

Another important signaling pathway is the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway. ERKs are involved in the regulation of meiosis, mitosis, and postmitotic functions in NSCs. The ERK pathway can be activated by many growth factors, cytokines, and other molecules. Ras, c-Raf, mitogen-activated protein kinase, and MAPK are upstream signaling proteins involved in the activation of ERKs. Activated ERKs increase the expression of many different transcription factors. These alterations affect the cell cycle and proliferation of NSCs. Focusing on the effect of the ERK pathway in stem cells, it has been shown that Erk signaling induces cell differentiation. Specifically, FGF activates ERKs, and the activation of ERKs provokes the differentiation of stem cells. This finding was confirmed in previous studies showing that inhibition of either the FGF receptor or ERKs eliminates neuronal differentiation of stem cells [42]. As described earlier, the release of FGF increases in the brain after stroke, which in turn enhances the neurogenesis caused by neural stem cells.

The Wnt/beta-catenin pathway is also involved in adult neurogenesis. Wnt3 is highly expressed in dentate gyrus hilar cells, and Wnt is reported to mediate neuroblast proliferation and neuronal differentiation via the beta-catenin pathway. This finding was confirmed by a study suggesting that inhibition of Wnt resulted in a marked decrease in neurogenesis [43]. NeuroD1, a pro-neurogenic basic helix-loop-helix (bHLH) transcription factor, is a downstream mediator of Wnt-induced neurogenesis. A study of NeuroD1 conditional knock-out mice showed that NeuroD1 is necessary for neurogenesis in the brain [44].

The Notch pathway is one of the most important signaling pathways in cell proliferation, differentiation, and apoptosis. Activation of the pathway begins with the binding of ligands to Notch receptors, which are single-pass transmembrane heterodimers. When ligands bind to the receptor, gamma-secretase mediates cleavage of the transmembrane domain, and the notch intracellular domain (NICD) is released into the cytosol. NICD forms a complex with the DNA-binding protein RBPj by translocating to the nucleus. The NICD–RBPj complex induces neurogenesis. It has been confirmed that the Notch pathway also plays vital roles in adult neurogenesis. Notch controls NSCs by promoting cell cycle exit and decreasing the adult neural

progenitor pool [44]. Notch 1 is also known to be important in dendritic arborization of immature neurons in the adult brain.

The Sonic hedgehog (Shh) pathway was discovered to participate in cell differentiation during the development period of the brain. Shh is a soluble extracellular signaling protein, and it activates the Shh pathway via a receptor complex consisting of the transmembrane receptor protein patched (Ptc) and its G protein-coupled co-receptor smoothened (Smo). Shh is now considered to be involved in neuronal differentiation in many different areas during development of the nervous system. Shh also regulates cellular migration in the adult brain, as well as self-renewal and proliferation of NSCs [44]. Defects in the Shh pathway in mice resulted in defective hippocampal neurogenesis.

Various growth factors and neurotrophic factors contribute to neurogenesis in the adult brain. For example, nerve growth factor (NGF), BDNF, neurotrophin 3 (NT-3), and neurotrophin 4/5 (NT-4/5) are famous neurotrophic factors. These factors bind to three different Trk receptors: NGF binds to TrkA; BDNF and NT-4/5 to TrkB; and NT-3 to TrkC. The binding of these factors to their respective receptors leads to activation of a diverse range of signal transduction cascades, which then induces neurogenesis in the hippocampus and enhances the survival of neurons [44]. The term growth factors refer to extracellular proteins that promote cell growth and maintenance. To date, fibroblast growth factor-2 (FGF-2), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) are the most well-known. These growth factors provoke neurogenesis through activation of the PI3K pathway and the Ras/Raf/Mek/Erk pathway as described above.

Neurotransmitters are small diffusible molecules that play a role in the chemical communication between neurons. Neurotransmitters are also known to be associated with proliferation, differentiation, and synaptic integration of adult neural progenitor cells. In addition, they aid neurogenesis. Glutamate, GABA, and dopamine are known to take part in neurogenesis in the adult brain. Glutamate is an excitatory neurotransmitter that can bind to NMDA, AMPA, kainic acid, and metabotropic glutamate receptors. Through binding to the NMDA receptor, glutamate induces the survival, proliferation, migration, differentiation, and appropriate functional integration of neuroblasts. AMPA and kainic acid receptors are also known to be involved in neural progenitor cell proliferation and neurogenesis [44]. GABA, the main inhibitory neurotransmitter, is necessary for neurogenesis. Especially, reactions with the $GABA_A$ receptor enhance neurogenesis by controlling neural stem cell proliferation. Dopamine is a catecholamine neurotransmitter and is critical in modulating movement. Recently, it was suggested that dopamine increases the proliferation of neural stem cells in the adult subventricular zone.

