CHAPTER 1 STROKE: THE SIZE OF THE PROBLEM

Strokes are currently classified into two major categories: ischemic and hemorrhagic. Ischemic stroke is caused by an interruption of the blood supply to at least one section of the brain, leading to sudden loss of function, while hemorrhagic stroke is attributed to the rupture of a blood vessel or an abnormal vascular structure.[1] Worldwide, a stroke occurs 1 every 2 seconds for an age-standardized incidence (new cases of strokes) of about 260 per 100,000 persons per year.[2] In 2016, there were reported 13.7 million new incident strokes globally and about 87% of these were ischemic strokes.[3] Currently, there are about 6 million stroke-related deaths annually equated to the second leading cause of death and about 100 million patients who remain disabled, the second leading cause of disability. The prevalence of stroke (stroke survivors) is reported to be about 500 per 100,000 persons annually. Approximately 70% of these strokes occur in low- and middle-income countries. The incidence of stroke rapidly increases with age, doubling for each decade after the age of 55.[4] Among adults aged from 35 to 44, the incidence of stroke is estimated to be 30 to 120 out of 100,000 people per year, whereas, for those aged 65 to 74, the incidence is estimated to be from 670 to 970 for every 100,000 people per year.[5–7] Stroke does occur among children, but its incidence, in comparison to adults, is substantially lower (approximately 1 to 2.5 out of 100,000 per persons per year), and roughly 50 to 75% of strokes among children are a result of hemorrhage.[5] Sickle cell disease is the principal cause of childhood stroke, with its highest reported incidence between the ages of 2 and 5 years.[8]

Even though overall stroke incidence currently remains stable or slightly decreasing worldwide and disability appears to be declining, the number of stroke victims is increasing. In fact, between 1990 and 2010, the global incidence rate of stroke remained stable, but the absolute number of incident strokes increased by 68%. Particularly, the absolute number of individuals affected by ischemic stroke significantly increased by 37%, while the absolute number of individuals afflicted by hemorrhagic stroke rose by 47%. However, over the same period, reductions were recorded in the mortality rates associated with ischemic stroke by 37% and hemorrhagic stroke by 38%.[9]

Most importantly, it is fundamental to consider that, while the increase in the absolute number of strokes is mainly associated with a growing global population, longer life expectancies and ageing populations, the reductions in the rates and disability is due to the improved education about stroke and its consequential diagnosis, prevention, and treatment.[10]

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CHAPTER 2

DIAGNOSIS OF STROKE

Pre-hospital stroke care

Stroke is a time-dependent disease. On average, 1.9 million neurons die, 14 billion synapses disconnect and 12 km of neural fibers are lost every minute from stroke onset. So, the sooner we intervene, the better the prognosis can be. A clear recognition of symptoms by the patient and persons around him at the time of event is the first step in the management of stroke. In fact, prolonged onset-to-arrival time at hospital is the greatest source of delays for care and therefore can be a major cause of patient ineligibility for reperfusion therapy.[1] Effective public education programs instruct on how to recognize stroke signs and symptoms, and stress the need to call for emergency medical assistance immediately; leading to earlier hospital presentation and therein increasing the proportion of patients eligible for acute therapies.[2] Several stroke prediction scales had been developed to aid not only patients but also clinicians and emergency medical staff to quickly identify acute stroke in the pre-hospital setting. Of these, the Cincinnati Prehospital Stroke Scale (CPSS), is a brief, practical, and easy-to-use scale that assesses facial palsy, asymmetric arm weakness, and speech disturbances, and each item is scored normal or not. If at least one of these items is abnormal, the patient is suspected of having a stroke.[3] A systematic review reported that CPSS can be helpful in detecting stroke with an overall sensitivity of 82.46% and specificity of 56.96%.[4] The CPSS was incorporated into the FAST acronym (Facial weakness, Arm weakness, Slurred speech, and Time) to educate on the early recognition of stroke signs and remind people of the importance to call emergency medical system immediately (Figure 2.1). Reported results from educational campaigns using FAST directed towards adults found that nearly all participants recalled stroke warning signs at 3-month follow-up.[5] Once symptoms are recognized, patients with acute stroke who receive earliest emergency medical services benefit from faster Emergency Department evaluations and are more likely to receive reperfusion therapy.[6] Furthermore, emergency medical dispatchers can play a key role in prehospital stroke care. To this regard, in a review of 911 calls and emergency medical service run sheets of patients with calls for suspected stroke, dispatchers were able to identify stroke with a high reliability whenever the caller described facial droop, weakness/fall, or impaired communication.[7] These are the same items used in the CPSS mentioned here before. The emergency medical response is another crucial component of prehospital stroke care and includes immediate evaluation of patients with early stabilization of clinical conditions, rapid transport (via ambulance or by helicopter), hospital pre-arrival notification and triage to an appropriate stroke center. Furthermore, a technologically advanced approach to prehospital stroke care has been the development of mobile stroke units: ambulances equipped with a computed tomography (CT) scanners and a stroke physician, either in person or via telemedicine.[8] Telemedicine for

