ZEBRAS NOT HORSES: ATYPICAL PRESENTATIONS OF CEREBRAL ISCHEMIA IN THE SETTING OF TIA AND STROKE DIAGNOSIS

By: Amanda Mathwig (Med 2)

Home for the Summer Program

Stonewall, Manitoba

Supervisor: Dr. Upali Weebedda

ABSTRACT

A 62-year-old woman with past history of COPD and paroxysmal atrial fibrillation presented to Stonewall ER with hesitancy initiating speech, dysarthria, tremor, and a general feeling of weakness and unsteadiness which had persisted for over 48 hours prior to arrival in emergency. Two days prior, she was diagnosed with TIA in an urban ER following physical exam and CT angiogram of carotid and Circle of Willis to rule out cerebrovascular accident. This patient's presentation in Stonewall ER with similar, persisting atypical symptoms from days prior suggested she was presenting with atypical CVA symptoms following a workup including history, physical examination, blood work and appropriate stroke protocol. Neurology was consulted, and she was referred for an appointment the following morning. After being deemed stable, the patient was discharged and it was later learned following her appointment with the neurologist that she had indeed experienced a mild stroke. A literature search revealed that cerebral ischemia implicated in TIA and stroke can result in atypical neurologic symptoms, posing a diagnostic challenge and often resulting in misdiagnosis and delayed intervention. For this patient, stroke diagnosis was delayed until visit with the neurologist, illustrating the challenge that atypical neurologic manifestations pose in clinical diagnosis of TIA and stroke.

CASE HISTORY

A 62 year old woman with past medical history of COPD, paroxysmal atrial fibrillation, and a pineal gland cyst presented to an urban emergency room with dysarthria after beginning to have difficulty initiating speech, the presence of a tremor and an overall feeling of unsteadiness beginning early in that morning. She described her experience of dysarthria as knowing cognitively the word she wanted to use, but periodically pausing and slurring as she tried to initiate vocalization of the word. Over the course of the morning, her speech improved, but did not return completely to normal. No headache was experienced, and visual changes including diplopia or blurred vision were not experienced. On exam in the emergency room, extra-ocular movements were normal in all directions with preserved visual fields. She was clearly oriented in place and time, reflexes were normal bilaterally and cranial nerves II to XII were found to be intact. There were no focal motor sensory deficits, a normal heel-shin test was seen, however, shakiness in the upper limbs when performing the finger-nose test was visualized. The remainder of the examination, including cardiac, respiratory, abdominal and head and neck were unremarkable and otherwise normal. Her atrial fibrillation was treated with diltiazem and ASA, and she had a smoking history of 47 pack years. A CT angiogram of the carotid and Circle of Willis was performed to rule out CVA. Imaging revealed a small focal density in the right common carotid artery which was thought to represent a small plaque ulceration, ruling in a possible extremely short segment dissection in to the differential. Alternately, it was thought that the focal density could represent a small focus of calcified plaque, but was seen to be less dense than the plaque in the contralateral left common carotid. Further, the carotid and vertebral arteries were widely patent in the neck, along with the major intracranial arteries. The diagnosis was made that this patient had experienced a TIA: seeing that at that point her symptoms were thought to have entirely resolved, the decision was made to transition to apixaban as stroke prevention for atrial fibrillation, and the patient was discharged.

Two days following, the same patient presented to Stonewall emergency with signs and symptoms still present. Vitals were stable, with HR at 90 beats/min, BP 137/96, respiratory rate 18/min and SpO2 96% on room air. She was still experiencing hesitancy and dysarthria initiating speech, along with a tremor and a general feeling of weakness and unsteadiness. Consistent with the initial presentation two days prior, there was no paresthesia, arm drift or facial droop but bilateral tremulous arms and legs were visible at rest. A neurologic workup revealed abnormal results, not consistent with a diagnosis of TIA, instead pointing towards an abnormal CVA presentation. Despite the bilateral tremor, it was more