Transcription factors, such as cAMP response element-binding protein (CREB), paired homeobox transcription factor 6 (Pax6), Ascl1 (Mash1), distal-less homeobox 2 (Dlx2), Tlx, Sox2, Emx2, and Tbr2, have also been linked with neurogenesis. CREB is a fundamental regulator of cellular growth and development. Phosphorylation of CREB by cAMP increases neurogenesis by stimulating neural stem cell proliferation. In addition, CREB is also known to be involved in the survival, migration, and differentiation of NSCs. Pax6 is vital for development of the telencephalon and restricts the differentiation of NSCs in the rostral migratory stream to neuronal cells. Ascl1 is involved in control of NSC fate during embryonic and adult neurogenesis [44]. Ascl1 enhances the differentiation of NSCs into GABAergic interneurons, especially in the olfactory bulb. Overexpression of Ascl1 in vivo increases the production of oligodendrocytes from NSCs. Expression of Dlx2 is associated with migration and proliferation of neuroblasts in the subventricular zone. Tlx is highly expressed in the developing brain and the adult brain and has been reported to regulate adult neurogenesis [44]. Namely, Tlx promotes the proliferation and differentiation of NSCs. Sox2 is associated with NSC proliferation and neurogenesis. Reduced level of Sox2 causes impaired NSC proliferation and decreased adult neurogenesis [44]. Additionally, Sox11 and Sox9 were found to act

as downstream mediators of neuronal differentiation. Emx2 is essential for proper morphogenesis of the CNS. Emx2 negatively controls the proliferation of NSCs by increasing the number of cells that undergo differentiation [44]. Trb2 is expressed in intermediate neuronal progenitors and affects neurogenesis [44].

Epigenetic regulators are also important in the regulation of neurogenesis. Epigenetic mechanisms involved in this process include DNA methylation and histone modification. Epigenetic modifications can result in new cellular phenotypes. Methyl-CpG-binding domain protein 1 (MBD1) is expressed in the adult hippocampus and has been confirmed to promote neuronal differentiation. Methyl-CpG-binding protein 2 (MeCP2) is also involved in neurogenesis in the adult brain. MeCP2 plays crucial roles in neuronal maturation and in NSC proliferation and differentiation. Growth arrest and DNA-damage-inducible protein 45 beta (GADDA45b) mediate NSC proliferation in the hippocampus and dendritic growth of newborn neurons. TET1 is known to regulate activity-induced neurogenesis in the adult hippocampus. The histone methyltransferase mixed-lineage leukemia 1 (Mll1) is closely linked with neuronal differentiation in the adult subventricular zone. Members of the family of fragile Z mental retardation proteins are associated with adult neurogenesis.

19.3 Conclusions

Although the exact mechanisms underlying the natural recovery process after stroke still need to be fully elucidated, two important mechanisms are thought to involved. First, synaptic plasticity, including axonal sprouting and synaptogenesis, is considered to be essential for successful recovery after stroke. These processes have been shown to occur around the peri-infarct area and sometimes even in the contralateral hemisphere. Second, neurogenesis caused by NSCs located in the subventricular zone and hippocampus also contributes to the recovery process. As described above, axonal sprouting, synaptogenesis, and neurogenesis occur through extremely complicated mechanisms. To help the recovery process after stroke and lessen the neurological sequelae of stroke patients, ways to increase axonal sprouting, synaptogenesis, and neurogenesis should be established based on the exact mechanisms.

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Neurorepair Strategies After Stroke

20

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Abstract

The emerging understandings on brain repair and plasticity have important implications for the development of neurorepair strategies in stroke. Peri-infarct tissue undergoes a major reorganization after an ischemic event in an attempt to ensure a spontaneous functional recovery. Altered neuronal excitability, angiogenesis, and neurogenesis are involved in the process, but it is believed that these can be further enhanced by rehabilitation, pharmacotherapy, and cell therapy. The major advantage of neurorepair as compared to neuroprotection is its wider therapeutic time window, which means that interventions are available for a larger percentage of stroke patients allowing also a combination of different therapies. Although experimental evidence is promising, the translation of restorative therapies into the clinic has proved more challenging than expected. This review will update the current state on how experimental approaches provide insights into brain repair and drive forward the development of new restorative treatments. Possible reasons for contradictory experimental and clinical data will be discussed.

