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Cerebrovascular Disease and Stroke (C Helgason and M Alberts, Section Editors)

Diagnosis and Misdiagnosis of Cerebrovascular Disease

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Opinion statement

Stroke is the leading cause of disability and the third leading cause of death in the USA. Ischemic and hemorrhagic strokes must be distinguished since treatment is quite different. Ischemic strokes account for 80 % of the total and recent advances in management of brain ischemia have added valuable options to the physicians' armamentarium. Wise selection and targeted treatment of patients is of paramount importance. Properly treated patients benefit significantly, while those erroneously diagnosed as ischemic stroke are exposed to potentially harmful side effects of therapy. Stroke can present in the form of several different clinical syndromes some of which are difficult to identify. Conversely, there are numerous conditions whose clinical presentation closely resembles stroke, also known as stroke mimics. Ancillary testing, especially imaging, is a crucial part of diagnostic evaluation, while clinical judgment, thorough knowledge of cerebrovascular anatomy and familiarity with characteristic stroke syndromes remain indispensable even in this era of technological advance.

Introduction

Stroke is a common and serious cause of death and disability. It is frequently encountered and managed in the emergency setting by emergency physicians, general practitioners, and internists. Early detection and appropriate acute diagnosis and management are critical in leading to good outcomes. Secondary prevention is also paramount in reducing disease burden in the population. In this article, we will review the frequency by which stroke is misdiagnosed, elaborate on the most frequent stroke mimics (SM)s, identify clinical features that can help distinguish cerebral ischemia from a mimic, and present the current diagnostic approach with emphasis on the role of imaging.

Overdiagnosis

Misdiagnosis of stroke can be due to "overdiagnosis" from attributing a non-stroke condition to stroke, or "underdiagnosis" from attributing true stroke symptoms to a non-stroke etiology.

Overdiagnosing a stroke is inevitable and expected, especially in the acute phase. The phenomenon of overdiagnosing stroke was investigated in a study in the early 1980s in which 821 consecutive patients admitted to a stroke unit were studied, and the initial diagnosis of stroke was found to be incorrect in 13 % of patients [1•]. Several nonvascular conditions present with acute neurologic symptoms resembling a stroke—stroke-mimics (SMs). The frequency of SMs is quite variable and depends on definitions, clinical settings, and chosen diagnostic methods. Several authors define SMs as definitive non-stroke diagnoses, while others include patients with "possible stroke." These studies found SMs with a frequency of 1.4 % to 25 % [2, 3]. One study performed in a setting representative of hospital-based stroke management in the urban setting, found a frequency of SMs of 19 % [4•].

Many of these studies emphasize the importance of clinical and diagnostic skill and experience. Significant difference in diagnostic accuracy between emergency room (ER) physicians and attending neurologists were found in some studies [1•], whereas others did not show such a trend [2, 5••]. Accuracy of diagnosis was found to be as low as 38 % by ER physicians in 1 study [6]. In contrast, a study at a university-based teaching hospital where a select group of ER doctors are an integral part of the stroke team showed a sensitivity of ER physician diagnosis to be 98.6 % with positive predictive value of 94.8 %. Including ER physicians as part of the team and providing phone or telemedicine consultation can improve diagnostic accuracy in the ER [5••]. Routine use of brain and vascular imaging and involvement of a neurologist increase the sensitivity and accuracy of diagnosis. Education and written guidelines for acute stroke treatment both in the ER and in out-of-hospital settings have a dramatic effect in moderating the drawback of physicians' inexperience in accurate diagnosis and treatment [2].

A recent study sought to validate the diagnosis of transient ischemic attack (TIA) made by general practitioners (GPs) and emergency physicians with the diagnosis made by neurologists. Non-neurologists considered "confusion" and "unexplained fall" suggestive of TIA and "lower facial palsy" and "monocular blindness" less suggestive of TIA. This study suggested that non-neurologists often label minor strokes and several nonvascular transient neurologic disturbances as TIA, and up to half of patients could be mislabeled with a diagnosis of TIA [7].