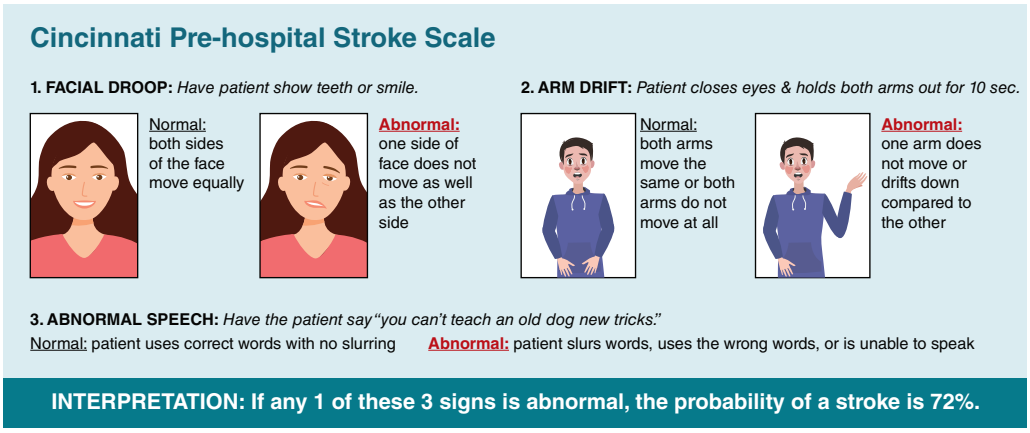

Figure 2.1.—Cincinnati Pre-hospital Stroke Scale.

stroke, uses state-of-the-art video telecommunications is a practical solution that maximizes the number of patients given effective acute stroke treatment across a region. In fact, telemedicine allows for, in real time, remote cerebrovascular specialized consultations worldwide, adding greater expertise to the care of any individual patient. Moreover, telemedicine assists the local Emergency Room physicians in performing a correct diagnosis of stroke, in performing a standardized stroke scale, such as the National Institutes of Health Stroke Scale (NIHSS), assess inclusion/exclusion criteria for revascularization therapies, obtain and interpret neuroimaging, review laboratory studies, and discuss the risk/benefits with the patient, family and local physicians.[9] In Italy, to ensure that all the healthcare personnel mentioned above collaborate together with the aim of reducing arrival times and to take the patient to the most appropriate hospital where the best possible treatment can be performed, the "Ictus Code" (Codice Ictus) was created; a path that is activated when the patient or anyone accompanying him/her contact the emergency medical system using CPSS.

Stroke mimics

Stroke is defined as a sudden onset of a focal neurological deficit in a recognizable intracranial vascular distribution resulting in a common clinical syndrome due to vascular occlusion or hemorrhage. This neurological deficit due to a stroke can range from mild weakness to paralysis or numbness on one side of the face or body. Furthermore, the patient can also be afflicted by sudden weakness, visual deficits, and aphasia in speaking and/or in comprehension. Nonetheless, a correct diagnosis of acute ischemic stroke is not always straightforward. In fact, "stroke mimics" represent up to one-third of cases of new neurological deficits. By definition, stroke mimics are diseases that share similar symptoms among neurological and number of medical conditions, thereby, they often confound the path to a correct diagnosis of an acute stroke (Tables 2.I and 2.II).[10, 11] The more common stroke mimics encountered include: seizures, migraine with aura, peripheral vertigo and functional disorders.