20.1 Introduction

Stroke is a leading cause of adult disability. Recent advances in acute stroke care have meant that more and more patients survive, but are left with permanent impairments. This, together with the aging population, is likely to result in increasing numbers of people living with the effects of stroke, as predicted by the recent Burden of Stroke report in Europe [1].

Less than 10% of stroke patients receive thrombolysis or mechanical thrombectomy due to their narrow treatment window. Thus, novel restorative therapies beyond acute care are urgently needed. Promoting neuronal repair and plasticity is a somewhat untapped strategy although it is claimed to underlie the functional recovery after a stroke. The major advantage of this approach as compared to acute treatments is its wider therapeutic time window, which means that interventions would be available for a larger percentage of stroke patients allowing also the combination of different therapies (Table 20.1).

Most stroke patients recover spontaneously, at least partially, during the first 3–6 months

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Table 20.1 Differences between acute and neurorepair strategies in stroke

	Neuroprotection/reperfusion	Neurorepair
Study design in experimental animals	Short-term studies (<7 day) with infarct size as main outcome	Long-term studies (1–2 month), which rely on behavioral outcome
Accessibility	Less than 10% of patients	Large percentage of patients
Therapeutic time window	Short, only hours	Days to months
Mechanisms	Necrotic cell death, free radicals, excitotoxicity, edema	Angiogenesis, neurogenesis, axonal sprouting
Joint therapies	Stroke unit	Rehabilitation, drugs, multidisciplinary support

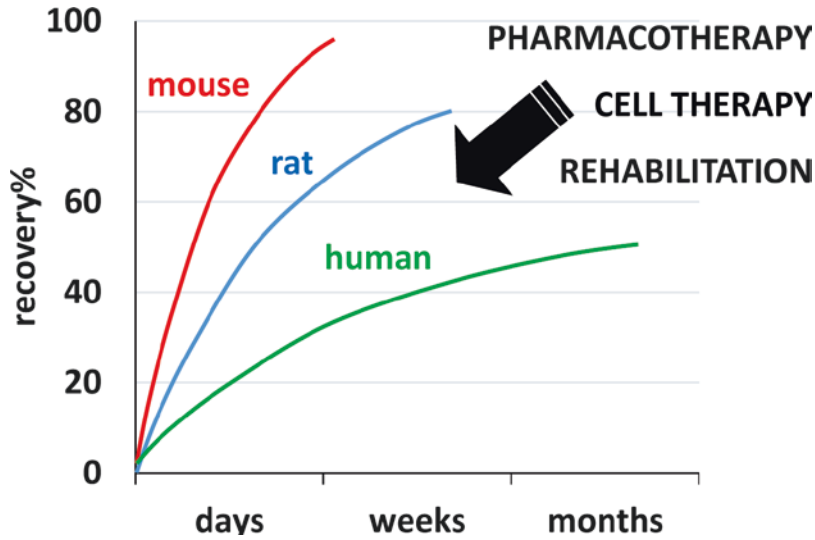

Fig. 20.1 Different spontaneous recovery profile in rodents and humans after stroke. Restorative therapies are suggested to facilitate recovery process through brain plasticity and repair. Combination therapies are expected to provide additive or synergistic effects

after a stroke [2]. However, mice recover within 1–2 weeks post-stroke and rats within 3–4 weeks despite the presence of extensive corticostriatal damage. The extreme plasticity of rodent brain in response to cerebral insults is one of neuroscience's greatest mysteries (Fig. 20.1). Early recovery is associated with the resolution of edema and inflammation, but later it seems to be the activation of the brain's own repair mechanisms such as altered neuronal excitability, angiogenesis, neurogenesis, and axonal sprouting that are responsible for the functional improvements. The tempting question is whether it would be possible to further enhance brain repair by rehabilitation, cell therapy or pharmacotherapy or their combination to maximize treatment effects (Fig. 20.1). Emerging evidence suggests that this might be true, although it is not known whether the mechanisms underlying spontaneous and therapy-induced recovery are exactly the same [3]. Furthermore, the mechanisms may differ in rodents and humans, explaining their different recovery profiles.