Underdiagnosis

Underdiagnosing a very serious but treatable condition like stroke has more serious ramifications. Patients who frequently fall victim to misdiagnosis are younger patients, as stroke is less common in this age group. Early diagnosis and treatment is of utmost importance in this group as they may survive for several years with post-stroke disability. Ischemic stroke in this population tends to

occur due to cardiogenic sources like PFO, arterial dissection, and vasculopathies [8]. A study by Chaturvedi et al. of young patients (aged 18 to 50 years) showed that 8 patients (14 %) were misdiagnosed, and they tended to be <35 years of age and had posterior circulation stroke symptoms. Seven out of the 8 patients were discharged from the emergency room, showing the potential loss of opportunity to thrombolyze ideal candidates, and the need for "young stroke awareness" among emergency department personnel [9]. This group also suggested that early performance of MRI in patients younger than 35 years of age with stroke-like symptoms and diagnostic uncertainty leads to greater accuracy of stroke diagnosis [10]. Another study confirmed that patients below 60 years of age and patients with vertebral artery dissection were more likely to have a cerebellar infarction misdiagnosed by physicians other than neurologists [11].

Posterior circulation strokes presenting with dizziness are challenging to diagnose among emergency physicians and neurologists alike [12]. On one hand, it was found that isolated dizziness, vertigo, or imbalance strongly predicts a noncerebrovascular cause (with only 3.2 % of all patients with dizziness symptoms being diagnosed with TIA or stroke), and only the symptom of imbalance is a predictor of stroke/TIA [13]. Transient isolated brainstem symptoms (eg, isolated vertigo, dysarthria, diplopia) due to vertebrobasilar ischemia occur in about 16 % of patients during the days and weeks preceding posterior circulation strokes [14]. Of all events occurring during the 90 days preceding a vertebrobasilar territory infarct, fewer than 10 % satisfied the NINDS definition of TIA [15]. The NINDS criteria state that most transient neurologic attacks (TNAs) with brainstem symptoms, such as vertigo, dysarthria, dizziness, or wooziness; focal symptoms suggestive of migraine, confusion, and amnesia, should not be diagnosed as TIAs. Only 22 % of patients with isolated brainstem TNAs sought medical attention before the stroke. Vascular etiology was suspected in only 1 of these cases, the remainder of whom were diagnosed as postural hypotension, peripheral vestibular disturbance, sepsis, migraine, and cranial nerve palsy [14].

Another issue is the radiological interpretation of data in emergency rooms. Alfaro et al. found that emergency physicians missed 69 % of all infarcts, 62 % of parenchymal hematomas, and 50 % of subarachnoid hemorrhages on non contrast head computed tomography scans (CT) [16]. However, they found that none of these patients were managed inappropriately. Conversely, emergency physicians should be aware of the low sensitivity of hyperacute CT in identifying infarcts, especially in the brainstem and cerebellum [17].

An important factor to be aware of is that overdiagnosis may be safer than underdiagnosis. In a study in which intravenous thrombolysis was administered to patients with acute ischemic stroke symptoms, misdiagnosis of acute ischemic stroke was documented in 10.4 % of cases [18]. There was no instance of symptomatic intracranial hemorrhage in SMs, indicating safety and favorable outcomes when intravenous thrombolysis was administered to these patients.

Stroke mimics and their identification

In this section we describe the most frequent SMs as identified in a number of relevant studies, followed by discussion of clinical characteristics that occur

more frequently in SM patients and could be of help when making a clinical diagnosis in the acute setting.

Epilepsy: seizures and postictal states

Epilepsy is one of the commonest SMs, with a frequency ranging from 6 % to almost 40 % of stroke-like conditions in various studies [1•, 19, 20]. It can cause focal neurologic dysfunction either as part of the epileptic activity itself or as a manifestation of postictal cortical suppression. Seizure activity involves neuronal discharge. This results in positive phenomena with highly variable semiology depending on the exact location of the seizure focus: limb movements, paresthesias, and visual phenomena have been described. A history of rapid spread can be often elicited, differing from the slow spread of migrainous aura and the abrupt onset of negative symptoms in brain ischemia. Postictal suppression results in neuronal dysfunction expressed clinically as negative neurologic symptoms and signs.