Table 2.I.—Commonly recognized stroke mimics.

Central nervous system conditions
▪ Post-ictal state with focal neurological signs (Todd's paresis)
▪ Non-convulsive status epilepticus
▪ Hemiplegic migraine
▪ Subdural or epidural hematoma
▪ Brain abscess
▪ Infective encephalitis or meningitides
▪ Intracranial tumors
▪ Multiple sclerosis
▪ Posterior reversible encephalopathy (PRES)
▪ Vasoconstriction reversible syndrome
▪ Recrudescence
Peripheral nervous system conditions
▪ Focal neuropathies
▪ Peripheral vertigo
Metabolic conditions
▪ Hypoglycemia
▪ Hyperglycemia
▪ Electrocytes dysfunction
▪ Acute liver failure
▪ Alcohol
Psychiatric conditions
▪ Conversion disorders
▪ Factitious disorders

Seizures

Focal seizures are one of the most frequent stroke mimics, particularly in patients having post-ictal Todd's and muteness paralysis which may be taken for acute stroke especially if the seizure had been unwitnessed. In these patients, an altered level of consciousness is common, recovery is generally rapid in most patients although rarely non-convulsive focal status epilepticus may present with prolonged aphasia or motor weakness.

Migraine with aura

Migraine with aura can be present without headache. Symptoms are usually "positive", as paresthesia or visual phenomenon, but weakness or numbness on one side of the body may be recorded. Symptoms are usually gradual during onset, that often eventually spread through other vascular territories. Basilar migraine is uncommon but the clinical presentation can include acute vertigo, dysarthria, ataxia and a decreased level of consciousness therein mimicking a stroke in the posterior circulation. In most cases, patients with migraine with aura can also affected by migraine without aura.

Peripheral vertigo

Acute vertigo is common seen in clinical practice, making it difficult to differentiate between peripheral (inner ear) or central cause (cerebellar or brainstem stroke). The presence of brainstem signs as dysarthria, diplopia, ataxia, weakness and numbness which are helpful in a correct diagnosis. However, these signs are not always present. Whenever isolated vertigo is the only symptom present, for a differential diagnosis, the following characteristics should be evaluated:

1. Neurological physical examination: in all patients presenting with an acute onset vertigo, a thorough neurological examination including the evaluation of nystagmus, the head impulse test (HIT) and the cover-uncover test should be carried out. Any focal brainstem deficits that direct the diagnosis towards central vertigo should be excluded such as cerebellar deficits, cranial nerve deficits (predominantly bulbar), cross-sensitivity and/or motor deficits (involving a side of the face and a contralateral arm and/or leg), conjugated

Table 2.II.—Differentiating clinical characteristics between stroke and mimics.

	Suggesting stroke	Suggesting mimics
Age	Older	Younger
Level of consciousness	Awake	Reduced Confusional state
Onset	Sudden Onset time can be determined	Gradual Onset time cannot be determined
Severity	Severe at onset	Fluctuations of symptoms
Risk factors	Vascular (*e.g.* atrial fibrillation)	History of migraine, systemic illness, seizure or cognitive impairment
Symptoms	Facial deficit Signs corresponding to vascular territory Urinary retention Babinski sign	No facial deficit No signs corresponding to vascular territory No urinary retention No Babinski sign
Blood pressure at onset	Increased	Normal

or disconjugated ocular motility deficits, and the presence of Bernard-Horner syndrome. The patient with peripheral vertigo can also experience balance disturbances but still able to ambulate, while the patient with central vertigo has more severe unsteadiness and therefore cannot walk or stand without falling. Furthermore, the patient with vertigo of peripheral origin can have an aggravation of symptoms when the eyes are closed. With opened eyes, a reduction in the severity of vertigo while staring at an object, may occur. Likewise, in the peripheral forms, nystagmus could disappear or decrease with fixation.