Stroke recovery studies are challenging because of the heterogeneity of patients, lack of consensus about which outcome measures or study design to use, when and how to deliver the therapy and whether joint therapies are needed [4]. Moreover, the majority of clinical studies have been so far uncontrolled, small and statistically underpowered. Experimental research may overcome some of these challenges. This review will update the current progress in the field of neurorehabilitation extending from experimental to early phase patient studies. The main focus will be on motor recovery, whereas important and common post-stroke complications such as depression, dementia, spasticity, and pain will not be reviewed.

20.2 Experimental Rehabilitation

Experimental rehabilitation is an emerging research area striving to understand the neurobiological basis of brain plasticity and recovery with the ultimate goal of developing restorative therapies for stroke. The major advantage is that one can control the heterogeneity that has plagued the published patient studies. In this way, one can concentrate on identifying specific and targeted questions about mechanisms of action, safety, and therapeutic efficacy. The recent guidelines for preclinical stroke recovery studies covering outcome measures from behavior to histology and imaging are expected to enhance the quality and rigor of experimental research and eventually to improve translational success [5].

Rehabilitative training is fundamentally different in rodents and stroke patients. In stroke patients, a therapist guides and assists patients while training of rodents is based on testing apparatus, reward, and/or aversive effects. Thus, a strong expertise in rodent behavior is needed to understand the animal's needs and preferences, to avoid extra stress and to reveal true treatment effects. Various approaches such as housing in an enriched environment (EE), voluntary and forced physical training, special rehabilitative training devices, forced use of a forelimb, and skilled reaching tasks have been introduced to mimic rehabilitation in stroke patients.

20.2.1 Enriched Environment

Housing in an enriched environment is used to provide multiple spatial, sensory, motor, and social stimuli to rodents [6]. An enriched environment consists of a large cage or cages with more space relative to standard housing conditions. The cages contain shelters, tunnels, ladders, and access to a running wheel to stimulate voluntary activity and exercise (Fig. 20.2). Different kinds of toys, varying in shape and size, are used and replaced regularly to expose the animals to novelty. In addition, an important component is social grouping, which means that animals are housed in groups of 8–12 allowing species-typical behaviors such as fighting and play.

EE improves not only sensorimotor but also cognitive functions post-stroke both in adult and aged rats [7]. However, the time when exposure to the enriched environment should be started or its duration seems to be critical for recovery and achieving permanent treatment effects. In fact, too early exposure to an enriched environment may exaggerate excitotoxicity and thus expand the infarct size [8]. Biernaskie et al. [9] showed that housing in an enriched environment combined with task-specific training could improve skilled forelimb reaching ability in rats when the procedure was initiated between 5 and 14 days after focal ischemia, but not later. In addition, as shown by Knieling et al. [10], one has to note that

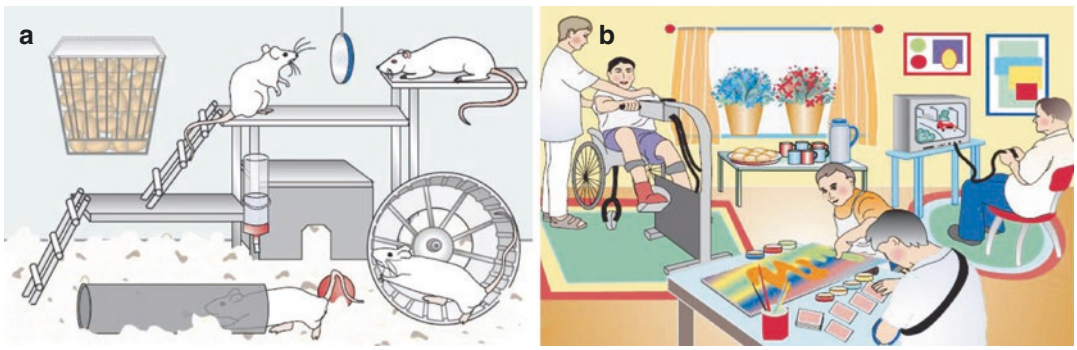

Fig. 20.2 Enriched environment (**a**) provides sensory, motor, spatial, and social stimuli to experimental animals mimicking rehabilitation of stroke patients (**b**) (from [58] with permission of Duodecim Medical Publications Ltd). A thorough understanding of laboratory animal behavior and crosstalk with rehabilitation professionals is needed for successful translation of experimental data

the enriched environment may not achieve a true functional recovery but rather some kind of compensation.

