Introduction

We would like to thank the authors of the following papers for choosing to publish their work in our open access special edition on cerebrovascular disease. It would be easy enough for all of them to publish their manuscripts in mainstream print-based journals. The concept of the open access journal: cutting edge, rapid turnaround, readily searchable, publication of scientific works; is extremely important. With increased access to novel concepts and supporting data, there is an increased ability to become discerning about the quality of data used to treat patients. We have divided this edition into three sections dealing with the acute treatment, diagnosis and management, and prognostication of cerebrovascular disease. We hope that these works will fuel critical thinking, novel ideas, healthy debate, and future studies.

Acute Stroke Treatment

In 1995, the NINDS trial was published and changed the face of acute stroke management, primarily by encouraging rapid evaluation and treatment. When stroke moved from an untreatable to treatable disorder, many studies like the ones following became possible. The inclusion/exclusion criteria for the administration of IV tPA were created as part of the research protocol and may not all be relevant in current clinical practice. The first paper is an example of a potential exclusion criterion not discussed in the original NINDS paper. In our aging population, cerebral amyloid angiopathy may be an important factor to consider in treatment of elderly patients with dementia. Since the advent of tPA, there have been a multitude of additional trials looking at other interventions (eg, intra-arterial lysis, neuroprotectants, novel thrombolytics such as TNK, and the acute use of antiplatelet agents). The second paper illustrates a potential role for clopidogrel loading in patients presenting with stuttering lacunar syndromes. Along with inclusion/exclusion criteria and novel treatments, the diagnostic measures for detecting and assessing severity of ischemia is also an evolving field. It is well recognized that along with the posterior circulation, the right hemisphere is grossly underestimated by the NIH Stroke Scale due to difficulty in quickly and accurately evaluating right hemisphere function. Though more difficult to diagnose, lesions of the right hemisphere are no less debilitating, and therefore reperfusion with acute treatment is of utmost importance. The final two papers address the importance of stroke within the right hemisphere, and innovative screening tools for right hemisphere dysfunction.
Cerebral Amyloid Angiopathy: A Hidden Risk for IV Thrombolysis?

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Abstract

Recombinant tissue plasminogen activator (t-PA) is the only FDA approved therapy for acute ischemic stroke. Cerebral microbleeds (CMBs) or cerebral amyloid angiopathy (CAA) are currently not contraindications, however, data regarding this complex issue are limited. We report 2 cases of fatal intracerebral hemorrhage (sICH) after IV t-PA, each with evidence of CAA. Patients with CAA may have increased risk for IV thrombolysis-associated sICH. We highlight the severe and catastrophic pattern of ICH, which may be a defining characteristic, and discuss the limitations of our current understanding of the risk of thrombolysis-associated ICH in patients with CAA and/or CMBs.

INTRODUCTION

Intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (t-PA) is the cornerstone of acute ischemic stroke therapy [1]. sICH complicates IV thrombolysis in 4.5 to 10% of patients [2,3]. It most commonly occurs in the infarct core within 36 hours of t-PA administration and remains the most devastating complication of thrombolysis with an associated mortality rate of up to 47% [4].

Cerebral amyloid angiopathy (CAA) is an important cause of primary lobar ICH in the elderly [5]. Deposition of amyloid beta increases the fragility of vessel walls causing spontaneous hemorrhages that commonly remain clinically silent. Diagnostic criteria for CAA (Boston criteria) exist, but definitive diagnosis requires pathologic examination. The premortem diagnosis of CAA relies on identification of lobar cerebral microbleeds (CMBs) with susceptibility-weighted (or T2*) MRI. The presence of CMBs is not a generally accepted predictor of increased risk for symptomatic ICH after IV thrombolysis, and few studies have prospectively studied this risk. We report 2 cases of sICH after t-PA, one with pathology-confirmed CAA and another with probable CAA. We discuss the risk-benefit analysis of thrombolysis in patients with CAA and propose that IV t-PA may be relatively contraindicated in patients who carry a diagnosis of at least probable CAA and/or have a high burden of CMBs. We also draw attention to the catastrophic pattern of these hemorrhages and suggest that it may be characteristic of IV t-PA-associated sICH in the presence of CAA.

CASE PRESENTATION

Case 1

An 81 year old African American woman with hypertension, hyperlipidemia, diabetes mellitus, and a prior transient ischemic attack presented with the acute onset of right face/arm weakness and difficulty speaking. Her NIH Stroke Scale (NIHSS) was 4. With good localization of symptoms to the left MCA territory, her presumptive diagnosis was ischemic stroke due to multiple vascular risk factors. She did not have a history of atrial fibrillation, and her symptoms did not suggest multifocal embolic infarctions. CT scan did not show any hemorrhage. In the absence of contraindications she received IV t-PA beginning 120 minutes after the onset of symptoms. Her symptoms improved during the infusion, but at the end she developed a moderate headache with confusion and new language deficits. Repeat CT scan demonstrated multifocal subdural, subarachnoid, and intraparenchymal hemorrhage (Figure 1A). Despite aggressive medical management, she progressed to herniation and brain death. On postmortem examination, the superficial cerebral and leptomeningeal small vessels showed diffuse wall thickening with eosinophilic deposits, and the involved vessels were remarkable for cracking in the wall and replacement of the medial layer by amyloid, creating a “vessel-within-vessel” or “double barreling” appearance (Figure 1B, C), consistent with grade 3 CAA [6].

Case 2

An 84 year old man with hypertension, diabetes mellitus, hyperlipidemia, and dementia presented with acute onset left-
Other studies have examined the risk of hemorrhage following thrombolysis in patients with CMBs, but not necessarily CAA. The large, prospective BRASIL study found no significant increase in the risk of sICH following thrombolysis in patients with CMBs [8]. A recent meta-analysis demonstrated a trend toward increased risk of ICH in patients with CMBs, but none of the individual studies reached statistical significance [9].

There are important limitations in applying the above evidence to thrombolysis in the setting of acute stroke. First and foremost, many studies looking specifically at pathologic evidence of CAA in the setting of hemorrhage were done in patients receiving thrombolysis for cardiac disease rather than stroke, and patients with parenchymal brain injury prior to t-PA administration likely have very different risks of hemorrhage. The studies specifically investigating stroke patients largely utilize the presence of CMBs which lacks diagnostic specificity. CAA is one of the primary diagnoses along with hypertensive angiopathy, but the differential diagnosis includes cavernous malformations, diffuse axonal injury, and other rare causes. These studies do not address the burden or location of CMBs which may help to differentiate between etiologies [10]. It is plausible that the underlying pathology of CMBs relates to the risk of hemorrhage, and animal models indicate a specific propensity for hemorrhage after thrombolysis in CAA [11].

The cases presented here contribute important additional evidence suggesting a relationship between CAA and t-PA-related sICH. Case 1 is, to our knowledge, the first reported pathology-confirmed case of CAA in t-PA-associated hemorrhage in the setting of acute stroke, and illustrates the difficulty of making this diagnosis clinically in the emergency setting as this patient did not have a good history of cognitive decline. In order to differentiate risk due to specific underlying pathology, further study is warranted to better characterize whether the pattern and burden of CMBs is associated with increased risk of thrombolysis-associated sICH. This will require prospective studies with pre-thrombolysis MRI, and a cost-benefit analysis is necessary, considering the cost and time delay of pre-treatment MRI versus prevention of sICH. Meanwhile, the potential for increased risk of t-PA-related sICH in patients with a high probability of CAA should be an additional factor considered in clinicians’ decisions to treat with thrombolysis.

**REFERENCES**

Case Report

Stuttering Lacunes: An Acute Role for Clopidogrel?

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Abstract

Introduction: Intravenous tissue plasminogen activator (IV tPA) has revolutionized the treatment of acute ischemic stroke. However, there remain situations when administration is relatively contraindicated (eg., arrival outside the accepted treatment window, mild or rapidly improving symptoms). Optimal treatment in these situations is less clear.

Case Series: We describe a small case series of 7 patients presenting with fluctuating symptoms concerning for a capsular warning syndrome (acute isolated motor and/or sensory deficits without cortical signs, usually attributed to small vessel pathology), often referred to as a “stuttering lacune”, who were orally loaded with 300mg of clopidogrel. Four of the 7 patients had complete resolution of their symptoms following the load. The others experienced stabilization of their deficits, but were discharged with mild persistent symptoms. Four patients had evidence of diffusion bright lesions on MRI, while the others had no evidence of infarction. None of the patients experienced hemorrhagic conversion of their infarct or other bleeding complications.