2. Nystagmus: is an involuntary "back-and-forth" movement of the eyes that can be present in the horizontal and/or vertical planes. A slower phase of this movement and a faster phase are distinguished: it is accepted that nystagmus beats on the right side when the rapid phase moves toward the right side and vice versa. This examination can be performed with the patient supine, lying on one side, or with his/her head hyperextended. Physiological nystagmus is generally present only in extreme gaze exposures, has small amplitude, can be exhausted after a few shocks and can be modulated (generally inhibited) by asking the patient to carefully stare at a target. Nystagmus of peripheral origin is generally associated with oscillopsia (vision of moving objects), while nystagmus that is not associated with oscillopsia probably will have a central origin. Peripheral nystagmus is partially or totally inhibited by fixation, therefore, it would be an error to look for nystagmus and its characteristics by having the patient follow the examiner's index finger. In fact, in this manner, the nystagmus may even disappear. For an optimal evaluation of nystagmus, the use of Frenzel glasses is required, given that they have backlit positive lenses that prevent fixation by blurring vision. Another option is to use a blank sheet of paper (A4) instructing the patient to look at it. The sheet is placed near a side of the patient's head. Since the sheet is blank, there are no targets that can be fixed, so the nystagmus is

not inhibited. Once the nystagmus has been determined, the patient will be asked to stare at a target which can be the examiner's finger: if the nystagmus reduces or disappears, this suggests the presence of a peripheral origin lesion. Moreover, peripheral nystagmus most often has a horizontal-torsional direction and always beats towards the same side regardless of the orbital position (unidirectional nystagmus). Its intensity can varie as the orbital position varies on the horizontal plane, being at its highest frequency when the patient is gazing directed towards the healthy side. On the other hand, a nystagmus is always of central origin (cerebellar) when it is bidirectional (beats right towards the right lateral gaze and beats left towards the left lateral gaze). A vertical nystagmus always has a central origin, as does a monocular nystagmus which can occur along with internuclear ophthalmoplegia.

3. Head Impulse Test: the patient is asked to stare at the examiner's nose. Thereupon, the examiner gently cradles the patient's head at the jaw line, instructing the patient to keep is neck muscles relaxed. Now, the examiner will move the patient's head to one side quickly while observing the patient's ability to keep his gaze fixed on the examiner's nose. The same maneuver must be repeated for the contralateral side. The test result is considered negative (absence of pathology) whenever the patient manages to keep his gaze fixed on the examiner's nose throughout the examination. While, the test result is considered positive (presence of pathology) when the examiner will turn patient's head towards the injured side and the patient is not able to keep his gaze fixed on the examiner's nose. In this case, the gaze will follow the movement of the patient's head for a short time, then the patient will make a correcting movement which will bring the gaze back to the examiner's nose. The test result is positive when the injured side is stimulated indicating the presence of a peripheral lesion, while a negative test result is associated with the presence of a central lesion.
4. Cover-uncover test: the examiner alternately covers one eye of the patient and then the other for 5 seconds. The test result is considered negative (absence of pathology), whenever the uncovered patient's eye does not move. However, there may be a small correction movement on the horizontal plane due to the presence of convergence. When an eye is uncovered and than makes a correcting movement in the vertical plane, which can be upward or downward, returning to the primary gaze, this suggests that the patient is affected by a latent "skew deviation". In this case, the test result would be considered positive. Any positive test result would most likely be due to a vertigo of a central origin.

The internal auditory artery is a terminal branch of the anterior inferior cerebellar artery (AICA) that supplies the VIII cranial nerve, the cochlea and the labyrinth. This terminal branch is extremely vulnerable to ischemia and its occlusion can determine an ischemia of the labyrinth, causing a vertigo with the clinical features of a peripheral syndrome mimicking labyrinthitis, vestibular neuronitis or Ménière's syndrome. The AICA, in addition to supplying the inner ear, it also supplies the lateral part of the pons, the middle cerebellar peduncle and the anteroinferior part of the cerebellum; therefore, it is usually associated with other signs of brainstem involvement which must be excluded. In some cases, vertigo may be isolated but, since the labyrinthine artery also supplies the cochlea, the presence of hearing loss (due to cochlear infarction as well as vestibular infarction) associated with vertigo should lead to the suspicion of an AICA occlusion, even in the absence of other neurological signs.