Most likely, it is the interaction of physical exercise, sensorimotor stimulation, and social component acting together, which account for the improved behavioral performance of stroke animals housed in an enriched environment. The underlying mechanism is not completely clear. A wide spectrum of repair mechanisms such neurogenesis in the subventricular zone, perilesional angiogenesis, dendritic morphology, and axonal sprouting across the midline into the denervated spinal gray matter is activated by cerebral ischemia and these same mechanisms can be further enhanced by an enriched environment [11]. In addition, various growth factors, especially brain-derived neurotrophic factor (BDNF), are likely to be involved.

The extent to which the promising data on environment enrichment can be translated into clinical practice needs to be clarified. A recent study highlighted that stroke patients living in a mixed rehabilitation unit were more likely to be engaged in activity compared to those receiving only routine ward activity programs [12].

20.2.2 Forced Physical Training Versus Voluntary Physical Exercise

Forced physical training usually involving treadmill running with electrical shocks to encourage animals to run whereas voluntary exercise is based on the provision of running wheel in a cage which the animal chooses to use or not. It has been reported that the recoveries of running and limb function and cognitive functions are better after forced physical exercise compared to voluntary exercise. Training between 1 and 5 days post-stroke seems to play an important role in the treatment effect [13]. It is poorly known the extent to which training-related stress and increases in blood corticosterone contribute to these results. Interestingly, forced use therapy alone without behavioral training (shaping) is not effective in stroke patients [14]. It has been suggested that both BDNF and stress-induced heat shock proteins 27 and 70 contribute to the improved recovery [15]. In addition, high-intensity training decreased Iba-1 positive cells and cytokine expression and increased pan-neurotrophin receptor p75 (p75NTR) expression in the ipsilesional hemisphere [16].

20.2.3 Constraint-Induced Movement Therapy

Learned non-use refers to the preference to use the unaffected upper limb after brain injury. Constraint-induced movement therapy (CIMT) is based on counteracting this preference by intense and repetitive task-orientated practice of the affected limb while the unaffected limb is restrained, inducing cerebral use-dependent cortical functions (Fig. 20.3a). The original form of CIMT contains three components or treatment packages: (1) intensive, graded practice of the paretic upper limb to enhance task-specific use of the affected limb for several hours each day for 2 weeks; (2) constraint or forced use therapy, with the non-paretic upper limb contained in a mitt to promote the use of the impaired limb; and (3) adherence-enhancing behavioral methods designed to transfer the gains obtained in the clinical setting to patients' real-world environment [14]. Later, protocols with varying doses, timing, and composition of therapy have been described (mCIMT). Kinematic studies suggest that the improvements are mainly based on adaptations through learning to optimize the use of intact end-effectors.

In rodents, immobilization of the unaffected forelimb forces the animals to completely rely on the impaired forelimb for a specific period of time (Fig. 20.3b). However, experimental data suggest that constraint is ineffective in stroke animals and may even do harm [17], which is at odds with human studies. Part of the reason for this contradiction may have been excessively early initiation of CIMT, often immediately after the ischemia induction, which is stressful and may eliminate any treatment effect. Another reason could be a lack of behavioral pressure (motivation) to use paretic forelimb despite constraint. In contrast, patient data show beneficial effects of

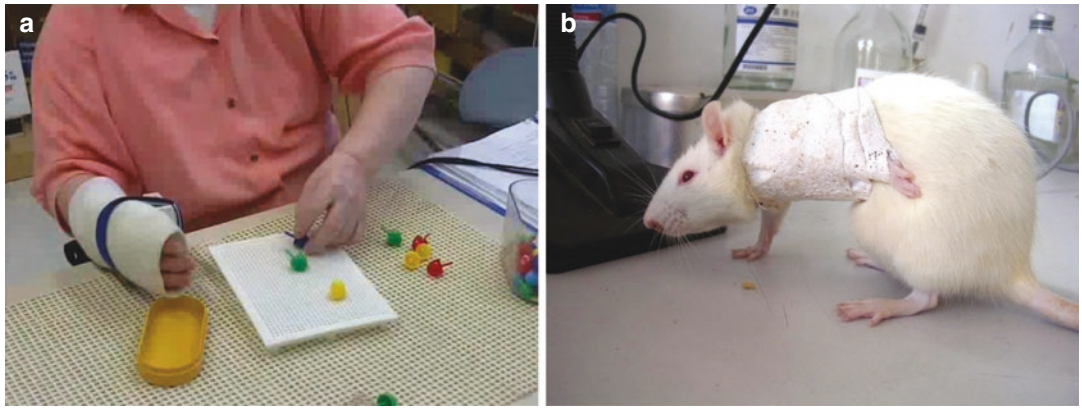

Fig. 20.3 Constraint-induced movement therapy (CIMT) reduces functional impairment in the affected upper extremity of patients with stroke by overcoming learned non-use (**a**). Immobilization of non-paretic forelimb by a cast can be used to model CIMT in rats (**b**)

CIMT on motor function, arm–hand activities, and self-reported arm–hand functioning in daily life, immediately after treatment as well as at long-term follow-up [14].