present on the left. Additionally, left-sided upper and lower extremity weakness was subtle but present. Her left eye was not able to demonstrate smooth pursuit, lagging during saccades while the right was normal. Tests of cerebellar function revealed left sided dysmetria in the finger-nose test, and dysdiadochokinesia attempting to perform a test of alternating palm of hand and back of hand tapping on thigh using the left hand. Further, tandem walking could not be performed due to feelings of imbalance and unsteadiness. She was able to walk a few steps, then began to stumble and required assistance. Neurology was consulted, and an appointment was made to see a specialist early the next day. Based on examination and suspected stroke/TIA protocol, her risk level was identified to be 2 out of 4, that of high risk for acute stroke, but level 2 due to fluctuating motor or speech symptoms having persisted for more than 48 hours prior to presenting to hospital. The appropriate action was taken based on protocol: following triage, consult, and referral to the neurologist, the patient was stable, and deemed to be cognitively and physically safe to discharge as symptoms had not changed while in the ER compared to the course of the last few days. The patient was discharged with family after being given advice to return if symptoms worsen or change.

Following up with the patient and neurologist in days following, it was discovered this woman had indeed undergone a mild stroke.

LITERATURE REVIEW

In days following this patient's first presentation to emergency and initial diagnosis of TIA, she experienced continuing symptoms similar to those she initially presented with persisting greater than 24 hours, atypical of the classic TIA presentation. These continued symptoms were ultimately what prompted her return to emergency in Stonewall, where an atypical presentation of cerebrovascular accident was diagnosed and neurology was consulted, then referred. A general survey of existing literature involving the diagnosis of TIA and stroke indicated that either pathology can present with atypical symptoms, posing a diagnostic challenge which can initially be misdiagnosed or missed, leading to delayed intervention. This patient's atypical clinical history, with transient atypical symptoms lasting longer than the historical time based definition of TIA, and an abnormal neurologic exam when presenting in Stonewall emergency, prompted generation of the clinical question: "What neurologic symptom presentations can be reflective of the atypical cerebral ischemic symptoms of TIA and stroke?" Focus was also placed on previous research that has helped elucidate connections between non-conventional presenting symptoms and cerebral ischemia as well as types of diagnostic imaging modalities used.

To survey the literature, a MEDLINE search was conducted using the terms: "((ischemic attack, transient[MeSH Terms]) AND (atypical presentation) AND stroke[MeSH Terms]", which did not produce any results. The search was altered, focusing only on TIA, using the terms: "((ischemic attack, transient [MeSH Major Topic]) AND atypical transient symptoms AND diagnosis[MeSH Major Topic])". This survey still proved to be narrow, revealing only 4 items, two of which were relevant to the subject matter. To analyze the literature available regarding atypical stroke presentation, a MEDLINE search including the terms: "(stroke[MeSH Terms]) AND atypical presentation" were used, which did not produce any results. UptoDate was consulted to assess typical clinical presentations of both TIA and stroke. Additionally, Elsevier Clinical Key and the University of Manitoba Library database was searched using variations of key words "transient ischemic attack", "atypical symptoms" and "stroke". Several articles regarding clinical presentation and diagnosis of TIA and stroke independently were found through aforementioned database searches. The literature survey indicated that recent attention has been directed towards elucidating the relationship between atypical symptoms, cerebral ischemia, and final clinical diagnoses with the goal of enhancing diagnostic ability to facilitate early intervention.

DISCUSSION

TIA and ischemic stroke share the same underlying pathophysiology of cerebral ischemia leading to hypoperfusion, oligemia, impairment of cerebral oxygen and glucose metabolism[1]**.** The two diagnoses differ on a pathologic basis in terms of the end condition of the tissue following the period of ischemia and often duration of neurologic symptoms. Pathologic processes that can lead to TIA and stroke are those that directly impact blood flow to the brain. Some of these processes include emboli, processes intrinsic to the vessel, inadequate cerebral blood flow, or vessel rupture[2]. Prior to the advent of improved imaging techniques, TIA was historically a clinical, time based diagnosis characterized by episodes of focal, temporal neurologic dysfunction lasting commonly less than an hour, but persisting no more than 24 hours[2]**.** As more sensitive diagnostic means became available with advances in neuroimaging, a tissue based redefinition of the diagnosis of TIA became possible. Support exists for the re-definition of TIA to exclude episodes of transient deficit resulting in a visible lesion on diffusion weighted MRI (DW-MRI)[3]. Evidence of a lesion and presence of tissue infarct visible on imaging instead constitutes a stroke diagnosis with this redefinition[3]**.** Supporting this redefinition, multiple studies have revealed that of those thought to have experienced a TIA, as many as 39% of patients included in one study, and approximately half of those in another showed evidence of infarction on DW-MRI[3]**.** The redefinition of TIA proposed by the TIA Working Group outlines that the new diagnosis constitutes a "brief episode of neurologic dysfunction caused by focal brain or retinal ischemia with clinical symptoms typically lasting less than 1 hour, and *without neuroimaging evidence of acute infarction*"[3].