Todd's paralysis is probably the most widely known postictal phenomenon, referring to hemiparesis contralateral to the hemisphere with the seizure focus. Known history of epilepsy, witnessed seizure activity, and identification of characteristic electroencephalogram (EEG) patterns, if obtained in a timely manner could point toward the diagnosis. Clouding of consciousness is much more common with seizures than it is with TIAs.

However, in many real life scenarios historical details are sparse and EEG is not readily available routinely, making the diagnosis often indistinguishable from stroke. To add to the diagnostic conundrum, a number of stroke patients often develop epilepsy, probably as a result of post-stroke gliosis [1•]. Brain imaging using CT or MRI perfusion can be helpful in recognizing occult seizures as the cause of a transient neurologic event. Regions of the brain participating in the seizures have increased perfusion, in contrast to brain ischemia patients who show underperfusion.

Migraine and migraine accompaniments

Migraine with aura is another commonly identified SM, comprising 10.6 %–45 % of SMs. [21, 22]. Migrainous aura is thought to be the clinical manifestation of the phenomenon of cortical spreading depression, a slowly evolving wave of electrophysiologic cortical hyperactivity followed in short succession by cortical suppression [23]. There are several characteristic clinical features that should point the clinician towards this diagnosis. Overwhelming predominance of positive phenomena at the beginning of the episode; visual disturbances in the form of flashing colorful lights, bright white zig-zag lines, collectively described as "scintillating scotomata" are characteristic [24]. Sensory disturbances in the form of paresthesias are very commonly described as well. Negative phenomena might ensue in the wake of positive phenomena; for instance positive visual symptoms might give way to a visual field defect and paresthesias are replaced by numbness. A key feature of migrainous aura is build-up and slow spread: Visual forms often become brighter and larger or move across the visual field during a period of minutes before they are slowly replaced by a scotoma. Similarly, tingling might start in the distal hand and gradually spread up in the arm, to be followed by numbness. In a very similar fashion, there is spread from one

modality to the other, as the wave of dysfunction slowly moves from one cortical area to another, usually in a postero-anterior direction. Slow resolution of visual symptoms is followed by sensory phenomena, which can be succeeded by language disturbances. Migrainous auras usually last 20–30 minutes, although on occasions they can persist for hours.

In contrast, spread of symptoms is rarely seen in cerebrovascular ischemia. Symptoms occur abruptly and with concurrent involvement of all affected modalities at onset. Stepwise progression of symptoms can occur, but not a shift from one modality to another. TIAs are by definition transient as are migrainous auras, and despite variability in their time duration, the great majority last less than 1 hour, usually a few minutes [25, 26].

Of particular importance are so-called migraine accompaniments of the elderly, essentially representing acephalgic migraine in patients older than 45 years of age with no prior history of migraine [27].Those resemble migrainous aura in many aspects, albeit the absence of prior migraine history, first appearance at a later age (typically over 45 years old) and co-existence of vascular risk factors add to the diagnostic challenge. Following CM Fisher's original description, presence of migrainous visual accompaniments was established to occur with a frequency of 1.23 % and a mean age of onset of 56 years. In 60 % of the subjects the symptoms were never accompanied by headache [28].

Conversion/somatoform disorder

Conversion disorder, hysteria, "functional," somatoform disorder are terms that can be found in the literature and are used interchangeably to describe occasions where despite thorough workup no underlying organic cause is found and the condition is considered to be psychogenic in nature. Their frequency highly varies among different studies, ranging from as low as 4 % to approximately 40 % [21, 22, 29, 30]. On average, approximately 25 %–30 % of situations mimicking stroke are psychogenic in nature [19, 20, 31]. The diagnosis can be particularly challenging, although on occasions patients' odd affective responses, psychiatric comorbidities, and a history of similar episodes might offer useful clues.