Conclusion: Our experience suggests that acutely loading with clopidogrel may be both effective and well tolerated in the treatment of stuttering lacunes.

INTRODUCTION

Intravenous tissue plasminogen activator (IV tPA) has revolutionized the treatment of acute ischemic stroke. However, there remain situations (eg, a patient presents outside the accepted time window or experiences rapid improvement of neurologic deficits), when administration is relatively contraindicated. Optimal treatment for these patients is less clear. The Fast Assessment of Stroke and TIA to prevent Early Recurrence (FASTER) trial suggests that administration of dual antiplatelet therapy acutely may reduce early recurrence in patients presenting with minor stroke or transient ischemic attack (TIA), [1] but was significantly underpowered.

We describe a small case series of patients presenting with fluctuating symptoms concerning for a capsular warning syndrome (acute isolated motor and/or sensory deficits without cortical signs, usually attributed to small vessel pathology) [2], often referred to as a “stuttering lacune”, who were orally loaded with 300mg of clopidogrel.

CASE PRESENTATION

A 53 year-old woman with history of hypertension was transferred from an outside hospital with a waxing and waning ataxic hemiparesis. At noon, she noted that her right hand seemed “clumsy.” She was unable to pick up the phone and her coffee mug “felt funny” when she tried to lift it. At 4PM, her right leg became heavy, as if it was going to give out from under her. Over the course of the evening these symptoms waxed and waned. The following morning when she noted continued difficulty climbing the stairs she made an appointment with her primary care physician. Her systolic blood pressure was over 200mmHg. She was sent to the Emergency Department (ED). In the ED, her blood pressure was 228/130 and it was noted that symptoms worsened with aggressive lowering of her systolic blood pressure to the 130s with intravenous labetalol. An MRI of the brain was performed that showed a diffusion bright lesion in the left internal capsule with corresponding hypointensity on ADC consistent with an acute ischemic stroke (Figure 1A). She was transferred to Johns Hopkins Bayview for further evaluation and management. On admission, her NIH Stroke Scale was 7 for mild dysarthria and hemiparesis (strength 4 of 5) with ataxia; however, symptoms dramatically waxed and waned throughout her hospitalization. At lower blood pressures, she developed significant dysarthria, a prominent facial droop, and dense hemiparesis (2 of 5 strength; unable to lift her arm or leg against gravity). A CT angiogram of the head and neck revealed no large vessel stenosis. An MRI of the brain was performed that showed a diffusion bright lesion in the left internal capsule with corresponding hypointensity on ADC consistent with an acute ischemic stroke (Figure 1A). She was transferred to Johns Hopkins Bayview for further evaluation and management. 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Patients, typically with small vessel risk factors, can experience fluctuating symptoms of all 7 patients. All patients were treated according to the standard of care, including evaluation by physical, occupational, and speech therapy. The typical length of stay was 2-3 days. None of the patients had hemorrhagic conversion of their infarct or other bleeding complications.

**DISCUSSION**

The capsular warning syndrome is a well described clinical phenomenon [2]. Patients, typically with small vessel risk factors, present with one of the classic lacunar syndromes as described in 1982 by C. Miller Fisher [3]. Symptoms wax and wane in intensity—often ranging from mild to dense hemiparesis in a matter of minutes. Anecdotally, these patients can be misdiagnosed as having recurrent TIAs. This “stuttering” of symptoms can be distressing to both the patient and physician. Before the results of the IST trial, [4] the capsular warning syndrome was occasionally treated with intravenous heparin. Now antiplatelet therapy is used. Despite conventional treatment, the majority of patients go on to irreversible infarction and significant clinical deficits [2-3].

There is some basis in the literature for the acute treatment of vascular events with 300mg of clopidogrel. In 2001, the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial showed that patients with non-ST elevation myocardial infarction had better outcomes at one year after an initial load of 300mg of clopidogrel followed by dual antiplatelet therapy, than those treated with aspirin alone [5]. Subsequently, CLAIR and CARESS showed that acute treatment with dual antiplatelet therapy (including a 300mg clopidogrel load) versus aspirin alone in large vessel cerebrovascular disease resulted in fewer microemboli observed by transcranial doppler, a surrogate marker for recurrent stroke risk [6-7]. Unfortunately, both studies were underpowered to show any difference in clinical outcomes (too few recurrent strokes observed).

The use of dual antiplatelet therapy in general for secondary stroke prevention has been more extensively investigated, with mixed results. Multiple large, randomized, placebo controlled studies (CHARISMA, MATCH, ESPS-2, ESPRIT) suggest that adding clopidogrel or dipyridamole to aspirin may decrease the risk of recurrent ischemia, particularly in certain groups of patients; however, the benefit was typically outweighed by the increased risk intracranial hemorrhage or other severe bleeding [8-11]. Recently, publication of the results from SPS-3 confirmed that, even with minor strokes, the rate of increased bleeding over a mean follow-up of 3.4 years was far greater than the reduction of recurrent ischemic events [12]. None of these studies examined loading with clopidogrel or the role of dual antiplatelet therapy in the acute setting. However, patients with intracranial stenosis enrolled in the SAMMPRIS trial who were treated with dual antiplatelet agents along with high dose statin therapy in the acute setting had lower rates of stroke recurrence in the first 90 days than previously published studies [13]. Additionally, the FASTER trial attempted to show that acute treatment with dual antiplatelet therapy may improve outcomes for other stroke subtypes by enrolling all patients with “minor strokes” (NIH Stroke Scale scores of <4). Unfortunately, the study was stopped prematurely secondary to issues with recruitment [1].

**Figure 1** Diffusion weighted MRIs of Patients 1,3,4, and 7 showing diffusion bright lesions in: A) internal capsule, B) corona radiata, C) midbrain, and D) internal capsule consistent with small vessel acute ischemic strokes. An * marks the site of diffusion restriction for each case.
It is possible that the patients in our series would have symptomatically improved on their own without treatment. However, the natural history of capsular warning syndromes is to progress to infarction [2-3]. Patients presenting with small deep lacunes do tend to recover well over the long term; however, we would argue that they commonly require short term physical therapy. The majority of our patients who were loaded with clopidogrel left the hospital completely, or nearly symptom free.

The risk of bleeding secondary to loading with clopidogrel is unclear. In general, small strokes are believed to have a lower risk of hemorrhagic conversion [14]. None of the patients that we have treated to date experienced intracranial hemorrhage. Additionally, by loading acutely with clopidogrel and then treating with aspirin alone rather than continuing dual antiplatelet therapy, we derive the benefit of the initial load without assuming the increased bleeding risk over the long term seen in previous studies.

Our case series is not without limitations. It is based on only a small number of patients who were not randomized. The average age was also only 59.6 years. Though hypertension, hyperlipidemia, drug use, smoking, and other vascular risk factors are prevalent in our population, and lacunar strokes in this age group are not uncommon, the younger age of our patients may result in poor generalizability, and raises the question of whether higher rates of hemorrhagic conversion may be seen in older individuals [14].

In conclusion, for stuttering small vessel lacunar syndromes in patients who do not meet criteria for treatment with IV tPA, there may be a role for orally loading with clopidogrel. In our small case series it appeared to be both effective and well tolerated. We await the results of POINT to elucidate the issue further.

REFERENCES


Right Hemisphere Ischemia is more likely to Cause Falsely “Mild” Symptoms and Poor Outcomes without Thrombolysis

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Abstract

Background: Rapidly improving or mild symptoms is the most common reason that acute stroke patients arriving within the approved time window are not treated with intravenous tissue-type plasminogen activator (IV tPA). We reviewed outcomes at discharge for patients excluded from IV tPA because of rapidly improving or mild symptoms, with the aim of being better able to identify patients who may benefit from thrombolysis.

Methods: All patients between April 2006 and June 2010 from our center who did not receive IV tPA with “rapidly improving or mild symptoms” as the reason for exclusion were identified. Poor outcome was defined as hospital discharge to location other than home or inability to ambulate independently at discharge.

Results: There were 66 patients excluded from tPA treatment because of rapidly improving or mild symptoms. Eleven patients (16.7%) had poor outcomes. In 6 patients (9%), poor outcome was due to neurologic deficit. All 6 patients with neurologic deficits had right hemisphere strokes, and one also had cerebellar infarcts.

Conclusions: Patients presenting with rapidly improving or mild symptoms do not universally have good outcomes. This may be particularly true in the case of right hemispheric ischemia where deficits are not fully reflected by NIHSS score. If a patient with a low NIHSS score is otherwise a candidate for tPA, a more detailed exam is warranted to better identify potentially disabling deficits that might benefit from thrombolysis.