Challenges associated with the tissue based definition exist partly due to the sensitivity and availability of imaging technology. In patients with suspected TIA, infarcts that occur are typically small, meaning that methods such as CT or conventional MRI with lower sensitivity for small infarcts pose a challenge in accurate diagnosis when utilized [1, 2]. Further, CT imaging technology can require up to 12 hours to demonstrate injury, delaying diagnosis and also posing a risk of increasing under-diagnosis of infarction and false-negative conclusions if used within this time window[1]**.** Diffusion weighted imaging is considered to be the superior brain diagnostic imaging modality over CT due to the fact that it is more sensitive and specific for cerebral infarct and evidence of injury can be detected earlier[1]. The use of more sensitive imaging methods such as DW-MRI has been seen to increase the incidence of patients with suspected TIA ultimately show evidence of infarct on imaging and have final discharge diagnoses of stroke as opposed to TIA[2].

In addition to allowing for more sensitive detection of cerebral infarct, advances in imaging have also been important in research involving atypical presenting symptoms of cerebral ischemia. Detection of infarction in the presence of a history of unconventional presenting symptoms of TIA or stroke has created support that neurologic manifestations previously attributed to non-ischemic causes can indeed be the result of cerebral ischemia and be seen in the setting of TIA or stroke. Using DW-MRI imaging, it was determined that approximately 10 percent of patients with an atypical presentation of TIA symptoms are found to have experienced infarct and have a positive imaging result[2]. Further, it has served to incite research allowing for more accurate characterizations of the manifestations of cerebral ischemia to include symptom presentations which commonly result in alternative, non-ischemic initial diagnoses such as seizure, migraine or intracerebral hemorrhage[2]. The ability to accurately recognize both typical and atypical symptoms of cerebral ischemia is crucial as it allows for more accurate and timely diagnoses, enabling preventative interventions to prevent subsequent stroke in the case of TIA or early intervention and recanalization in the case of stroke.

Historically the diagnosis of TIA has been seen to have low inter-observer agreement, partly attributable to conventional time based definitions that have existed[4, 5].Other factors influencing the discrepancy in inter-observer agreement are associated with an unclear definition of which atypical symptoms suggest cerebral ischemia; non-specific symptoms such as blurred vision, dizziness, pain, generalized weakness and syncope are included by some physicians, while classic atypical symptom presentations such as isolated brain stem symptoms are not considered evidence of cerebral ischemia by others[4]. The diagnosis of TIA has received critique, termed one "of convenience" and a "waste basket for

