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SECONDARY HEADACHE (M ROBBINS, SECTION EDITOR)

Migraine as a Stroke Mimic and as a Stroke Chameleon

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Abstract

Purpose of Review This review details the frequency of and ways in which migraine can be both an ischemic stroke/transient ischemic attack mimic (false positive) and chameleon (false negative). We additionally seek to clarify the complex relationships between migraine and cerebrovascular diseases with regard to diagnostic error.

Recent Findings Nearly 2% of all patients evaluated emergently for possible stroke have an ultimate diagnosis of migraine; approximately 18% of all stroke mimic patients treated with intravenous thrombolysis have a final diagnosis of migraine. Though the treatment of a patient with migraine with thrombolytics confers a low risk of complication, symptomatic intracerebral hemorrhage may occur. Three clinical prediction scores with high sensitivity and specificity exist that can aid in the diagnosis of acute cerebral ischemia. Differentiating between migraine aura and transient ischemic attacks remains challenging. On the other hand, migraine is a common incorrect diagnosis initially given to patients with stroke. Among patients discharged from an emergency visit to home with a diagnosis of a non-specific headache disorder, 0.5% were misdiagnosed. Further development of tools to quantify and understand sources of stroke misdiagnosis among patients who present with headache is warranted.

Summary Both failure to identify cerebral ischemia among patients with headache and overdiagnosis of ischemia can lead to patient harms. While some tools exist to help with acute diagnostic decision-making, additional strategies to improve diagnostic safety among patients with migraine and/or cerebral ischemia are needed.

Keywords Acute ischemic stroke · Diagnostic error · Stroke mimic · Migraine · Migraine with aura

Introduction

Rapid diagnosis of acute ischemic stroke is imperative due to the time-dependent nature of many acute stroke therapies [1, 2] as well as the increased risk of recurrence shortly after even minor or transient index ischemic events [3]. On the other hand, the pressure to make fast diagnostic and treatment decisions may lead to stroke overdiagnosis [4]. Erroneously identifying patients as having cerebral ischemia when they have an alternative cause of their symptoms can result in patient harm [5]. There are thus two broad categories of ischemic stroke misdiagnosis: stroke mimics and stroke chameleons. Stroke mimics are false-positive cases and stroke chameleons are false-negative cases [6]. Although there are important differences between stroke mimics and stroke chameleons, the US National Academy of Medicine has identified both overdiagnosis and underdiagnosis as major public health problems, noting that improving the diagnostic process is "a moral, professional, and public health imperative" [7••].

Diagnostic error among patients with suspected ischemic stroke or transient ischemic attack (TIA) remains a persistent challenge. A recent meta-analysis found that the overall rate of cerebrovascular misdiagnosis in the emergency setting was roughly 9%; a false-negative rate of 8.7% and a false-positive rate of 7.3% were found [8•]. Migraine can be misinterpreted as an ischemic stroke or TIA (i.e., stroke mimic) [9••, 10, 11], or, alternatively, migraine can be posited as an initial diagnosis in cases of unrecognized cerebral ischemia (i.e., stroke chameleon) (Table 1) [8•, 12, 13]. Dangerous cerebrovascular diseases that are non-ischemic (e.g., intracerebral hemorrhage, posterior reversible encephalopathy syndrome [PRES]) can present with isolated headaches and be initially misdiagnosed as migraine or other headache conditions [14, 15], but such misdiagnosis is likely less frequent [16••]. This may be related to the fact that intracranial bleeding

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Table 1 Basic matrix of migraine as a stroke mimic and as a stroke chameleon

		Disease	
		Ischemic stroke	No ischemic stroke
Diagnosis given	Stroke	True	False-positive stroke (i.e., stroke mimic). • Frequent correct diseases missed: - *Migraine* - Seizure - Psychiatric disease
	Not stroke	False-negative stroke (i.e., stroke chameleon). • Frequent incorrect diagnoses given: - *Migraine* - Benign vertigo - Altered mental status	True

can be reliably ruled out by non-contrast head CT whereas acute ischemic cerebrovascular disease cannot [17–19].

The pathophysiologic relationship between migraine and cerebral ischemia is complex. Migraine with aura is a well-recognized stroke risk factor, aura symptoms can mimic focal neurologic deficits, and migraine can cause cerebral infarction [20, 21]. On the other hand, acute ischemic stroke can cause a secondary headache or trigger a migraine attack [22]. This review will focus on migraine as a mimic and as a chameleon of ischemic cerebrovascular disease, with a special emphasis on recent findings.