Toxic/metabolic disturbances

Several metabolic derangements can present with global or focal neurologic dysfunction. Their frequency among SMs ranges from 3 % to 30 % [21, 22]. Glucose level abnormalities, especially hypoglycemia, are probably the most widely recognized, often presenting with focal neurologic deficits indistinguishable from stroke. In the study of Bunser et al. where 30 % of SMs were found to be metabolic in nature, 53 % of those were secondary to hyponatremia. Glucose fingerstick check and routine labwork performed in every patient as part of the acute stroke protocol, minimizes the likelihood of missing the diagnosis.

Tumor

Tumors and other space occupying lesions such as subdural hematomas can present with focal neurologic semiology. Their frequency is relatively low: 4 %–13 % [20, 21, 29]. Features from the history (progressive course) and

imaging, obtained routinely in all patients in the acute phase help differentiate them from other etiologies of focal neurologic dysfunction.

Encephalitis/meningitis

Encephalitis, meningitis, and other infectious processes were found in 7 %–14 % of SMs [2, 20, 21]. Fever, meningismus, headache, and signs of systemic infection should alert the clinician to the possibility of this alternative diagnosis.

Demyelination

There are several demyelinating disorders of the CNS including multiple sclerosis (MS), neuromyelitis optica, and acute disseminated encephalomyelitis. Practically, multiple sclerosis is by far the most commonly encountered, representing 14 % of SMs in a study [2]. Neurologic symptoms of MS can present in an acute fashion, resembling brain ischemia. More specifically, the clinician should be aware of a particular syndrome: short-lived paroxysms of dysarthria (less than 1 minute) with or without ataxia were described in MS patients in the 1960s and since then further reports have reliably replicated the original observation [32–34]. They can be the first clinical manifestations of the disease [35]. Further reports including imaging correlates have almost unequivocally revealed lesions in the brainstem, usually below the level of the red nucleus in the midbrain [36, 37].

Younger age, absence of classic vascular risk factors, and characteristic clinical syndromes such as optic neuritis, internuclear ophthalmoplegia, cerebellar syndromes, and myelopathic symptoms, and signs referable to spinal cord demyelination are useful clues. Ancillary testing, including MRI imaging and possibly CSF studies is of paramount importance in establishing the diagnosis.

Miscellaneous

A number of other conditions mimic stroke: peripheral vestibular disorders (6.2 % in 1 study) [21], cranial neuropathies (Bell's palsy being the most common), and syncopal events are not uncommon.

Transient global amnesia, a term introduced in the 1960s, is an enigmatic phenomenon characterized by acute onset anterograde amnesia of short duration, usually lasting a few hours [38]. It occurs more frequently in ages older than 60 years, often precipitated by physical activity and preservation of neurologic function, including language, during the ictus are key features [39]. Although several mechanisms have been postulated, neither ischemia, nor seizure activity are demonstrable and prognosis is favorable [40, 41].

Peripheral neuropathies, particularly pressure palsies with unlar, radial, median, or peroneal nerve involvement can often be mistaken for stroke. Recognition of specific patterns of weakness and sensory deficits with root or nerve distribution, and history of inciting event such as trauma or assumption of abnormal posture for prolonged period of time (eg, during surgical procedure) are useful clues.

Confusional states, especially in the elderly, were found to comprise 3 % of the stroke-like conditions [1•]. In this patient group, coexistence of dementing illness, vascular risk factors, and history of prior stroke pose a particular di-

agnostic challenge. Of all the neurodegenerative disorders, Lewy-body dementia is known for acute or subacute fluctuations in cognition that often alert caregivers and are notoriously difficult to distinguish from acute neurovascular events [42].

Clinical and demographic characteristics of patients with stroke mimics

Since advancing age and cardiovascular risk factors such as hypertension, diabetes mellitus, hypercholesterolemia, and atrial fibrillation are considered risk factors for stroke, an association between those and stroke would be expected. In patients with SMs the severity of the neurologic deficit at presentation and long-term outcome is more favorable, given that many of the SMs are reversible conditions without significant brain damage.