diagnosis of transient, non-specific symptoms"[4]. Ultimately, inability to accurately determine evidence of cerebral ischemia reduces ability to intervene and take effective preventative measures which is of importance considering that up to 5% of true episodes of TIA will be followed by a stroke within 48 hours, and appropriate treatment following TIA can lead to 50-80% reduction in stroke risk[1, 5]. Typical symptoms of TIA are characterized by transient, focal neurologic symptoms produced by cerebral ischemia that can be attributed to a specific region in the brain without evidence of acute infarction usually lasting less than one hour[1,2]. Symptoms predominantly seen suggesting cerebral ischemia or infarction typically include those involving loss of function which are commonly referred to as negative symptoms[1]. Typical negative symptoms include motor weakness, decreased or altered speech, and diminished visual field or decreased sensation[1]. Atypical symptoms seen to be associated with cerebral ischemia or infarction include isolated brain stem symptoms such as dysarthria, diplopia, or hearing loss; isolated focal sensory symptoms, gradual symptom build up, and march or progression of symptoms from one body part to another[2]. As mentioned earlier, approximately 10 percent of patients with an atypical presentation of TIA symptoms have been found to have a positive result of infarct on DW-MRI[2]. In one study, 16% (of 275 patients) who had experienced a vertebrobasilar infarction had experienced transient ischemia in days preceding which had manifested as atypical isolated brainstem symptoms such as diplopia or dysarthria[2]. Further, a retrospective study confirmed the hypothesized postulate that vertebrobasilar ischemia and resulting isolated brainstem related neurologic symptoms, classically considered atypical manifestations of cerebral ischemia, were commonly present in days leading up to vertebrobasilar ischemic stroke[6]. 22% of the patients who had experienced a vertebrobasilar stroke experienced heralding of the isolated ischemic brainstem symptoms prior to stroke[6]. However, due to the atypical nature of these symptoms, only 10% of the patients who had experienced these neurologic episodes prior to stroke satisfied the NINDS criteria for TIA diagnosis and as a result were not diagnosed or treated with stroke prophylaxis[6].

Another study reviewed the clinical importance of isolated atypical transient symptoms in the setting of suspected TIA. Of 2398 patients with suspected TIA, 9.6% experienced atypical isolated symptoms including dysarthria, motor deficit, partial sensory symptoms, diplopia, ataxia, vertigo, or unusual cortical visual symptoms. Researchers discovered that 22.5% of patients presenting with dysarthria, 19.9% that had experienced complete motor deficit, and 11.3% that had experienced complete sensory deficit had in fact experienced an acute infarction determined by DW-MRI[5]. The rate of infarction seen in patients with isolated typical symptoms was comparable to or lower than the rates of 22% and 12.5% respectively seen in patients with atypical symptoms of isolated transient dysarthria and partial sensory symptoms[5]. In those who had experienced dysarthria and partial sensory symptoms, the risk of symptom reoccurrence and one year brain infarction was as frequent as in patients with isolated typical transient symptoms[5]. In contrast, other atypical isolated symptoms such as diplopia, ataxia, vertigo, or unusual cortical visual symptoms were found to be non-ischemic 91.3%, 98.6%, and 100% of the time respectively[6]. These findings reinforce the notion that not all atypical symptoms suggest ischemia or possible infarction equally, however, they emphasize the importance of not overlooking atypical symptoms as their infarction rate can be comparable to the infarction rate seen in the setting of typical symptoms.

Despite the amount of literature and diagnostic algorithms dedicated to stroke identification and diagnosis, false negative and false positive diagnoses of stroke still occur. One meta-analysis determined that when paramedics applied a variety of different prehospital screening tools, up to 30% of subsequently confirmed acute strokes are missed[7]. False negative cases, referred to in the literature as "stroke chameleons", go under-diagnosed largely due to atypical symptom presentation that do not score in favour of acute stroke in diagnostic algorithms based on typical symptom presentation[7]. Public campaigns including the mnemonic "FAST" based on the Cincinnati Prehospital Stroke Scale and the "suddens" message have served to improve public education on typical signs and symptoms of acute stroke, enabling for rapid detection and timely diagnosis[8]. Rapid diagnosis is crucial as the therapeutic window for

reperfusion therapies to restore cerebral perfusion in the setting of acute ischemic stroke is narrow[8]. Some of the most predictive, typical examination findings for the diagnosis of acute stroke are included in the FACE mnemonic and "suddens" message, which can be seen below.

FAST message for stroke warning signs
F, face: does the *face* look uneven? A, arm: does 1 *arm* drift down? S, speech: does their *speech* sound strange? T, time: if any of these signs observed, it is *time* to call 911.

Figure 1: FAST mnemonic for stroke symptom recognition[8].

The 5 "suddens" stroke warning signs
Sudden numbness or weakness of face, arm, or leg, especially on 1 side of the body. Sudden confusion, trouble speaking or understanding speech. Sudden trouble seeing in 1 or both eyes. Sudden trouble walking, dizziness, loss of balance, or coordination. Sudden severe headache with no known cause.