Migraine as a Mimic

Migraine as an Ischemic Stroke Mimic

As defined by the International Classification of Headache Disorders, third edition (ICHD-3), migraine with aura consists of "recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other CNS symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms" [23]. The aura is a complex of neurologic symptoms that typically begin before the onset of headache, but may continue into the headache phase or, in some cases, begin afterward [24, 25]. Recognized aura symptoms include visual (most commonly), sensory, speech and/or language, motor, brainstem, and retinal phenomena [26]. The aura is responsible for the focal deficits associated with migraine attacks [23]. It is therefore unlikely for migraine without aura to be an ischemic stroke/TIA mimic—although headache without aura remains an important stroke chameleon. Additionally, aura can occur in the absence of headache (i.e., typical aura without headache) further complicating a clinician's ability to avoid stroke or TIA overdiagnosis [27].

A number of phenomenological facts highlight the conundrum of differentiating migraine aura from ischemic stroke or TIA. Because aura symptoms may be multiple, they can masquerade as stroke syndromes. For example, a combination of visual (hemianopsia) and hemiparesthetic aura may suggest infarction in the posterior cerebral artery territory. Although multiple aura symptoms usually proceed in succession unlike stroke symptoms, which are unlikely to evolve over time [28], in practice, obtaining a history of progression of symptoms may be difficult in the emergency setting [29, 30]. Furthermore, patients often have difficulty describing aura symptoms [26]. For example, patients may report acute rather than gradual or spreading onset and/or incorrect lateralization [23, 29, 31], which further complicates distinguishing between migraine aura and stroke on clinical grounds. Aura symptoms have a defined duration of 5–60 min, but the maximal aura duration is 60 min multiplied by the number of symptoms. Rarely, aura symptoms can persist for a very long time—months or even years [32–34]. Beyond 1 week, such symptoms are defined by the ICHD-3 as persistent aura and may be difficult to differentiate from stroke, which can be defined as "clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death," provided that other etiologies are excluded, even in the absence of additional evidence of cerebral infarction [35].

Hemiplegic migraine, any migraine with aura including motor weakness, is perhaps the primary headache disorder most likely to be mistaken for stroke. It is very rare, with a prevalence estimated at 0.01%. Among patients with hemiplegic migraine, motor symptoms typically last up to 72 h but may persist for weeks [36]. An entity dubbed non-familial migraine with unilateral motor symptoms (MUMS) may be another important stroke mimic [37]. In a retrospective study comparing patients with self-reported unilateral motor weakness and migraine to control patients with migraine, the 24 patients with MUMS had more symptoms of migraine, cranial autonomic activation, and allodynia than controls. Unilateral weakness in MUMS was usually ipsilateral to the headache, associated with sensory complaints, and reported to have spread in a rostro-caudal pattern. On neurological examination, MUMS weakness always had a give-way character, and

facial involvement was rare; more than half of patients with MUMS reported weakness between migraine attacks. Since they found similar rates of psychiatric illness in cases and controls, the study authors suggest that the unilateral weakness seen in MUMS is due to a disordered protective reflex in the context of severe allodynia, but more evidence is needed to support their claim [38]. Studies designed to measure how often MUMS is an acute stroke mimic and to better characterize the minority of stroke mimic patients with functional neurological disorders are needed [39].