ABBREVIATIONS

IV tPA: Intravenous recombinant tissue plasminogen activator; GWTG: Get with the Guidelines database; NIHSS: National Institutes of Health Stroke Scales

INTRODUCTION

Intravenous recombinant tissue plasminogen activator (IV tPA) remains the only approved treatment for acute ischemic stroke. Despite its approval for use in stroke for 15 years, only 3.4% to 5.2% of patients with acute stroke receive tPA [1]. The most common reason patients are excluded from treatment, when they arrive within the approved time window, is “rapid improvement or stroke severity too mild.” [2-5]. It has previously been found that patients excluded from IV thrombolysis for mild or rapidly improving symptoms do not universally have a benign course [6-9]. As many as 20-32% have a poor outcome at discharge.

We reviewed outcomes of consecutive patients from a single center who did not receive thrombolytic therapy with “rapidly improving or minor symptoms” as the reason for exclusion from treatment, with the aim of being better able to identify patients in this group who may benefit from thrombolysis.

METHODS

We used the AHA/ASA “Get with the Guidelines” (GWTG) database to identify consecutive acute ischemic stroke patients between April 2006 and June 2010 from University of Maryland Medical Center who did not receive IV tPA. The GWTG data in combination with the medical record were reviewed to identify those patients with “rapid improvement or stroke severity too mild” as the only reason documented by the treating vascular neurologist for exclusion from thrombolytic therapy. If the documentation indicated fluctuation of symptoms, with more severe symptoms prior to time of thrombolytic
treatment decision, patients were considered to be in the “rapid improvement” subset. Demographic data, stroke risk factors, baseline National Institutes of Health Stroke Scale (NIHSS) scores, discharge location and ambulatory status were recorded prospectively in the GWTG database and extracted for this study. The medical records of patients with poor outcome were reviewed retrospectively to determine details of hospital course, infarct location, and reasons for poor outcome. Poor outcome was defined as hospital discharge to location other than home or inability to ambulate independently at discharge. Patients were considered to have a non-neurologic reason for poor outcome if hospital notes documented no or only very minor residual neurological deficits and other medical or social reasons as the primary factors in patient not being discharged to home.

Differences between the groups were assessed using the two-tailed Fisher exact test for dichotomous variables and the unpaired t-test for continuous variables with the InStat 3 program (version 3.1a; Graph Pad Software).

RESULTS AND DISCUSSION

During the study period, 1036 patients with acute ischemic stroke were admitted to our center. Of those, 168 patients (16%) were treated with IV tPA. There were 66 patients excluded from treatment with IV tPA for “rapid improvement or stroke severity too mild”. Eleven (16.7%) of those patients had poor outcomes. Patients with poor outcomes were significantly older in comparison to patients with good outcomes (mean age 72.4 years vs. 63 years; p=0.0021), but there were no other significant differences in baseline characteristics (Table 1).

Of the 11 patients with poor outcome, 5 were attributed to deconditioning and poor general medical condition and 6 to continued neurologic deficits (Table 2). All six patients with continued neurologic deficit and poor outcome had right hemisphere infarcts. Patient 6 had a right frontal lobe infarct and also a left superior cerebellar infarct, which required a posterior craniotomy and decompression to treat malignant cerebellar edema.

Of the 6 patients with poor outcome due to continued neurologic deficit, 4 had improving deficits and 2 had consistently mild deficits, whereas all 5 of the patients with non-neurologic reason for poor outcome had consistently mild deficits from onset to the time of evaluation for thrombolytic therapy. This trend toward patients with poor outcome being more likely to have improving rather than consistently mild deficits was not statistically significant due to small numbers. Possible reasons for this trend toward worse outcome in the “rapidly improving” group include: overly optimistic interpretation of the degree of improvement or assumption that improvement seen would continue rather than plateau, or patients with more severe deficits at some point remaining more prone to worsen back to prior deficit severity. We were unable to explore this further due to lack of detailed documentation of serial examinations.

The predominance of right hemisphere infarcts in our patients with poor outcomes due to neurologic deficit is striking. Known predictors of poor outcome at discharge in patients excluded from thrombolysis for improving or mild symptoms include: an initial NIHSS ≥10 with rapid improvement, and a persistent large vessel occlusion [7,8]. We know of no previous studies reporting right hemisphere localization as a possible predictor of poor outcome in this patient population. It has been shown that the NIHSS assigns more points for equal volume infarcts of left hemisphere compared to the right [10,11]. Therefore, a low NIHSS may conceal a large right hemisphere stroke burden that could result in poor outcome if not treated. A study comparing baseline NIHSS score and long term outcome showed this may also be true for posterior circulation strokes, as patients had a

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Abbreviations: NIHSS: National Institutes of Health Stroke Scales; CHF: Congestive Heart Failure.
higher probability of an unfavorable outcome with relatively low NIHSS scores in the posterior circulation compared to anterior [12].

Age was the only baseline characteristic with a significant difference between patients with good vs. poor outcome. This may represent a bias against giving IV tPA in elderly patients. Or it could reflect the poorer baseline medical status in the elderly, with older patients generally doing worse regardless of the intervention. This is supported by our finding that in five of the 11 patients with poor outcome it was due to general deconditioning rather than specific new neurologic deficits.

In agreement with prior reports, we found rapidly improving patients and patients with continuously mild symptoms may not be at equal risk for poor outcomes [7,8]. At the time when the patients in this study were entered into the Get with the Guidelines database, the “mild” and “rapidly improving” reasons for not treating with tPA were combined into one data point. Since then, they have been separated into two different categories. So, outcomes in these patients can be more easily tracked going forward to confirm this finding. Limitations of our study include the use of a retrospective chart review and small numbers.

CONCLUSION

Our findings support the practice of not using a strict NIHSS threshold when making treatment decisions, especially for patients who present with non-dominant hemisphere symptoms. Before the decision is made to withhold thrombolytics because the symptoms are “mild” or “rapidly improving”, a more detailed exam may be warranted to better assess for deficits that are not picked up on the initial NIHSS but may still contribute to disability. Treatment with tPA for patients with mild stroke has been found to be safe, supporting more liberal treatment in this patient population [13,14]. Recent analysis estimated that about 2000 patients per year would not be disabled (with a savings of $200 million/year) if patients with NIHSS less than 5, and otherwise eligible, were treated with tPA [15]. More research is needed to help guide treatment in this large group of stroke patients.

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Cite this article
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Right Hemisphere Dysfunction is Better Predicted by Emotional Prosody Impairments as Compared to Neglect

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Abstract

Background: Neurologists generally consider hemispatial neglect to be the primary cognitive deficit following right hemisphere lesions. However, the right hemisphere has a critical role in many cognitive, communication and social functions; for example, in processing emotional prosody (tone of voice). We tested the hypothesis that impaired recognition of emotional prosody is a more accurate indicator of right hemisphere dysfunction than is neglect.

Methods: We tested 28 right hemisphere stroke (RHS) patients and 24 hospitalized age and education matched controls with MRI, prosody testing and a hemispatial neglect battery. Emotion categorization tasks assessed recognition of emotions from prosodic cues. Receiver operating characteristic (ROC) analyses were used to compare tests in their ability to distinguish stroke patients from controls.

Results: ROC analyses revealed that the Prosody Score was more effective than the Neglect Battery Score in distinguishing stroke patients from controls, as measured by area under the curve (AUC); Prosody Score = 0.84; Neglect Battery Score = 0.57. The Prosody Score correctly classified 78.9%, while Neglect Score correctly classified 55.8% of participants as patients versus controls. The Prosody Score was similar to the total NIH Stroke Scale in identifying RHS patients (AUC=0.86, correctly classifying 80.1% of patients versus controls), but the tests only partially overlapped in the patients identified.

Conclusions: Severe prosody impairment may be a better indicator of right hemisphere dysfunction than neglect. Larger studies are needed to determine if including a bedside test of Prosody with the NIH Stroke Scale would most efficiently and reliably identify right hemisphere ischemia.