The mechanisms underlying the effect of CIMT are related to brain plasticity and functional reorganization of the brain. CIMT decreases the expressions of extracellular signal-regulated kinases (p-ERK) in the bilateral cortex and hippocampi, inhibits the Nogo-A, Nogo receptor, RhoA, and Rho-associated kinase pathways in the peri-infarct cortex. By overcoming the intrinsic growth-inhibitory signaling, CIMT apparently enhances the outgrowth and possible synapse formation of corticospinal tract fibers from the intact side of the brain to the denervated cervical spinal cord [18]. This was associated with increased expressions of synaptic markers in the denervated cervical spinal cord in stroke rat and improved behavioral recovery. It has also been demonstrated that CIMT after stroke significantly increased the expressions of stromal cell-derived factor 1 (SDF-1) in the cortex and dentate gyrus, leading to enhanced neurogenesis and functional recovery [19].

20.2.4 Skilled Forelimb Use

While stroke survivors with motor deficits strive for recovery in all aspects of daily life, neurorehabilitation is often task-specific and does not generalize to movements other than those being trained. In rodent stroke models, this problem has been poorly investigated as the training is often the same as the parameter that measures motor function. Motor training by pellet reaching focuses on highly specific skilled grasping ability and requires intensive training and practice of the impaired forelimb.

A recent meta-analysis revealed that skilled reaching training did not affect the infarct volume, but it enhanced running function by 11.2% and improved the limb function by 26.7% [13]. The effect of skilled training was comparable to forced physical training. More importantly, task-oriented motor training seems to generalize to other motor functions as well in stroke rats [20].

The task-specific rehabilitative training increases the density of dendrites and synapses and promotes motor map reorganization in the perilesional cortex [21]. Interestingly, neurogenesis in perilesional cortex is also involved in the motor map reorganization induced by skilled forelimb training [22]. Causality was elegantly shown by the use of cytosine-ß-D-arabinofuranoside, which suppresses endogenous neurogenesis and inhibited behavioral recovery. Another study showed that skilled forelimb training enhanced sprouting of new connections to the denervated forelimb area of the spinal cord contributing to recovery [23]. Skilled reaching training also

enhances the contralateral corticorubral tract plasticity in stroke rats, possibly by inhibiting the Nogo-A/NgR1 pathway [24].

20.3 Stem Cell Transplantation

Much hope has been placed on stem cells not only in stroke but in general in neurodegenerative diseases. Intracranial transplantation and intravascular infusion are two major strategies to deliver cells to the damaged area. Intracranial transplantation allows targeted delivery, but is invasive and the number of patients who eventually would have access to this therapy would be minimal. Cells are usually injected into intact tissue during the chronic phase. Placement in the cystic space may require a supporting scaffold to enhance survival and integration with host tissue. Intravascular delivery, which is relatively noninvasive, allows for treatment during the acute phase. However, most of the cells become entrapped in the lung after intravenous infusion followed by relocation into internal organs. Cell modifications such as pronase treatment may increase lung clearance targeting cells to inflammatory tissue [25]. Intra-arterial cell infusion is another way to circumvent pulmonary circulation, but is associated with complications such as microocclusion, raising safety concerns [26], although these can be controlled by adjusting cell dose and infusion speed.

It was initially suggested that the transplanted cells would replace the lost neurons. However, it seems that the cells are not even able to enter the brain [27]. The current understanding is that transplanted cells may activate the brain's self-repair mechanisms through central and/or systemic immunomodulation as well as promoting the secretion of various growth factors. The therapeutic effect does not depend on cell product, dose, or delivery route. It remains to be seen the extent to which the therapeutic effect can be further enhanced by combined pharmacotherapy or rehabilitation. Stem cell transplantation can activate neuronal repair, which then can be further enhanced by rehabilitation, as shown by the synergic effect seen after treadmill running and intravenous delivery of mesenchymal stem cells in stroke rats [28, 29]. However, it may be difficult to discriminate a stand-alone effect without additional experimental groups complicating study design.