Differentiating between a migraine attack and acute cerebral ischemia can be particularly challenging in the acute setting. When a patient potentially with ischemic stroke is eligible for intravenous thrombolytic therapy, waiting for their neurological symptoms to improve or evolve over time to achieve diagnostic clarity is not advisable [40]. A number of clinical scores have recently been developed to help clinicians efficiently and effectively differentiate between stroke and stroke mimics acutely. Though none of these scores were exclusively designed to distinguish between true cerebral ischemia versus primary or secondary headache conditions, patients with a final diagnosis of migraine were included in each of the scores' derivation cohorts. The FABS score assigns points according to the presence of six variables: the absence of facial droop, negative history of atrial fibrillation, age < 50 years, systolic blood pressure < 150 mmHg at presentation, history of seizures, and isolated sensory symptoms without weakness at presentation. A total of five stroke mimic patients included in one of the FABS derivation cohorts had a final diagnosis of migraine [41]. A FABS score ≥ 3 identified stroke mimics with 90% sensitivity and 91% specificity among patients with symptoms of acute ischemic stroke and negative head CT within 4.5 h of symptom onset [42••]. The TeleStroke Mimic-Score (TM-Score) was developed via a review of telemedicine stroke consultations requested in the emergency setting [43, 44]. The TM-Score is a prediction rule that calculates the percent likelihood of being a stroke mimic based on age, history of atrial fibrillation, history of hypertension, history of seizure, presence facial weakness, and NIHSS > 14. In receiver operating characteristic curve (ROC) analysis, the TM-Score performed well; the area under the curve (AUC) was 0.75 in the derivation cohort, 0.71 in the internal validation cohort, and 0.77 in the external validation cohort. In the derivation cohort, headache/migraine with or without aura was the alternative diagnosis in 2.9% of included stroke mimics [43, 44]. Finally, the 2CAN score was developed for use in the inpatient setting based on a review of data from requested emergent inpatient stroke codes at a single academic center. Three patients with migraine were included in the derivation cohort. Points are based on the clinical deficit scale (i.e., a simplified stroke scale derived from items on the NIHSS), history of a recent cardiac procedure, history of atrial fibrillation, and being a new patient. A 2CAN score of ≥ 2 had 92% sensitivity and 69% specificity for identifying patients with ischemic stroke [45].

Migraine as a Transient Ischemic Attack Mimic

The diagnostic distinction between TIA and migraine may be more difficult than that between migraine and stroke due to the lack of a gold standard for the diagnosis of TIA, with marked diagnostic disagreement even among expert clinicians [46]. Migraine with aura is perhaps the most common TIA mimic [47–49]. Additionally, the presence of headache has been shown to predict diagnostic discordance among TIA patients between emergency medicine physicians and neurologists [50].

A TIA is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction [51]. In clinical practice, however, there is persistent variability as to which patients have advanced neuroimaging to assure the absence of infarction [52]. Minor stroke and TIA portend a high risk of ischemic stroke in the near future [3]; failure to diagnose TIA can delay timely initiation of secondary prevention, including dual antiplatelet therapy, which can significantly reduce recurrent stroke risk [53]. Meanwhile, overdiagnosis of TIA may expose patients to unnecessary testing, inappropriate treatments, and costs [54, 55]. Several clinical features can help distinguish migraine aura with or without headache from TIA. Among patients with transient neurologic deficits, older age, male gender, and history of stroke, hypertension, or dyslipidemia were significantly more frequent among patients with TIA as opposed to those with migraine with aura or migraine aura without headache [56].

Recent work has highlighted definitional issues concerning TIAs and migraine as a stroke mimic [57, 58••]. When applying the ICHD-3 beta criteria to 120 consecutive patients diagnosed with TIA after MRI or CT, more than 25% of patients fulfilled the criteria for migraine with aura when only one attack was considered [57]. In a related study, the same group developed explicit diagnostic criteria for TIA, using the format of the ICHD, which were then tested for sensitivity in 120 patients previously diagnosed with TIA, and for specificity in 1542 Danish and Russian patients previously diagnosed with migraine with aura. The sensitivity of the proposed TIA criteria was 99% and the specificity was 95–96% [58••]. Although further testing is required, the development of operationalizable diagnostic criteria is a promising direction in the disambiguation of TIA and migraine with aura.

Frequency of Migraine with Aura as Mimic of Cerebral Ischemia

In general, stroke mimics represent a non-trivial amount of possible patients with stroke evaluated in the acute setting.

In a large single-center study including 8187 consecutive patients referred by the ED for evaluation of possible stroke (i.e., stroke code called), 30% were stroke mimics [59]. In a recent systematic review, migraine was the third most commonly reported diagnosis after seizures and psychiatric disorders among stroke mimics [9••]. Almost 2% of all patients evaluated in the ED for possible stroke have migraine; migraine with aura was the final diagnosis in approximately 18% of stroke mimic patients acutely treated with thrombolysis included in the systematic review [9••]. Somewhat reassuringly, the risk of adverse events with thrombolytic treatment of stroke mimics was very low (~0.01%), and no cases of intracerebral hemorrhage were found [9••]. However, in the aforementioned systematic review, new data from the Safe Implementation of Treatment in Stroke (SITS) investigators was not included. The SITS investigators recently reported that one of the five cases of intracerebral hemorrhage noted among 429 treated stroke mimics had migraine [10]. Rates of treated and untreated stroke mimic patients and related patient harms should continue to be monitored across institutions to assure diagnostic safety. Importantly, methods to improve diagnostic consensus among providers after a patient has received thrombolysis and experienced symptomatic improvement are needed [60].