ABBREVIATIONS

ADC: Apparent Diffusion Coefficient; AUC: Area Under the Curve; DWI: Diffusion Weighted Imaging; FLAIR: fluid attenuation inversion recovery; NIHSS: National Institutes of Health Stroke Scale; RHS: right hemisphere stroke; ROC: Receiver Operating Curve; USN: Unilateral spatial neglect;

INTRODUCTION

It is generally believed that the most common cognitive deficits following right hemisphere stroke are unilateral spatial neglect (USN) and extinction with double simultaneous stimulation [1]. USN is typically defined as an inability to detect, attend or respond to stimuli on the side of space contralateral to brain damage, while detecting and responding to stimuli on the ipsilesional side [2]. Approximately 25-30% of acute right hemisphere stroke patients have USN [3]. The only “right hemisphere” cognitive deficits evaluated by the NIH Stroke Scale (NIHSS) are neglect and extinction [4]. One limitation of this fact is that the NIHSS may be less sensitive to right hemisphere than...
left hemisphere stroke, or may underestimate the volume of right hemisphere stroke [4].

However, the right hemisphere has other cognitive functions that are less widely recognized that may be at least equally important from a functional standpoint and may provide clinical markers that are more reliable than USN for indicating the presence or severity of right hemisphere stroke (RHS). Adding evaluation of such cognitive functions could improve detection and evaluation of outcome of RHS. For example, the right hemisphere is critical for emotional prosody (expression or comprehension of emotional meaning through speech prosody, such as variations in pitch, intensity, and rate). Individuals with right hemisphere lesions have shown difficulty identifying emotions (such as happy, angry, sad, and fearful) of the speaker during human communication. The predominant role of the right hemisphere in processing emotional prosody is corroborated by studies recording event-related brain potentials [5]; fMRI studies showing right hemisphere activation in association with prosody judgments [6,7]; a left ear advantage for prosody using the dichotic listening paradigm [8,9]; and lesion studies of judging emotional meaning from prosody [10-14]. There are a number of other “right hemisphere deficits” that have clear functional consequences, such as anosognosia and apathy (see, 15, 16), integration of information to comprehend discourse, interpret metaphor, draw inferences, and so on (see, 17) for review). It is also crucial for both affective empathy (the ability to recognize and respond to affective experiences of another person; (18, 19) and cognitive empathy (the ability to take the perspective of another person). However, impairments in many of these cognitive functions are difficult to objectively quantify on a scale of more than a few points. One reason USN may have been used so frequently as the primary marker of right hemisphere cognitive function is that it is relatively easy to measure the severity with a variety of bedside pencil and paper, computer, or other standardized tests. We hypothesized that impairment in comprehension of emotional prosody, which can also be measured on a scale of 0-100% accuracy on objective and reliable tests, is even more sensitive and specific for RHS than is USN.

MATERIALS AND METHODS

Participants

A series of 28 patients with acute RHS (mean age 55 years old and mean education 14 years) and 24 patients with transient ischemic attacks (TIA) admitted to Johns Hopkins Hospital, Baltimore, USA were recruited for this study. TIA participants were included as age and education matched controls without evidence of brain lesion on MRI and resolution of presenting symptoms at the time of testing, but with similar socioeconomic background as the stroke patients and same testing environment as the stroke patients. All patients were examined on the clinical and behavioral tests within 48 hours from the admission to the hospital. Exclusion criteria included: bilateral brain damage, injury to brainstem/cerebellum, history of other major neurological or psychiatric illness or previous stroke, and positive toxicology screens for drugs of abuse or alcohol.

Imaging: Lesion location for all patients was identified by the neuroradiologist and technicians on MRI sequences, which included: Axial diffusion weighted imaging (DWI) trace sequences and apparent diffusion coefficient (ADC) maps; fluid attenuation inversion recovery (FLAIR) to evaluate for old strokes, susceptibility weighted images to evaluate for hemorrhage, and T2 weighted sequences to evaluate for other lesions. Technicians masked to behavioral assessment measured volume of infarct on DWI.

EXPERIMENTAL TASKS

Emotional prosody tasks

Two categorization tasks evaluated emotional processing for prosodic features alone. In the word identification task (word ID), participants were presented utterances that were semantically neutral but communicated specific emotions through the prosody (e.g., I am going to the other movies). In the monosyllabic identification task (monosyllabic ID), participants were presented with monosyllabic utterances that conveyed specific emotions through prosody (e.g., ba ba ba ba ba ba ba).

In word and monosyllabic ID tasks, participants listened to each utterance (from an audio file) and then identified the emotion of the speaker based on the prosodic features in a six forced-choice response format (alternatives - happy, surprise, angry, sad, disinterest, neutral) presented as a picture and as a word on a laptop or on paper. Stimuli for each of these tasks were specifically developed to assess comprehension of emotional prosody in patients as well as healthy adults and this type of stimuli has been used successfully in previous studies [14,20]. The administration time for these two tasks ranged from 5.4 to 7.6 minutes.

Neglect tasks

Hemispatial neglect tests administered as part of the Stroke Cognitive Outcomes and REcovery (SCORE) study included: [1] copy scene (copying the "Ogden scene": a house, a fence, and two trees; there are 36 total components to the picture, so each missing component yields a percent error) ; [2] a gap detection test (identifying the gaps in small and large circles [21]. In this test, a sheet of paper filled with 10 whole circles, 10 circles with gaps on the left, and 10 circles with gaps on the right was presented to the patient. Patients were instructed to cross out the circles with the gaps and to circle the full circles on the paper. This test was administered at midline of the patient’s body. For each task, the number of errors and the total number of stimuli were tabulated. Errors on each side of the page and/or stimulus were recorded in order to distinguish between viewer- and stimulus-centered neglect. The test is administered twice, once with large circles, and once with smaller circles. The administration time for these tasks ranged from 2.9 to 5.8 minutes. Error rate on the SCORE neglect tests potentially ranged from 0-100%.

Neglect and extinction as scored on the NIH Stroke Scale (NIHSS) were also recorded for each patient. The NIHSS scores were obtained by reading through the admission history and physical notes, progress notes from the first full day of admission, and discharge summaries. If NIHSS was not documented, a retrospective NIHSS was calculated using the algorithm used by Williams et al., 2000 [22]. Neglect is assessed on the basis of describing a complex picture, reading words and sentences, and eye movements (pursuits). Extinction is assessed with double
simultaneous stimulation in tactile and visual modalities. Each participant was scored as having neglect [0-1], extinction [0-1] or both (maximum of 2 possible points).

Procedure

Ethical approval of the study was obtained from the Johns Hopkins Institutional Review Board, and informed written consent was obtained from all participants prior to testing. Participants were tested in their individual rooms in the Stroke ward. Testing was carried out in one session; these tests were part of a larger battery that included assessment of prosody production and imitation, as well as other cognitive assessments. Auditory stimuli were presented by a laptop over headphones controlled by Presentation software (NeuroBehavioral Systems, USA). Stimuli within each task were randomized and then played over high quality, volume adjustable headphones at a comfortable listening level. They were instructed to listen carefully to each utterance and then make a judgment about the emotion of the speaker. Most patients responded by pressing a button on a Cedrus 730 response box. For these patients, the response alternatives (verbal labels) were presented centrally on the computer screen as well as marked on the response box. However, for the initial 18 patients, response alternatives were presented on paper, and the patient simply pointed to the emotion of the speaker. There was no time limitation for the participants and the next trial was presented only after the participant had provided a response. There was not a marked difference in the administration time for the two subtests when the paper version was used versus the computer version.

Statistical analyses

Firstly, to examine the performance of the two participant groups (RHS, TIA), two 2 x 2 ANOVAs were conducted separately for prosody identification and neglect tasks. Secondly, Receiver Operating Characteristic (ROC) analyses were conducted to identify a more accurate cut-off point that could help identify the probability of disease in individual participants [23]. ROC curves were created by plotting the range of sensitivity and specificity pairs for each participant’s error rate, with case status (stroke versus TIA) as the classifier variable. A global assessment of the performance of the test is given by the area under the ROC curve (AUC). That is, AUC provides an estimate of the accuracy of the diagnostic test in discriminating between the patients and controls. AUC’s were compared for different tests in their characteristics relative to case status. In addition to the AUC, when evaluating the usefulness of a screening measure to identify those individuals with cognitive impairment, the cut-off point would be chosen to ensure that most cases were detected (high sensitivity; >80% is desirable) but not at the cost of many false positives (goal specificity; >60% is acceptable; 24). Therefore, cut-offs were selected that maximized the sensitivity (>80%) of the tests while maintaining an acceptably low false positive rate (specificity > 60%).