Over the past 20 years, experimental evidence has accumulated for significant neuroprotection and/or improved behavioral recovery by cell products in stroke. An enlightening example is a recent meta-analysis on mesenchymal stem cells that showed that 44 out of 46 studies were effective in stroke animals [30]. However, publication bias partly explains these over-positive results. It is expected that the issued STEPS guidelines will continuously advance and accelerate preclinical research, eventually improving translational success [31].

Promising experimental evidence has formed the foundation for early phase clinical studies; however, the results are difficult to interpret because of small, statistically underpowered study design without proper control groups [32]. The safety and feasibility of administering different types of stem cell therapies in stroke seem to be reasonably ascertained, but the therapeutic efficacy needs to be confirmed by conducting larger and properly controlled studies. The MASTERS study was one of the first attempts with 1129 patients to study efficacy [33]. Unfortunately there was no evidence of any significant improvement in the neurological outcome at the 90 days' follow-up.

20.4 Pharmacotherapies

Pharmacotherapy is commonly given to patients recovering from the stroke to prevent further complications (e.g., recurrent stroke, seizures). It is well known that some of the commonly administered drugs may retard recovery and should be avoided [34]. There are no drugs approved to enhance functional recovery after stroke, but a number of drugs have been shown to be beneficial in experimental animals and in early phase clinical studies [35–37]. The following three examples will be discussed: noradrenergic phar-

macotherapy, selective serotonin reuptake inhibitors, and drugs affecting neuronal excitability.

20.4.1 Noradrenergic Pharmacotherapy

Amphetamine increases brain noradrenaline release and is one of the most extensively studied drugs shown to promote recovery of function in animal stroke models. When combined with a task-relevant experience, a single dose of d-amphetamine given 24 hr. following unilateral sensorimotor cortex ablation in rats resulted in an enduring enhancement of motor recovery [38]. Subsequently, this has been repeated in middle cerebral artery occlusion model [39]. The effect of amphetamine on recovery seems to depend on the location and extent of brain injury, the dosing and timing of amphetamine, and the type, intensity, and timing of concomitant behavioral training [40]. The promising experimental data have prompted a number of small patient studies with variable results [41, 42].

In addition to amphetamine, methylphenidate has been evaluated in a small, randomized, controlled trial of post-stroke rehabilitation [43]. Twenty-one stroke patients were randomized at day 18 post-stroke to receive either methylphenidate or placebo plus physiotherapy for up to 3 weeks. The authors reported a beneficial effect for methylphenidate on depression scores, motor function, and functional independence. Efficacy is difficult to ascertain in such a small study as this was a heterogeneous sample of stroke patients, many patients had high initial motor scores and drug doses and follow-up were variable. In addition, L-threo-3, 4 dihydroxyphenylserine (L-DOPS), a precursor of noradrenaline, was administered at a dose of 300 mg to 27 patients with chronic stroke for 1 month [44]. Significant improvements were observed in gait and hand motor function.

Despite decades of efforts, the cautious conclusion is that too few patients have been studied with too many variable study designs to make it possible to draw any definite conclusions about the effects of amphetamine alone or with physiotherapy treatment on recovery from stroke. To take this further, a major challenge is to find public funding for these kinds of trials. In addition, given so many failures with neuroprotective drugs, pharmaceutical companies may not be interested in investing in another clinical trial, especially when more attractive drug candidates for the same indication are available.

20.4.2 Selective Serotonin Reuptake Inhibitors

Depression is an important consequence of stroke that impacts on recovery, but is often not adequately treated. Antidepressants are effective for post-stroke depression. A Cochrane review analyzing data for 13 drugs including serotonergic reuptake inhibitors (SSRIs) stated that these drugs confer benefits in the complete remission of depressive symptoms and in the improvement of the depression scale score [45]. Another meta-analysis identified 44 randomized controlled trials that compared outcomes between central nervous drug treatment and placebo [46]. Selective serotonin reuptake inhibitors improved gross motor function, disability, and quality of life, but there was insufficient evidence for their use in enhancing global cognition. In particular, gross motor function was improved by fluoxetine, whereas disability was improved by paroxetine, citalopram, and fluoxetine. More importantly, there was less evidence for the use of anti-Alzheimer drugs, anti-Parkinson drugs, central nervous system stimulants, and piracetam to promote stroke recovery. In the large FLAME study, fluoxetine was investigated in 118 patients with ischemic stroke and hemiplegia or hemiparesis [47]. A 20 mg dose of fluoxetine or placebo was given during 3 months after the onset of stroke of physical therapy. The drug with physiotherapy enhanced motor recovery after 3 months, the patients receiving the drug has significantly higher Fugl-Meyer motor scores as compared to placebo.