Future Directions for Stroke Mimics

There are a number of potential routes to reduce stroke mimic rates. To begin with, facilitating the use of existing scores in clinical practice to acutely discriminate mimics from true cerebral ischemia may be useful. Additionally, developing scores and clinical decision support tools specific for migraine with aura is a promising future direction. Advanced neuroimaging may also improve diagnostic accuracy. Protocols for the selective use of hyperacute MRI have already been used in some centers to improve stroke diagnostic accuracy [5, 61]. However, the utility of MRI is limited in minor and posterior circulation strokes [62–64] as well as for aborted strokes [65]. Biomarkers of recent cerebrovascular events would be invaluable diagnostic tools for the purpose of distinguishing MRI-negative ischemic events from migraine aura, as well as other mimics. Endothelial P-selectin has been identified as a marker of endothelial activation and therefore a potential biomarker of TIA in a mouse model [66•]. Similar approaches leveraging the cerebrovascular inflammatory response as a "vascular footprint" may prove promising [67]. The ongoing Ischemia Care Biomarkers of Acute Stroke Etiology (BASE) trial aims to validate blood-based biomarkers that may not only differentiate among stroke etiologies but also differentiate TIA from acute ischemic stroke as well as TIA from non-ischemic, transient neurologic attacks (NCT02014896) [68].

Migraine as a Chameleon

The relationship between stroke and migraine as a stroke chameleon is complex. As a first step, differentiating between cases where headache and migraine occur in close temporal proximity versus at separate times is useful (Fig. 1) [22]. When a patient presents with headache at the same time or in close temporal proximity to acute ischemic stroke or TIA symptom onset, the two events are synchronous and thus related. Secondary headaches precipitated by stroke/TIA can have a migrainous semiology [23]. Rarely, stroke can occur during the course of a typical migraine with aura attack (i.e., migrainous infarction) [21, 69]. There may be other instances where stroke/TIA triggers a migraine attack or when a migraine attack triggers stroke/TIA so that the two events occur in close temporal proximity to each other [22]. Despite the different subtypes of synchronous stroke/TIA, headache, and migraine events, all of these instances represent opportunities for misdiagnosis insofar as if cerebral ischemia is not identified, then a false-negative stroke diagnosis will be made.

Alternatively, patients with cerebral ischemic events may have headaches not temporally related to their stroke/TIA. This includes patients with active migraine with aura or a history of migraine with aura who suffer a stroke/TIA as well as patients with prior stroke/TIA who suffer a migraine. Migraine attacks and cerebral ischemia that occur asynchronously thus may be unrelated; both migraine and stroke are highly prevalent in the population [72, 73]. However, even when not temporally associated, migraine with aura and stroke/TIA can be related since migraine with aura is a well-established risk factor for cerebrovascular disease [70]. Additionally, migraine can change or develop after a stroke [23]. Finally, a single underlying process can cause both migraine and cerebrovascular disease (Table 2) leading to either synchronous or asynchronous events (Fig. 1). When migraine and stroke are not synchronous, diagnostic errors are likely less frequent than when the two events occur in close temporal proximity. But, if a patient with asynchronous headache and migraine is misdiagnosed, whether they are a stroke mimic or a stroke chameleon will depend on their presenting symptoms and their true underlying disease process.

Secondary Headaches in Patients with Stroke/TIA

Secondary headache is a de novo headache type that appears "in close temporal relation to another disorder that is known to cause headache" [23]. The headache may semiologically resemble migraine (or another primary headache type) but is nevertheless considered a secondary headache. The ICHD-3 stipulates that scientific evidence must exist showing that the primary disorder is capable of causing headache as is the case with most cerebrovascular diseases [23].