RESULTS AND DISCUSSION

Results

A 2 x 2 ANOVA with factors of Group (RHS, TIA) and Prosody (word ID, monosyllabic ID) revealed a significant main effect of Group, $F[1,50] = 29.22, p < 0.00001$ and a main effect of Prosody, $F[1,50] = 8.51, p < 0.01$. Post-hoc Tukey’s (HSD) inspection of the group effect revealed that the RHS patients (M=0.49% errors) made significantly more errors than the TIA group (M=0.25% errors). Also, the prosody main effect showed that both the groups tend to make more errors in the prosody word ID task (M=0.43% errors) as compared to the monosyllabic ID task (M=0.33% errors). A 2 x 2 ANOVA with factors of Group (RHS, TIA) and SCORE Neglect (viewer-centered, stimulus-centered) did not reveal any main or significant effects. The neglect scores from the NIHSS were also similar. Out of 28 patients, 3 patients showed signs of neglect, 5 patients showed signs of extinction, and 2 patients had both neglect and extinction. All individuals with neglect on either test also had impaired prosody. A summary of the mean error rate for the prosody and SCORE neglect tasks is shown in the table 1.

The ROC analysis showed that the Prosody Score was more effective than the SCORE Neglect Score in distinguishing stroke patients from controls, as measured by the ROC curve (AUC for the overall Prosody Score = 0.84; AUC for the overall Neglect Score = 0.57). The overall Prosody score of >31% error correctly classified 78.9% of the participants versus controls. For the overall Prosody score, the sensitivity was 92.9% and the specificity was 62.5%. For the prosody word ID task, an error rate of > 37% had a sensitivity of 82.1% and specificity of 66.7% (correctly classifying 75% of participants as patients versus controls). An error rate of > 33% on the prosody monosyllabic ID task had a sensitivity of 78.6% and specificity of 79.2% (correctly classifying 78.9% of participants as patients versus controls). ROC curves are shown in Figure 1. In contrast, the AUC for SCORE neglect summary score was 0.55 for both viewer-centered and stimulus-centered neglect measures. At most, the SCORE Neglect Score could classify 55.8% of patients vs. controls. Of 28 RHS patients, only 5 (17.9%) patients made fewer errors than the cut-off point on the prosody word ID task and 6 (21.4%) patients made fewer errors than the cut-off point on the prosody monosyllabic ID task; whereas 24 (85.7%) patients made 0% errors on the SCORE Neglect tests. The possible range of cut-off points for the sensitivity and specificity for prosody scores on the two ID tasks and neglect measures are shown in Figure 1.

The AUC for NIHSS Neglect was 0.63 and for Extinction was 0.57, and for both was 0.66. Again, prosody was significantly better than NIHSS neglect/extinction in distinguishing stroke patients from controls in this study. Using quintile scores for Prosody Recognition (so that they would have similar scales, rather than comparing a 100 point continuous scale to a 3 point scale), the AUC for Prosody was significantly higher than the NIHSS neglect/extinction score of 0.2 ($\chi^2 = 4.0; p = 0.047$).

The SCORE neglect tests identified three stroke patients with neglect who were not identified by the NIHSS as having neglect, but two were identified as having extinction on the NIHSS. The NIHSS identified 7 patients as having extinction, but one was a control.

The AUC for the total NIHSS score was 0.86; it classified 80.8% of patients. Three patients were detected with prosody who were not detected with NIHSS; both had cortical strokes (two parietal, one frontal). Two patients were detected with...
Table 1: Demographics and mean error rates on the prosody and neglect tasks for RHS and control participants.

<table>
<thead>
<tr>
<th>Participants</th>
<th>Age</th>
<th>Education</th>
<th>Sex</th>
<th>Prosody ID</th>
<th>Neglect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>word</td>
<td>monosyllabic</td>
</tr>
<tr>
<td>RHS (n=28)</td>
<td>55.93</td>
<td>13.62</td>
<td>12 female</td>
<td>0.54</td>
<td>0.43</td>
</tr>
<tr>
<td>SD</td>
<td>11.69</td>
<td>2.94</td>
<td></td>
<td>0.19</td>
<td>0.22</td>
</tr>
<tr>
<td>Controls (n=24)</td>
<td>51.71</td>
<td>13.33</td>
<td>16 female</td>
<td>0.30</td>
<td>0.21</td>
</tr>
<tr>
<td>SD</td>
<td>10.11</td>
<td>3.95</td>
<td></td>
<td>0.22</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Abbreviations: SD: standard deviation

NIHSS who were not detected with the prosody summary score; one had a subcortical infarct and one had an infarct in the motor strip. Therefore, the most effective classification of right hemisphere stroke patients versus controls was with the NIHSS score combined with the Prosody Score, yielding an AUC of 0.89 (CI 0.81-0.98). Together, they classified 82.7% of patients. Table 2 summarizes the sensitivity and specificity of each test.

Discussion

The current study investigated whether deficits in emotional prosody comprehension are more sensitive than neglect for identifying acute stroke in the right hemisphere. The ROC analysis shows that RHS patients have a higher probability of showing significant impairment in processing emotional prosody than showing significant neglect or extinction. The overall Prosody Score could classify 78.9% of patients vs. controls. In contrast, the SCORE Neglect tests could classify only 55.8% of patients vs. controls, and NIHSS neglect/extinction could classify 63.5% of patients vs controls. The SCORE neglect tests detected three additional stroke patients beyond those detected by NIHSS neglect test, but two of those three were also detected by the NIHSS extinction test. NIHSS extinction identified 7 participants with extinction, but one of these was a control. Still, NIHSS neglect plus extinction was slightly better in detecting right hemisphere
stroke than the SCORE neglect tests alone (without extinction). Nevertheless, testing prosody detected 15 more patients with right hemisphere stroke than the NIHSS neglect plus extinction. The two prosody subtests took minimally more time (5.4-7.6 minutes) compared to neglect subtests (2.9-5.8 minutes) and slightly more equipment. Although we presented the audiofiles on a laptop, they could as easily be presented from a smartphone, i-pod, or other electronic storage device. We have also presented the response alternatives on either paper or laptop. The neglect tests were "paper and pencil" tests, but laptop versions could be created, particularly for the gap detection test.

Cancellere and Kertsez, 1990 proposed that impairments in recognition of emotions from prosodic cues in patients with right hemisphere lesions may be due to attentional difficulties [12]. The current study does not provide clear support for this hypothesis. In spite of spared performance on neglect tasks, many RHS patients were profoundly impaired on the prosody tasks. Our study indicates that neglect (one type of spatial attention) and emotional prosody impairment are independent deficits caused by a stroke in the right hemisphere. There is other evidence that RHS patients have significant difficulty in comprehension of emotions from prosody without visual neglect [13]. However, such findings do not rule out that other types of attentional deficits may underlie both prosodic impairments and neglect.

Some brain regions have been identified that can result in both emotional prosody comprehension impairment and neglect. Using multivariate pattern analysis of activation during a gender recognition task during event-related functional MRI of young healthy adults, Ethofer and colleagues [2009] observed that each emotion category had a different localization of activation. However, all emotion categories activated voxels in bilateral mid superior temporal gyrus (STG, [25], implicating the role of mid STG in processing prosodic features irrespective of the emotion category. Right STG has been associated with left USN [1,26-28] or at least left stimulus-centered neglect [29]. Several studies have implicated the right inferior frontal gyrus in evaluative judgments of emotional prosody [30,31] and inferior frontal lobe in neglect tasks [32,33]. Patients in our study who had lesions in frontal, temporal and parietal regions. An overlay of lesions of all the patients is shown in Figure 2.

One account of the rare neglect in RHS patients in this study is that we might not have used adequately sensitive tests of USN. However, the NIHSS also demonstrated that only 18% patients had neglect. Additionally, we have previously used these tests along with more traditional tests such as line bisection, line cancellation, reading, clock drawing, and have found that these two tests identified virtually all patients with neglect [34].

An alternative account of the rare neglect in RHS patients in our study is the relatively small lesions (0.2 cc to 98.8 cc range; mean = 53.79 cm³). Severity of extinction and neglect correlates with the volume of infarct [35] and volume of hypoperfusion [36] in acute stroke. Moreover, the patients were relatively young compared to some previous studies (range= 33-75; mean=55.25 years), although the age was average age of stroke patients for our hospital. Previous studies have shown that neglect is more common and more severe after right hemisphere stroke in older individuals [37,38]. Therefore, spared performance of many of our RHS patients on neglect tasks suggests that either [1] the spatial attention network is intact in the majority of our patients, or [2] hemispatial neglect requires “two hits”: damage to one component of the spatial attention work, and damage to a more general attentional system for vigilance. This latter hypothesis is consistent with the model of Corbetta and Schulman [39], which accounts for neglect in large right MCA strokes as damage to both the bilateral dorsal spatial attention network and the right-dominant, nonspatial ventral attention network. It may be that comprehension of emotional prosody is a better marker of right hemisphere stroke than neglect in unselected, diverse stroke patients (many of whom have small strokes, and now have average age of 55), while neglect remains a strong marker of large right MCA stroke. The important point is that neglect is not the only cortical function that is impaired after RHS. The addition of test of other right hemisphere cortical functions, such as prosody, would improve detection of RHS.