One should note that fluoxetine does not improve behavioral recovery in experimental stroke models [48, 49], indicating that mood,

anxiety, and other psychological issues may make a significant contribution to efficacy of fluoxetine in stroke patients. In addition, the underlying mechanisms are poorly known, but as well as blocking serotonin uptake, fluoxetine decreases inflammatory cytokine production by microglia, enhances production of neurotrophic factors, increases axonal sprouting and the production of new synapses, increases proliferation of glial precursor cells, and even increases hippocampal neurogenesis [50]. Although some antidepressant drugs and BDNF seem to interact, this can be beneficial because they exert different, but coordinated, effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus [51].

Although larger studies are recommended to confirm the efficacy of fluoxetine after stroke, off-label use of fluoxetine to facilitate motor recovery in rehabilitation centers is common.

20.4.3 Other Drugs

Other drugs such sigma-1 receptor agonist, ephrin-A5 blockade, glibenclamide, and ropinirole have been tested in experimental settings and small patient studies [35–37]. Drugs already on market with good safety records, offer an accelerated way to study the role of novel mechanisms in stroke recovery. For example, there is emerging evidence showing increased expression of Na^+-K^+-Cl^--co-transporter 1 (NKCC1) in perilesional tissue after stroke that leads to deranged chloride homeostasis and a shift of GABA-mediated hyperpolarization to depolarization. Bumetanide, a specific antagonist of NKCC1, is a loop diuretic widely used in clinical practice. Infusion (i.c.v.) of bumetanide 1 week after ischemia, restores deranged chloride homeostasis, enhances axonal sprouting of the corticospinal tract (CST), and increases endogenous neurogenesis together with improved behavioral outcome in stroke rats [52]. In addition, cortical excitability can be modulated through AMPA/NMDA receptors and GABA signaling. Inhibiting tonic (extrasynaptic) GABA facilitates behavioral recovery in mice after cerebral photothrombosis [53] whereas enhancing phasic (synaptic) GABA signaling using zolpidem has improved performance in sticky label test [54]. Another drug with potential for clinical application in stroke is memantine, which is an NMDA antagonist used to treat Alzheimer's disease. Memantine has improved sensorimotor recovery in stroke mice in non-neuroprotective manner and this is associated with increased area of forelimb sensory maps, decreased gliosis, and increased angiogenesis in perilesional tissue [55]. Taken together, alterations to glutamate and GABA signaling offer novel, specific targets to control peri-infarct excitability. Modifying this sensitive balance improves behavioral recovery after stroke, but if not properly controlled, may at worst even lead to seizures.

20.5 Other Neurorepair Strategies

Repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) are techniques that generate electric currents in the brain to modify cortical excitability. Synaptic structural plasticity is suggested to be involved in stimulated cortex. Animal studies and phase I and phase II trials in patients have proven safety, feasibility, and efficacy; however, a recent meta-analysis of clinical studies revealed either no benefit or only some minor benefit in a subpopulation of stroke patients [56]. In addition, robot-assisted therapy, virtual reality, games, and music are just some of the novel approaches with unexplored potential in stroke patients [57], although they would be challenging to model in rodents.

20.6 Conclusions and Future Perspectives

At present, rehabilitation is considered to be the only effective treatment to enhance functional recovery in the acute and chronic stages after stroke. Much effort has been expended on identifying medications that could increase the capacity for brain regeneration and maximize the gains

not only of motor but also of cognitive functions. In particular, drugs that are already on market are attractive candidates to facilitate recovery (e.g., memantine, zolpidem). The combination of pharmacotherapy, cell therapy, and intensive rehabilitation is another strategy to activate multiple regenerative mechanisms and improve therapeutic efficacy. Whatever the chosen strategy, the crucial task is to identify patient populations that would benefit from restorative therapies, for example, by using biomarkers. A meta-analysis of experimental and clinical studies may also aid in the stratification of patients. More importantly, future clinical trials should be randomized, controlled, and possess the statistical power to tackle heterogeneous patient populations undergoing a recovery.

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