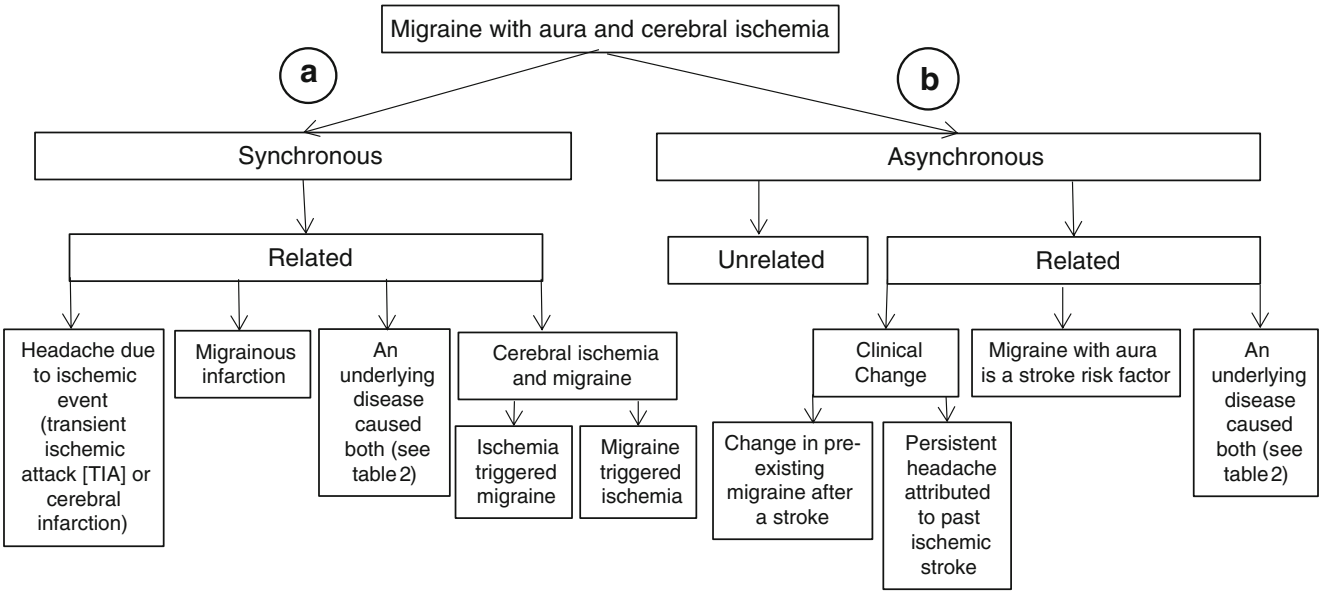

Fig. 1 Schema of clinical connections between migraine with aura and cerebral ischemia. There are a variety of ways in which a migraine attack and cerebral ischemia can be related. A headache can occur in close temporal proximity (synchronous) to an acute cerebral infarction suggesting a close relationship between the two [22]. When the events are synchronous (A), headache may be caused by ischemia or one may trigger the other. Rarely, migrainous infarction can occur [21]. If cerebral ischemia and migraine are asynchronous (B), the two events may be unrelated (i.e., stroke due to extra-cranial atherosclerotic disease in a patient with migraine) or related. Stroke can lead to a persistent headache or, among patients with pre-existing migraine, a change in headache semiology can occur after stroke [23]. Another source of relatedness between cerebral ischemia and migraine is the fact that migraine with aura is an independent stroke risk factor [70], and structural brain changes are seen in migraine with aura patients [71]. Finally, a migraine attack and an episode of cerebral ischemia can occur either synchronously or asynchronously when both are due to the same underlying condition (e.g., CADASIL) as detailed in Table 2

The pathophysiology of headache in ischemic stroke/TIA has not been fully elucidated. Cortical spreading depression triggered by cerebral ischemia, release of inflammatory or cytotoxic substances due to tissue injury, and stroke-induced damage to structures involved in physiologic pain processing have all been posited [90]. It is not uncommon for patients with true ischemic stroke or TIA to complain of a headache [91, 92]. For example, in a multicenter hospital-based stroke registry of 2196 patients, investigators found that 27% of patients experienced headache at symptom onset [92]. Head pain associated with acute stroke has been described as dull or pressing in quality, unilateral or bilateral, and tension type or migraine type [92, 93]. Headache features have poor sensitivity and specificity for acute cerebrovascular pathology, with the exception of the "thunderclap" onset of headache associated with subarachnoid hemorrhage [94]. In a recent meta-analysis of 15,721 patients across 23 studies reporting diagnostic accuracy for ischemic stroke, transient ischemic attack (TIA), and subarachnoid hemorrhage (SAH) in the emergency setting, investigators found that migraine or non-migrainous headache was the most common diagnosis (26.1%) in cases of misdiagnosis [8•]. Other factors associated with a missed diagnosis of stroke among patients who present with headaches included younger age, female gender, and non-white ethnicity [8•].