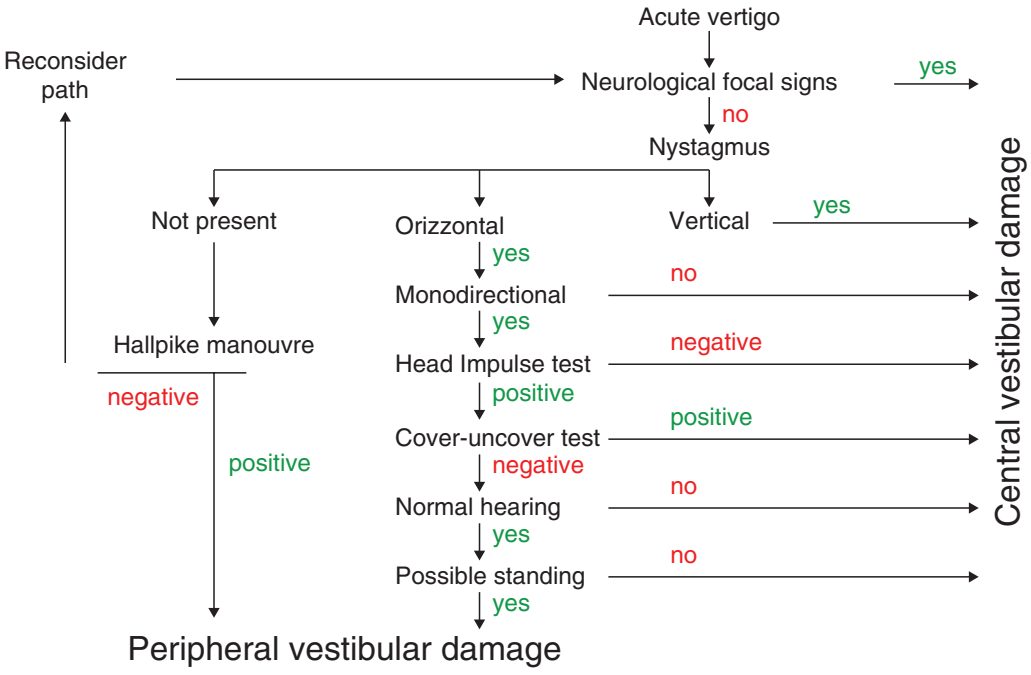

Figure 2.2.—Flow chart differentiating between peripheral and central causes of acutely isolated vertigo.

An evaluation carried out by an otolaryngologist should always include the performance of the Hallpike maneuver, in order to diagnose a paroxysmal positional vertigo.

Figure 2.2 shows a flow chart that differentiates the peripheral or the central cause of an acute isolated vertigo.

Functional disorders

Functional neurological disorder presents with limb weakness or numbness typically lateralized, often with a dense paresis of the limbs with a complete facial sparing. Regarding functional leg weakness, Hoover's sign has the best clinical utility and can be conducted when the patient is seated or lying down to reveal any normalization of hip extension on the weak side during hip flexion of the nonparetic lower limb. Regarding the upper limbs, downward drift with pronation indicates cortical weakness. However, drift without pronation is a typical finding in patients with functional arm weakness.[12]

Additionally, in 1896 Joseph Félix Francois Babinski described the Babinski sign. Stimulation of the lateral plantar of the foot normally leads to plantar flexion of the toes. Babinski sign occurs when stimulation of the plantar aspect of the foot leads to the extension of the allux. Also, there may be fanning of the other toes.[13] The presence of Babinski sign suggests damage of the pyramidal tract of the central nervous system. In fact, Babinski in 1898 wrote: "the presence of the toe phenomenon excludes hysteria".[14]

Other frequent functional disorders include: 1) sensory disturbances in half of the body (midline splitting). The exact splitting of sensation in the midline, is likely a functional sign