CONCLUSION

The important finding of our study is that impairments in comprehension of emotional prosody is a common indicator of acute right hemisphere dysfunction – even more common than hemispatial neglect or extinction in some populations. These results indicate that acute stroke assessment could be improved by including a test (perhaps a downloadable audio file for a mobile phone) of prosodic comprehension. Furthermore, the addition of evaluation of prosody comprehension may improve our measures of effectiveness of interventions to salvage right cortical function, such as reperfusion therapies. However, the effectiveness, reliability, and efficiency of testing prosody comprehension at bedside (e.g. in an Emergency Department setting, which might require headphones) would need to be tested in a much larger study with an independent population.

ACKNOWLEDGEMENTS

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**Table 2: Comparison of sensitivity and specificity of SCORE Neglect, NIHSS, and Prosody tests.**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>% Correctly classified</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCORE Neglect Test</td>
<td>14.30%</td>
<td>100.00%</td>
<td>55.80%</td>
</tr>
<tr>
<td>NIHSS Extinction</td>
<td>17.90%</td>
<td>95.80%</td>
<td>53.90%</td>
</tr>
<tr>
<td>NIHSS Neglect+Extinction</td>
<td>35.70%</td>
<td>95.80%</td>
<td>63.50%</td>
</tr>
<tr>
<td>Total NIHSS Score</td>
<td>75.00%</td>
<td>87.50%</td>
<td>80.80%</td>
</tr>
<tr>
<td>Prosody</td>
<td>92.90%</td>
<td>62.50%</td>
<td>78.90%</td>
</tr>
</tbody>
</table>

**Abbreviations:** SCORE: Stroke Cognitive Outcome and Recovery; NIHSS: National Institutes of Health Stroke Scale

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**Figure 1 Lesions overlay of the RHS patients.** An overlay of the lesions of the 28 patients with the right hemisphere stroke (RHS). Nine slices are presented with all strokes from all the patients overlaid.
Disorders and Stroke, RO1NS47691 (to AEH)

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Hillis et al. (2014)
Email: argye@bmi.edu

Common risk factors for stroke have been well studied; however, the more uncommon etiologies and medical effects of stroke are only now becoming clear. The first paper is a nice description of mechanical compression of a major artery resulting in continued embolization. This mechanism would not have been diagnosed without careful thought and imaging. It reminds us of the importance of a complete evaluation and expanded differential, particularly in those without the “typical” vascular risk factors. Hypercoaguable states secondary to cancer represent another area deserving of discussion. Cryptogenic stroke is a universally frustrating problem. Dearborn and colleagues detail one institution’s approach to these patients. A majority of the morbidity and mortality in stroke has been reduced by simple interventions: prevention of aspiration pneumonia, fever, and deep vein thrombosis. Prior to implementation of these measures, it was not uncommon for a relatively small stroke to result in death from medical complications. The last paper highlights a more rare, but equally devastating medical complication of both anterior and posterior circulation strokes, whose prevention strategies may be different due to different underlying etiologies.
Position Dependent Carotid Impingement Causing Recurrent Strokes

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3Department of Surgery, University of Maryland School of Medicine, Baltimore MD, USA

Abstract

We report the case of a young man with recurrent strokes over a four year period, all occurring after leaning forward. He had suffered damage to the right subclavian and right carotid arteries in a car accident 20 years prior. Review of history and imaging concluded that all of his infarcts had been in the distribution of the right carotid artery. CT angiogram revealed that a segment at the origin of the right common carotid artery was adjacent to the sternum and kinked at the point of contact. Proposed mechanism of infarcts is position dependent intermittent vessel damage causing thrombosis and distal embolization. The patient underwent surgical repair, with no further events. This case highlights the importance of evaluating structures adjacent to vessels in patients with cryptogenic strokes.

ABBREVIATIONS

MRI: Magnetic Resonance Imaging; MRA: Magnetic Resonance Angiogram; CT: Computed Tomography; MCA: Middle Cerebral Artery; PCA: Posterior Cerebral Artery; TIAs: Transient Ischemic Attacks.

CASE PRESENTATION

A 39 year old man came to Neurology clinic for a second opinion. His general health status was good, with none of the common stroke risk factors. At age 19, he had been in a car crash with trauma to the chest requiring surgery to repair damage to the aorta, right subclavian, and right common carotid arteries. He recovered well, with no symptoms until age 36 when he had his first stroke. Upon straightening up after leaning over during yard work, he developed a “head rush” feeling followed by visual problems, dysarthria, left facial droop and left hand numbness. Most of the symptoms resolved in a couple days, with residual left upper quadrantanopsia. An angiogram showed thrombus in the right carotid bulb, for which he underwent carotid endarterectomy. He was discharged on warfarin, aspirin, and atorvastatin.

Six months later, he had another episode of left hand numbness after bending forward. His anticoagulation was subtherapeutic, and MRI was positive for right cortical stroke. Symptoms resolved after about a week. Four months later he was admitted for a transient episode of “head rush” after bending over, was again found to be subtherapeutic on warfarin, and placed on heparin IV. The following day, he complained of increased vision problems, and was found to have a right occipital intracerebral hemorrhage. Anticoagulation was stopped and he was discharged on clopidogrel.

After that admission, he developed migrainous headaches consisting of pain on the right side of his face, head, and eye in association with flashing lights in the right eye. He also noticed recurrent episodes of the “head rush” feeling after leaning forward. These were sometimes followed by transient feelings of warmth and paresthesias on his right face.

Eight months later, he developed frequent episodes of lightheadedness and tingling in his right arm after actively using the arm. He was found to have right subclavian stenosis and subsequently underwent axillo-axillary bypass. The right arm symptoms and lightheadedness resolved, but the migraines and “head rush” episodes persisted.

Six months later, he had another episode of dizziness and left hand numbness after bending over. MRI revealed a right cortical stroke, and evaluation with MRA head and neck, EEG, echocardiogram, and hypercoagulable labs was unremarkable. Four months later, he had an episode while leaning over to shovel snow of head rush followed by flushing of his right face, left sided weakness, dysarthria, and confusion. MRI showed multiple small infarcts in the right MCA and PCA territories. His symptoms improved to residual left hand weakness only.

At this point, he presented to our clinic for further evaluation. Based on his history and prior imaging, all of his strokes and TIAs appeared to be in the distribution of the right internal carotid
artery (including the occipital infarcts, secondary to a large right posterior communicating artery and diminutive P1 segment of the right posterior cerebral artery). To better evaluate his vasculature, a CT angiogram was performed. Initial report was of patent vessels throughout. Careful attention to the origin of the right common carotid artery showed that the vessel was in contact with the sternum, with a kink in the vessel at the area of contact (Figure 1). Bending forward could put additional pressure on the vessel in this location, causing vessel injury, with subsequent thrombus formation and artery to artery embolization. It could also cause transient hypoperfusion leading to the head rush sensations, with warmth and paresthesias on the right side of the face likely a result of changes in blood flow in the external carotid artery.

The imaging findings and proposed mechanism of strokes were discussed with the patient, and the decision made to proceed with surgical reconstruction.

SURGICAL DESCRIPTION

The axillo-axillary bypass graft previously placed across the midline was dissected out, and extensive adhesiolysis was performed to free the heart from the anterior chest wall, and to dissect out the ascending aorta. The previous aorto-carotid and aorto-to-subclavian bypass grafts were avoided to prevent embolization of debris within them. The ascending aorta was then clamped with a partial occluding clamp and an opening made about 3 cm above the aortic valve. The proximal end of a custom-designed bifurcated Dacron graft (Terumo, Vascutek, Scotland, UK) was anastomosed to the ascending aorta. The right common carotid artery was then transected and anastomosed to the graft. The previous aorto-carotid graft was freed from the manubrium posteriorly, transected as proximally as possible to its origin from the aorta, and removed. The previous axillo-axillary bypass graft was then transected and anastomosed to the free end of the new bifurcated graft, and the remainder of the previous axillo-axillary graft was resected and removed. A Doppler device was used to confirm good flow in both the right common carotid artery and the right axillary artery, and the chest was closed.