The frequency of headache among patients with TIA varies in the literature between 16 and 36% [95, 96]. In a seminal study of headache features in 3126 patients with minor stroke or TIA by the Dutch TIA Study Group, headache occurred in 18% of patients [95]. More recently, in a study of 120 consecutive patients with TIA, those with TIA case-control were more likely to have suffered a migraine attack within the prior year, had a headache within the prior week, or were to present with a new headache type as compared to controls. Headache in the week prior to TIA was more frequent in posterior circulation TIA than anterior circulation TIA [97]. The diagnostic utility of headache as a TIA warning symptom requires future research.

It is worth noting that headache complaints are more common in patients with intracranial hemorrhage [98, 99] and cerebral venous thrombosis [100–102] than those with cerebral ischemia, but a detailed discussion of this association is beyond the scope of this review Table 2.

Migrainous Infarction

Migrainous infarction is defined by the ICHD-3 as "one or more migraine aura symptoms occurring in association with an ischemic brain lesion in the appropriate territory demonstrated by neuroimaging, with onset during the course of a typical migraine with aura attack" [23]. Migrainous infarction

Table 2 Other conditions associated with both migraine and cerebrovascular events

CADASIL
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a genetic vasculopathy affecting the small cerebral vessels. It presents with early-onset small vessel disease, stroke, subcortical dementia, and migraine with aura. Aura can be unusually prolonged [74].

SMART
Stroke-like migraine attacks after radiation therapy (SMART) denotes a syndrome characterized by migrainous headache, "stroke-like" reversible neurologic symptoms, seizures, and transient gyriform gadolinium-enhancement, occurring as a delayed sequela of cerebral radiation [75].

HaNDL
The syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL) presents with episodic migraine-like headache with associated aura-like neurologic deficits and CSF lymphocytic pleocytosis. The disease is self-limiting. An autoimmune etiology has been proposed [76].

MELAS
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is maternally inherited mitochondrial disorder. Its clinical manifestations include "stroke-like" neurologic deficits, which, however, do not respect vascular territories, migraine-like headaches with or without aura, dementia, epileptic seizures, and other manifestations of multi-organ involvement [77].

RCVS
Reversible cerebral vasoconstriction syndrome (RCVS) presents with thunderclap headache, which may be triggered by sexual activity, vasoactive drugs, exertion, emotion, and/or Valsalva maneuvers; thunderclap headache can recur. Headache may be the only symptom (majority of cases), but ischemic infarction, intracranial hemorrhage, and seizures can occur. Diagnosis is made based on clinical criteria and the presence of reversible angiographic abnormalities [78].

PRES
Posterior reversible encephalopathy syndrome (PRES) refers to a heterogeneous disorder characterized by (usually) reversible subcortical vasogenic edema, variable neurologic symptoms (including encephalopathy, headache, seizure, and visual disturbances), and the presence of typical predisposing conditions (hypertensive crisis, pre-eclampsia, eclampsia, renal failure certain autoimmune disorders, or cytotoxic drugs). The pathogenesis is presumed to be a failure of cerebral autoregulation and/or increased vascular permeability. Both cerebral ischemia and intracranial hemorrhage can be seen in PRES [79].

Sneddon syndrome
Sneddon syndrome is a progressive non-inflammatory thrombotic arteriopathy characterized by livedo reticularis and recurrent cerebral ischemia. Other neurologic and systemic manifestations, including headache, are also seen. The etiology may be idiopathic or associated with autoimmune diseases such as systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APLS) [80].

CAA
Cerebral amyloid angiopathy (CAA) results from beta-amyloid deposition in the small cortical and leptomeningeal arteries. CAA can present with lobar hemorrhages, dementia, and transient focal neurological episodes (TFNE) sometimes termed "amyloid spells." Since TFNE can consist of both positive and negative neurological symptoms, they can mimic cerebral ischemia as well as migraine aura [81].