Figure 2: "Suddens" message stroke warning signs[8].

The classic presentation of abrupt symptom onset is not always present in those who experiencing a stroke. Atypical symptom presentation leading to misdiagnosis in stroke chameleons result commonly in alternative diagnoses of altered mental status, syncope, hypertensive emergency, systemic infection, movement disorders or delirium[9]. In the emergency department setting, the National Institute of Health Stroke Scale (NIHSS) is a commonly used stroke screening exam but has received critique due to its weighting of symptoms caused by dominant hemisphere anterior circulation strokes over strokes of alternative origin in the brain[7]. Stroke chameleons are more likely to have ischemic strokes in the posterior circulation than those with accurately diagnosed strokes. Posterior circulation ischemia can produce atypical neurologic manifestations, such that heralding ischemic attacks leading up to subsequent posterior ischemic stroke is missed. Related to the under diagnosis of posterior circulation stroke, findings like truncal ataxia, nausea or vomiting are signs of posterior circulation ischemia and achieve scores of zero on the NIHSS[7].

One retrospective study determined that of 2303 patients with a final discharge diagnosis of ischemic stroke or TIA, 39.9% presented with atypical symptoms that were initially attributed to conditions other than stroke[9]. Researchers determined that the most common atypical symptoms in these patients from their sample included disorders of somatic sensation (33%), alterations in level of consciousness (30%), and disorders of speech/language (11%)[9]. Other manifestations including motility disorders, special sense, seizures and neuropsychiatric symptoms were less commonly seen. The Greater Cincinnati Northern Kentucky Stroke Study discovered that 14% of patients of a 2027 person cohort were identified as stroke chameleons, having initially been given a false negative diagnosis other than stroke prior to being given their discharge diagnosis of stroke[7]. Of the stroke chameleons identified in this study, 67% were seen to have symptoms of speech difficulty[7].

Conclusion

The identification of atypical manifestations of cerebral ischemia and diagnosis of acute TIA and stroke continues to be a challenging area in clinical practice. The case of discussion in this report illustrates the challenges faced in diagnosis of atypical cerebral ischemic symptoms when available imaging modalities are limited. Improvements in technology have enhanced the ability to detect, however, improved diagnostic algorithms including atypical manifestations, increased physician awareness, and a high degree of clinical suspicion is essential in order to provide timely care and optimize long term patient outcomes.

References

1. Duca A, Jagoda A. Transient ischemic attacks: advances in diagnosis and management in the emergency department. *Emerg Med Clin N Am.* 2016;34(4):811-835.
2. Furie KL, Ay H. UpToDate, Inc. Initial evaluation and management of transient ischemic attack and minor ischemic stroke. Jul 2019.
3. Oppenheim C, Lamy C, Touze E et al. Do transient ischemic attacks with diffusion-weighted abnormalities correspond to brain infarctions? *Am J Neuroradiol.* 2006;27(8):1782-1787.
4. Behrouz R. Transient ischemic attack: a diagnosis of convenience. *Am J Emerg Med.* 2017;35(12):1979-1981.
5. Lavallee P, Sissani L, Labreuche J et al. Clinical significance of isolated atypical transient symptoms in a cohort with transient ischemic attack. *Stroke*. 2017;48:1495-1500.
6. Paul N, Simoni M, Rothwell. Transient isolated brainstem symptoms preceding posterior circulation stroke: a population based study. *Lancet Neurol*. 2013;12:65-71.
7. Liberman A, Prabhakaran S. Stroke chameleons and stroke mimics in the emergency department. *Curr Neurol Neurosci Rep*. 2017;17:15-26.
8. Nentwich L. Diagnosis of Acute Ischemic Stroke. *Emerg Med Clin N Am.* 2016;34:837-859.
9. Chompoopong P, Rostambeigi N, Kassar D et al. Are we overlooking stroke chameleons? A retrospective study on the delayed recognition of stroke patients. *Cerebrovasc dis.* 2017;44:83-87.