The patient was kept on dual antiplatelet agents (Plavix 75mg daily and aspirin 81mg daily) for 3 months and then switched to 81 mg aspirin alone. He recovered well from the surgery and reported no further episodes of focal symptoms or head rush. His migraine headaches also resolved post-operatively.

DISCUSSION

Boney abnormalities causing vessel damage are a rare but important cause of stroke, as the underlying lesion may be amenable to surgical correction. One of the authors has previously reported a case in which a congenital boney abnormality of the occiput was found to be causing recurrent vertebral artery damage and strokes [1]. Cerebral embolism can also be seen with damage to the subclavian artery from a cervical rib in the thoracic outlet syndrome [2]. Typically, the carotid artery is not in a position where it can be damaged by surrounding structures, although an intriguing association has been found between styloid process length and carotid dissection [3]. In this case, the prior injury and reconstruction brought the carotid into an unusual position relative to the sternum.

This case demonstrates that careful review of not just the vessel lumen, but also the surrounding structures can sometimes reveal a cause of stroke. CT angiogram is an imaging modality that allows for excellent visualization of both vessels and surrounding boney structures. 3-dimensional reconstruction programs that allow for rotation of the image and viewing from alternative angles can sometimes reveal lesions that are not immediately apparent in standard imaging protocols.

REFERENCES

Introduction

Cancer and ischemic stroke independently carry a large burden of morbidity and mortality as the second and fourth leading cause of death in the United States [1]. They each represent an enormous expenditure as a percentage of health care resources, manifested by lost productivity and disrupted family structures due to death and dependency. Cancer patients frequently have strokes, both from traditional risk factors and from mechanisms thought unique to malignancy. An autopsy study of patients with known cancer at time of death showed 15% of patients suffer from stroke diagnosed pathologically; [2] however only half of these strokes were noted during life. In addition, patients with venous thromboembolism are more likely to be diagnosed with cancer in the ensuing years, suggesting that hypercoagulability may be an important first presentation in cancer [3]. Patients with stroke and cancer have poorer clinical outcomes and longer hospital stays compared with stroke patients without cancer [4]. Unfortunately, detection, prevention, and treatment of stroke in cancer patients have been largely understudied. In addition, clinicians in many stroke centers must grapple with the fairly high rate of embolic-appearing stroke where no etiology is found. This rate of cryptogenic stroke has been quoted as high as 26-40% of patients [5-8]. It is tempting to consider hypercoagulability from a previously undiagnosed cancer as a possible etiology in such patients [4,9]. In this review, we will focus on the data linking stroke and cancer as well as propose a testable algorithm for cancer screening in the patient with cryptogenic stroke. Future directions should focus on validating patient-care algorithms in prospective clinical trials to provide an evidence base for this important issue.

Background

The most frequent causes of stroke in cancer patients are traditional cerebrovascular risk factors such as hypertension, hyperlipidemia, diabetes, atrial fibrillation and tobacco use [10-12]. Vascular risk profiles of cancer patients are similar when compared to patients without cancer who were admitted to a stroke unit [13]. Nevertheless, the classification of “cryptogenic” stroke, meaning that no cause was identified despite detailed investigation, is more common in stroke patients with cancer, [10] suggesting an association between malignancy and unknown mechanisms leading to stroke. Of note, 67% of strokes in cancer patients appear as multiple embolic events on imaging in one study [14] suggesting that clot formation and embolization may often be the culprit. Although cancer can co-exist and even accelerate traditional cerebrovascular risk factors, we hypothesize that in a certain subset of patients, cancer causes stroke more directly. Multiple mechanisms, supported by multiple lines of evidence, may link stroke with cancer. We explore each below. Findings are summarized in Table 1.

Hypercoagulability

Perhaps the most important and underreported mechanism by which cancer can cause stroke is via abnormal coagulation cascades. The eponymous Trousseau’s syndrome, first described in 1865, referred to migratory thrombophlebitis in a patient with a visceral carcinoma, [15] but has since been expanded to describe any hypercoagulable state associated with cancer [16]. Coagulation disorders, such as disseminated intravascular coagulation (DIC), are more likely to be seen in stroke patients with cancer than without [4,11,12]. Cancer patients with cryptogenic stroke were found to have elevated D-Dimer levels compared to stroke patients without malignancy [9].

Although many malignancies have been associated with hypercoagulability, adenocarcinoma is frequently linked with clotting disorders as well as malignancy-associated stroke and, therefore, bears special consideration. In Japan, the incidence of colorectal cancer has been reported to be 16 per 10,000 person-
Central.

The clotting cascade [24]. In addition, these cytokines inhibit monocytes, and cancer cells to express TF, thereby potentiating blood sludging [23,24]. These cytokines induce endothelial cells, sloughing of vascular endothelial cells as well as increased coagulant cytokines such as TNF-alpha, IL-1 and IL-6, causing of local chemical mediators. Malignant cells release pro-coagulant cytokines, resulting in the generation of thrombin [23,24]. TF has been found in symptomatic atherosclerotic cancers (81% in one sample assay), and is known to be a cysteine proteinase which directly cleaves factor X to Xa, ultimately potentiating thrombi via production of mucin, a high molecular weight “sticky” molecule that is glycosylated and secreted normally by endothelial cells. Adenocarcinomas especially of the pancreas, colon, breast, lung, prostate, and ovary can secrete this molecule directly into the bloodstream, precipitating a viscous, and hypercoagulable state [15,18]. Mucin can interact with certain cell adhesion molecules (CAM), on endothelial cells, platelets, and lymphocytes to induce the formation of platelet rich microthrombi.

Further, tumor cells can release pro-coagulant molecules directly, the most well known of which are tissue factor (TF) and cancer pro-coagulant (CP) [19,20]. TF is a protein that binds to factor VII to potentiate the coagulation cascade, and thereby thrombosis. TF has been found in symptomatic atherosclerotic plaques in carotid stenosis, prompting the hypothesis that TF destabilizes plaque [21,22]. CP is released by the majority of cancers (81% in one sample assay), and is known to be a cysteine protease which directly cleaves factor X to Xa, ultimately resulting in the generation of thrombin [23,24].

Tumor-endothelial reactions are important for release of local chemical mediators. Malignant cells release pro-coagulant cytokines such as TNF-alpha, IL-1 and IL-6, causing sloughing of vascular endothelial cells as well as increased blood sludging [23,24]. These cytokines induce endothelial cells, monocytes, and cancer cells to express TF, thereby potentiating the clotting cascade [24]. In addition, these cytokines inhibit Protein C activation thus decreasing a natural “brake” on the anticoagulation system [20]. Platelet activation is also increased in cancer patients, likely from multiple mechanisms of locally released cytokines and secreted proteins by tumor and elevated levels of von-Willebrand factor [20].

Venous-to-arterial embolism

Perhaps the most well recognized clinical presentation of hypercoagulability is deep venous thrombosis and/or pulmonary embolus. These venous clots may lead to stroke via a direct venous-to-arterial shunting – sometimes referred to as “paradoxical” emboli. There is debate about whether venous to arterial thrombo-embolization via a patent foramen ovale (PFO) occurs. The likelihood of having a stroke in patients with PFO is doubled, suggesting that something about the shunt increases stroke risk [25]. On the other hand, neither the size of the PFO or the degree of venous-to-arterial shunting correlated with risk of stroke recurrence [26]. One interesting study found an increased rate of pelvic thrombosis in patients with cryptogenic stroke, some of whom had a PFO, suggesting a possible mechanism [27]. Nevertheless, it seems reasonable that increased risk of venous clots increases the risk of paradoxical embolization [28].

Nonbacterial thrombotic endocarditis

Another common mechanism relating stroke and cancer is nonbacterial thrombotic endocarditis (NBTE), previously known as marantic endocarditis. In NBTE, sterile vegetations develop on the cardiac valves, in descending order of frequency: aortic, mitral, and a combination of aortic and mitral [29]. The mechanism is thought to arise from disrupted fibrin attaching to...
previously undamaged valves in high flow areas and developing a network onto which platelets can adhere. Transesophageal echocardiography (TEE) is thought to be more sensitive that transthoracic echocardiography (TTE) in detecting valvular vegetations [30]. Often a TEE is not part of a standard stroke workup. In a retrospective study of 24 patients with cancer were found to have NBTE, [4] which is frequently associated with adenocarcinoma [31]. Systemic emboli occur in nearly 50% of patients with NBTE, with cerebral emboli being quite common [29,32]. The diffusion MRI pattern in patients with NBTE was uniformly found to have multiple widely distributed small and large strokes, whereas those with bacterial endocarditis had more varied stroke patterns, sometimes involving a single vascular distribution [33].