Moyamoya angiopathy
Moyamoya angiopathy is a chronic cerebral vasculopathy that is characterized by progressive bilateral stenosis of the distal internal carotid arteries and their major proximal branches. Both Moyamoya disease and Moyamoya syndrome are associated with cerebral ischemia as well as intracerebral hemorrhage. Headache is a common manifestation of the disease; these headaches most often are migrainous in quality [82].

Unruptured vascular malformations
Unruptured cerebral arteriovenous malformations (AVM) can present as attacks of migraine with aura, often with ipsilateral lateralization, particularly in the case of occipital AVMs [83]. The headache of arteriovenous fistulas (AVF) more commonly manifests with pulsatile tinnitus, ophthalmoplegia, and/or a positional component [23]. Sturge-Weber syndrome (SWS) is a genetic neurocutaneous disorder characterized by facial capillary malformation ("port-wine stain"), leptomeningeal angiomatosis, and increased intraocular pressure. Patients with SWS may present with focal deficits, seizures, stroke-like episodes, various non-neurologic symptoms, and hemiplegic migraine-like attacks [84, 85].

Giant cell arteritis (GCA)
Giant cell arteritis (GCA) is a predominantly large- and medium-sized vasculitis most commonly affecting older patients. Headache with variable features, constitutional symptoms, and polymyalgia is typical presenting symptoms. When cranial and cervical arteries are involved, cerebral and retinal ischemic events can occur [86].

Cervical artery dissection
Cervical artery dissections are a common cause of stroke in young adults. The characteristic accompanying headache is severe, sudden-onset, and ipsilateral to the dissection site, but headache may also be non-specific in character or reported as neck pain [87].

CVT
Cerebral vein thrombosis (CVT), clotting in the dural sinuses, or cortical veins may cause both cerebral ischemic and hemorrhage. Headache is a highly common presenting feature of this rare disease; headache may be thunderclap-type, progressive, or even migrainous in quality. Encephalopathy, seizures, and signs of elevated intracranial pressure are also seen [88].

Susac syndrome
Susac syndrome is an autoimmune condition affecting the microvasculature of the brain, retina, and inner ear. It is characterized by the clinical triad of encephalopathy, branch retinal artery occlusions, and sensorineural hearing impairment. Headaches, which may be migraine-like in character, are often an early feature [89].

occurs mostly in the posterior circulation and in younger women [69]. True migrainous infarction is a very uncommon event. For example, in the Lausanne Stroke registry, although migraine was common among young patients with ischemic stroke, only 0.3% of ischemic strokes were classified as migrainous infarction [21]. The scope of the problem of misdiagnosis of migrainous infarction is not known.

Migraine Triggered by Stroke

In contrast to secondary headaches induced by cerebrovascular ischemia, it has also been observed that pre-existing headache disorders can be exacerbated by acute ischemic stroke [22,103]. Multiple potential mechanisms linking ischemia and migraine have been explored [104].

Microembolism has been proposed as a possible cause of cortical spreading depression and migraine aura [105, 106] and could account for the higher frequency of white matter lesions of presumed ischemic etiology in migraine with aura patients [71]. In a mouse model, pharmacologically induced thrombosis of single penetrating cortical arterioles consistently produced both cortical spreading depression and delayed ischemic lesions [107]. Research into the complex relationship between cortical spreading depression, microembolism, and ischemia will continue.

Migraine as a Stroke Risk Factor

Migraine with aura, but not migraine without aura, confers about a twofold increased risk of developing acute ischemic stroke [70, 108]. The association is highest in young women with migraine with aura who smoke and use oral contraceptives, a combination which increases stroke risk about ninefold relative to women without migraine with aura [109]. Migraine may also increase the risk of cervical artery dissections [110]. In the Atherosclerosis Risk in Communities (ARIC) study, migraine with visual aura was associated with a significantly increased risk of cardioembolic stroke over the 20-year study period [111•]. The underlying pathophysiology accounting for increased stroke risk in migraine with aura patients has not been elucidated but is independent of traditional cardiovascular risk factors [108]. Patients with migraine also have a higher prevalence of structural brain abnormalities on MRI [71, 112–114], but the practical clinical consequences of this association are uncertain.