These observations were confirmed by a number of studies. SM patients are consistently found to be younger than patients with established ischemic stroke diagnosis [2, 18–22, 30, 43]. One study in particular found that in patients younger than 50 years, approximately 1 in 5 patients with a stroke-like presentation had no stroke, in contrast to less than 1 in 20 for patients aged 50 years or older [22].Conversely and of equal importance, the same study showed that older patients should be regarded with more caution, as some initially assigned to the SM group were eventually found to have an ischemic stroke.

Another characteristic that emerges consistently is lower National Institutes of Health Stroke Scale (NIHSS) score on presentation [18–21]. SM patients were found to be 5 times more likely to have a NIHSS score of 1–4 [19]. Lower incidence of cardiovascular risk factors is seen in SM patients, though this is not a consistent finding, and when identified it represented a trend rather than a statistically significant difference [18, 20, 21].

SM patients are significantly more likely to present with left hemispheric symptoms [2, 20, 21, 43–45]. More specifically, global aphasia without hemiparesis was consistently found to be a very common clinical presentation in SM patients (10 times more likely than acute ischemic stroke) [45].

On the contrary, older age, definitive time of symptom onset, definite history of focal neurologic symptoms, and NIHSS >5 and especially >10 significantly increased the odds of ischemic stroke [4•].

Functional outcome has consistently been found to be favorable in SM patients with no deaths and more than 90 % functional independence in long-term follow-up [2, 18–20, 30, 45].

Suggested diagnostic approach

Kidwell and Warach coined the term “acute ischemic cerebrovascular syndrome” to encompass both TIAs and strokes [20]. TIAs and strokes have the same cause and each carries similar frequencies of further brain ischemia and infarction. Patients with clinical TIAs often have brain infarcts on imaging so that these events are not really transient. The importance lies in applying the same diagnostic and therapeutic rigor in evaluating all patients with acute cerebrovascular events regardless of timing.

The diagnosis of an acute cerebrovascular ischemic event requires thorough history taking including the pace of onset, duration, and resolution of symptoms (in case of TIA), nature of symptoms, circumstances at the time of

onset, prior similar episodes, associated features, vascular risk factors, family history etc. A detailed physical and neurologic examination including fundoscopy and cardiovascular assessment (cardiac rhythm, bruits in the neck, orbit, groin, peripheral pulses, electrocardiogram) are important. When the diagnosis between a vascular and non vascular cause is difficult to distinguish by history and examination, a neurologist with subspecialty training in stroke can be a very helpful consultant. The importance of urgent assessment and intervention in patients who have TIAs and minor strokes was shown in a study that showed a decreased frequency of subsequent strokes from 10 % to 2 % [46••].

The investigations that should be carried out on an urgent basis include brain parenchymal neuroimaging and vascular imaging. These studies are important irrespective of when the patient presents. Knowing the nature, location, and cause of the event is crucial in planning effective treatment. Many patients will also need cardiac rhythm monitoring, cardiac and aortic imaging, atherosclerotic and other laboratory testing and sometimes, tests for rarer disorders to clarify the etiology of brain ischemia and hemorrhage.

Neuroimaging plays a fundamental role in diagnosis and management decisions in acute stroke. Imaging in patients with acute stroke should be targeted toward assessment of the 4 Ps – parenchyma, pipes, perfusion, and penumbra – as described by Rowley [47].

Non-contrast head CT is the most widely available and convenient modality in the acute setting. It is a useful screening tool to rule out hemorrhage, tumors or established infarcts (greater than 6–12 hours old). In patients who have TIAs and minor or very early strokes, no abnormalities are expected to be seen on CT. MRI, and more specifically diffusion weighted imaging (DWI) is superior for detecting acute as well as small areas of brain ischemia. This includes patients with TIA, of whom one-third are found to have lesions attributable to brain ischemia [48]. It is also the superior modality for detecting posterior circulation ischemia, an area of frequent misdiagnosis [49].

