General Facts of Stroke

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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.

1.1 Introduction

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

C.-H. Lee
Department of Neurology, Jeonbuk National University Hospital, Jeonju, Republic of Korea

S.-H. Lee (✉)
Department of Neurology, Clinical Division, Seoul National University Hospital, Seoul, Republic of Korea

Korean Cerebrovascular Research Institute, Seoul, Republic of Korea
e-mail: sb0516@snu.ac.kr

S.-H. Lee (ed.), *Stroke Revisited: Pathophysiology of Stroke*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1430-7_1

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.

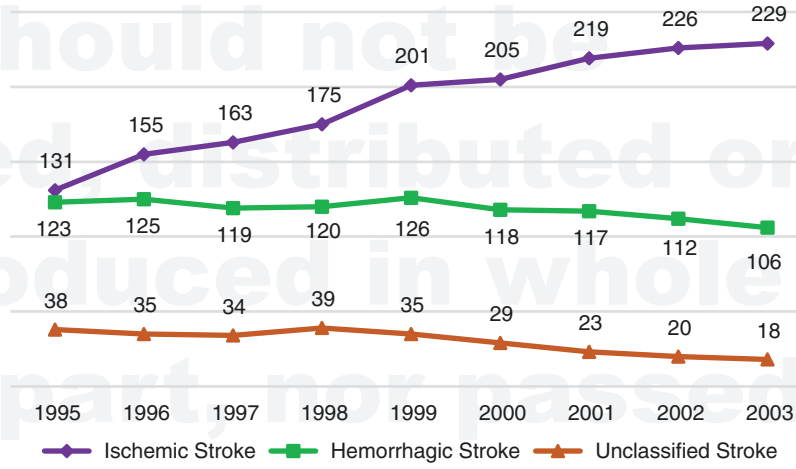

Fig. 1.1 The incidence per 100,000 of stroke according to the stroke classification in the Republic of Korea (1995–2003). Adapted with permission from Journal of Stroke, Copyright Korean Stroke Society

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

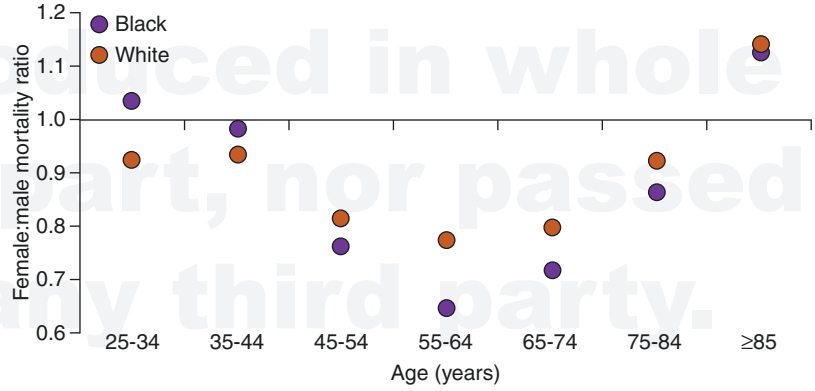

Fig. 1.2 Female-to-male mortality ratio according to age-related stroke in the United State (1999~2003). Adapted with permission from Lancet Neurology, Copyright Elsevier

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-

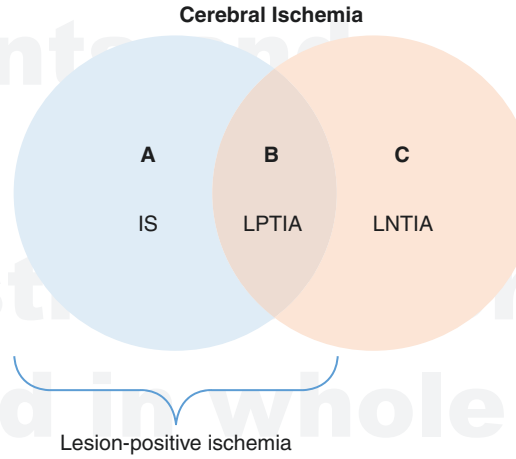

Fig. 1.3 New concept of TIA and stroke. Cerebral ischemia can be classified into three types (A, B, C) according to persistence of neurological symptoms and imaging findings, and A and B can be bound to lesion-positive ischemia. *IS* ischemic stroke, *LPTIA* Lesion-positive transient ischemic attack,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