Missed Strokes

The vast majority of patients presenting for emergent evaluation of headache do not have acute cerebrovascular disease or any dangerous pathology [115]. However, there is emerging data that a subset of patients who complain of headache are misdiagnosed at index emergency department (ED) presentation. To date, most studies of stroke chameleons have come from cohorts of patients admitted to the hospital from the ED with an admission diagnosis that was not stroke, but who were discharged with a diagnosis of stroke [12, 116–118]. Patients thought to have a benign headache; in contrast, are likely to be discharged directly from the ED to home ("treat-and-release visit") making them more difficult to track compared to inpatients. Administrative claims databases have recently been used to quantify rates of missed cerebrovascular disease diagnosis among patients with treat-and-release ED visits. In a large cross-sectional study using administrative data, 187,188 patients hospitalized for cerebrovascular disease (i.e., stroke, SAH, and TIA) were identified, and it was found that nearly 13% had been discharged from an ED within 30 days prior to admission suggesting possible misdiagnosis. Treat-and-release ED visits for headache were among the most common visit type [13]. In a separate study using administrative claims from six states, 0.5% of the included 2,101,081 patients discharged from an ED with a non-specific headache diagnosis returned with a serious neurological condition within 30 days. The most frequent condition these patients returned for was ischemic stroke. Though this is a small percentage of treat-and-release headache patients, given that headache is a common reason for ED visit, the authors extrapolated that on the national level, their results translate to approximately 40,000 misdiagnosed headache patients annually [16••]. More work is needed to identify headache patients at increased risk of short-term stroke admission as well as to identify factors associated with diagnostic errors resulting in a stroke chameleon diagnosis. The use of data sources that allow for patient tracking after ED discharge and across healthcare institutions is an important way to measure rates of headache misdiagnosis [119•].

Other Conditions

Several very rare conditions may be manifest with migraine type headaches and associated cerebrovascular disease. These entities are listed and described briefly in Table 2 as a signpost to interested readers, but a thorough discussion of these disease entities is beyond the scope of this paper.

Future Directions

As previously mentioned, work on improving the utilization of existing clinical decision tools, developing strategies to improve appropriate neuroimaging use, and identifying biomarkers of cerebral ischemia may help reduce rates of stroke chameleons as well as stroke mimics. Using multi-institutional databases to continue to quantify diagnostic error rates is another important area of growth in improving diagnosis and eventually developing operationalizable metrics [119•, 120]. To assure quantification is accurate, more work is likely needed to develop a standard approach to stroke mimic identification, particularly after thrombolysis administration [60].

There are a few additional strategies to improve stroke/TIA diagnostic accuracy among patients who complain of headache that warrant exploration. Since the distinction between migraine with aura and stroke/TIA must often be made on clinical grounds, witness observations may provide important information for disambiguation of the two. Such accounts may provide clarification regarding past migraine attacks or disclose symptoms or signs of which the patient may be unaware. This approach has been recently shown to be useful in patients with transient loss of consciousness, another common diagnostic quandary for neurologists [121]. Another approach may be to harness machine learning to improve stroke

diagnostic accuracy. A deep learning natural language processing model recently showed an impressive predictive capacity for identifying a cerebrovascular cause among patients with TIA-like presentations [122].

Conclusion

Migraine is both an important mimic of cerebral ischemia as well as a chameleon. The prevalence of headache among patients with acute cerebral ischemia, the diverse nature of migraine aura phenomenology, and the limitations of current diagnostic neuroimaging contribute to diagnostic uncertainty. The absence of explicit diagnostic criteria for TIA or an objective marker that a cerebrovascular event has occurred are impediments to discriminating between migraine aura and TIA. Additionally, the lack of established guidelines for the identification of stroke mimics and the absence of standard measurement tools to track rates of stroke misdiagnoses present significant challenges to researchers in this space. Clinical judgment based on an assessment of vascular risk and careful attention to clinical phenomenology is still necessary to adjudicate between true migraine attacks and cerebrovascular diseases. Developing clinical decision support tools, encouraging the use of existing clinical scores, identifying cerebrovascular biomarkers, improving neuroimaging utilization, and further exploring approaches used to improve diagnostic accuracy in similar disease states represent important future directions.

Compliance with Ethical Standards

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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