Some patients with stroke risk factors and characteristic clinical syndromes do not show DWI positive areas of infarction. Early imaging and small brainstem infarctions are factors that can lead to false negative scans [29, 50]. Some areas of brain are underperfused but not yet infarcted ("stunned"). Although a normal DWI scan should alert clinicians to consider non-ischemic etiologies, brain ischemia remains the best clinical diagnosis in many of these patients, stressing the importance of clinical judgment, thorough knowledge of cerebrovascular anatomy and familiarity with characteristic stroke syndromes. In these patients, vascular imaging and perfusion studies are very helpful. Vascular imaging is important in establishing the status of both intracranial and extracranial vessels, to understand the etiology and risk of further ischemic events, and to formulate a treatment plan. The modalities available are carotid Doppler, transcranial Doppler (TCD), CT and MR angiography, and conventional angiography.

An important concept in acute cerebrovascular pathophysiology is that of the "ischemic penumbra." Acute brain ischemia results in a central infarcted tissue core with a surrounding region of stunned cells that is called an ischemic penumbra, which is underperfused but not yet infarcted. Residual blood flow comes from inadequate antegrade flow through stenosed vessels and from collateral blood vessels. The penumbra is a dynamic entity that exists within a narrow range of perfusion pressures; the duration of the delay in recanalization is inversely related to the size of the penumbra [51]. The

ischemic penumbra can be evaluated by CT and MR perfusion methods, appearing as a larger perfusion than diffusion zone. This concept has important therapeutic implications for selection of patients for acute therapy. Thrombolytics are used in patients who have occluded neck or intracranial arteries without large brain infarcts, and do have a large penumbral area. Thrombolytics should not be given to patients who have large infarcts and minimal or no penumbral zones since they have little benefit and have an important risk of hemorrhage after recanalization [52].

Cardiac and aortic imaging are also essential in some patients to establish the etiology of cerebrovascular events, especially cryptogenic in nature. Echocardiography is used to detect lesions associated with sources of embolism such as regional wall motion abnormalities, cardiac thrombus or mass, endocarditis, aortic arch atheroma, and patent foramen ovale (PFO). EKG and prolonged telemetry is recommended in patients with cryptogenic brain ischemic events to detect cardiac ischemia and paroxysmal atrial fibrillation. The optimal duration for outpatient telemetry has not yet been established but recent studies have found significant increases in detection of paroxysms of atrial fibrillation with monitoring for 7 or 30 days or longer [53].

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Conflict of Interest

Dr. Vasileios-Arsenios Lioutas reported no conflicts of interest relevant to this article.
Dr. Shruti Sonni reported no conflicts of interest relevant to this article.
Dr. Louis R Caplan reported no conflicts of interest relevant to this article.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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This is a reference to a study performed on 821 patients admitted to an acute stroke unit that evaluated the frequency and causes of misdiagnosis of stroke. The study found that the initial diagnosis of stroke was incorrect in 13% of patients, and the most common causes were seizures, confusional states, and syncope. This study demonstrated the importance of clinical skill in making a correct diagnosis, with accuracy ranging from 38% to 89%.

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This is an observational, prospective study carried out in an urban teaching hospital with a 16-bed stroke unit and access to typical laboratory and imaging investigations necessary for a thorough stroke workup. The authors sought to identify the frequency of stroke mimics and bedside pointers to the diagnosis of stroke. Three hundred-fifty consecutive presentations of "brain attack" suspicious for acute stroke were studied. A definitive non-stroke diagnosis was made in 19% of cases. Seizure was the most frequent mimic (21.1%). Clinical, bedside pointers to stroke diagnosis included severe deficit (especially NIHSS >10), exact time of symptom onset, lateralization of neurologic symptoms, and signs and presence of cardiovascular risk factors in the appropriate clinical context. Those were identified after multivariate analyses.

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