Direct tumor effects

Direct tumor effects, either from tumor compression, or from tumor embolism are another cancer specific mechanism of stroke. Metastases to the brain, as well as primary brain tumors, can cause direct compression of blood vessels, either by direct tumor invasion or via tumor bed edema, [34-36] leading to cerebral ischemia and subsequent infarction in the territory distal to the affected vessel. This presentation can be difficult to clinically differentiate from tumor progression alone. It bears special mention that direct tumor effects can also lead to hemorrhagic stroke within the cranial vault. Hemorrhagic conversion of brain metastasis is a relatively rare occurrence in a population of non-hypertensive hemorrhagic strokes (1 to 10% of cases) [37]. Melanoma, renal cell carcinoma, and choriocarcinoma are some examples of tumor types with a tendency for hemorrhagic conversion based on case studies [37,38]. The mechanism is likely related to necrosis of tumor beds, which are rich in vasculature.

Other rare causes of direct cancer effects leading to stroke include embolism to the brain from metastasis in the heart [39-41]. Tumors that are most likely to affect the heart include melanoma, which has a high rate of hematologic spread, carcinomas of the lung, breast, esophagus or hematologic malignancies, although many tumor types have been reported [42,43]. Primary cardiac tumors, such as atrial myxomas, although benign also have embolic potential, [42,44] and hematologic malignancies can result in strokes by directly affecting intracranial structures and/or blood flow. Hyperviscous obstruction of end vessels from the malignant hematologic cells, as exemplified by polycythemia vera, can lead to decreased perfusion and stroke [45,46]. Intravascular lymphomatosis, also known as angiotropic lymphoma or neoplastic angioendotheliosis, is primarily of B-cell origin and can cause multiple territory cerebral infarcts by an infiltrative process. Other organs are typically spared, although skin involvement is not uncommon [36,47,48]. This is often an elusive diagnosis, as much of the testing for systemic disease can be negative.

Cancer-associated treatments and stroke

Radiation treatment effect causes stroke by unique mechanisms [49]. Head and neck radiation causes a vasculopathy of medium and large sized vessels that often presents years after radiation exposure. This vasculopathy is not well characterized, but may be associated with accelerated atherosclerosis [50-53]. Regardless of the underlying pathophysiology, the changes can lead to radiological findings similar to Moyamoya syndrome. Patients develop stenosis of the carotid vessel with abnormal netlike vessels and transdural anastomosis distal to the stenosis [54]. Head and neck radiation therapy (HNXRT) may almost double the risk of stroke, with the exception of adjuvant breast radiation therapy where neck exposure is minimal [55]. Squamous cell carcinoma is the most common cancer treated using HNXRT. In one analysis, the overall rate of stroke was 1.44 times higher in the radiation therapy cohort than the reference cohort [56].

Some chemotherapeutic agents have also been associated with an increased risk of stroke, such as cisplatin, methotrexate and L-asparaginase, however the mechanisms are poorly understood [57,58]. They are thought to be related to thromboembolic events (both venous and arterial). For example, L-asparaginase has been associated with cerebral venous thrombosis in children treated for leukemia [36]. The antiangiogenic agents thalidomide and lenalidomide have been associated with stroke [59-61] and are associated with a high risk of VTE [62,63].

Bevacizumab, a monoclonal antibody against VEG-F receptors, is used in a variety of cancer types including glioblastoma multiforme and other solid tumors. It is associated with a 3% arterial thrombotic event rate, [62] however pooled analysis did not show an increased risk of VTE [64,65]. In treatment of solid tumors, including breast, colon and non-small cell lung cancer, bevacizumab plus chemotherapy, compared with chemotherapy alone, has a hazard ratio of 2.0 for arterial thrombotic events [65]. A retrospective analysis of the cohort with glioblastoma multiforme in treatment trials for bevacizumab showed a stroke rate of 1.9%, and a hemorrhagic stroke rate of 1.9%. The attributable risk from the drug rather than malignancy or traditional risk factors is unclear [66].

Screening for cancer in the patient with cryptogenic stroke

The data suggests that cancer is either directly or indirectly responsible for stroke in a certain subset of patients (as opposed to just coexistent with vascular risk factors). As such, clinicians should consider screening for occult cancer in a subset of cryptogenic stroke patients. However, the subset of patients requiring stroke-promoted cancer screening, the optimal diagnostic approach, and how the approach should differ based upon age, clinical presentation, and associated risk factors, has yet to be determined. Using existing data, we suggest an approach that may help to diagnose occult cancer as well as provide testable hypotheses for future improvement of this methodology in stroke patients with cryptogenic stroke (Figure 1). We focus on diagnostics associated with occult cancer-induced hypercoagulability, since other causes of cancer-induced stroke (e.g. direct tumor effects and treatment effects) are often apparent.

Our approach assumes that patients with an identifiable stroke etiology (e.g. atrial fibrillation) do not need stroke-promoted cancer screening, as the cause of stroke is already evident. Our approach includes stroke patients of all ages, as we freely admit that that the optimal age to screen for cancer in
cryptogenic stroke patients is not known: older stroke patients are more likely to have cancer; [67] on the other hand, younger stroke patients are more likely to have a cryptogenic classification thus prompting further investigation [68].

We begin with imaging characteristics. Multiple embolic events (involving the brain and/or other organs) or presence of VTE, prompts a more extensive work-up. Generally, we do not consider lacunar stroke to be related to cancer-associated hypercoagulability since lacunar stroke occurs through different mechanisms [69,70]. When a cryptogenic stroke appears embolic, we expand the medical history to include symptoms suggestive of cancer (i.e., the presence of “B” symptoms such as unexplained fevers, weight loss, and malaise). This should also include questioning for environmental exposures associated with cancer incidence (e.g., smoking and carcinogen exposures).

We perform a careful general physical examination including a breast or testicular exam in the appropriate setting. Next, consideration is given to the evaluation of serum markers (such as D-Dimer) known to correlate with the diagnosis of cancer, which could help to raise or lower suspicion [71,72]. D-Dimer has an unknown sensitivity as a screening tool, but elevation in cancer patients with stroke is well documented [73-75]. The presence of one or more of these “red-flags” should prompt further workup: (1) contrast enhanced CT scanning of the chest, abdomen, and pelvis (PET scanning is a viable alternative), (2) ensuring that the patient is up-to-date on age appropriate cancer screening, and (3) consideration of trans-vaginal ultrasound in high risk women (age >50 years, age >25 with family history) [76]. Testicular ultrasound is not an effective screen for testicular cancer in men [77].

Treatment of cancer-related stroke

In the patient with cancer and stroke, identification of stroke risk factors independent of cancer is of utmost importance. “Classic” cerebrovascular risk factors (hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, carotid disease, and tobacco use) remain the leading etiologies of stroke and risk factor modification is therefore paramount. Atrial fibrillation should still be considered over hypercoagulability of cancer in patients with embolic appearing strokes, and, if discovered, anticoagulation initiated. Patients without a proven need for anticoagulation (e.g., hypercoaguable state such as Factor V Leiden disorder, large vessel dissection, atrial fibrillation, etc.) should be started on an anti-platelet agent. Managing hypertension, hyperlipidemia, and diabetes; offering smoking cessation counseling; providing life-style modification counseling; and encouraging medication adherence are essential.

Patients with known cancer and probable cancer-related stroke bear special consideration. We should note at the outset that there are no direct studies that address treatment of any of the presumed cancer-induced stroke mechanisms discussed above. Of particular concern is prevention of hypercoagulability-induced stroke. Available data suggest hypercoagulability-induced stroke is a real entity, but difficult to diagnostically confirm or design a treatment plan effectively acknowledging the risks and benefits.

It remains to be seen whether there is a role for anti-platelets in the secondary prevention of cancer-related stroke (adenocarcinoma or otherwise). More data exist with respect to anticoagulation. One study measured the effect of anticoagulation (using unfractionated heparin, low molecular heparin, or warfarin) on micro-embolism [78]. Transcranial Doppler (TCD)
was used in stroke patients with cancer to determine the embolic signal in the middle cerebral artery (MCA). Patients were divided into those with conventional stroke mechanism, and those with presumed hypercoagulability. Embolic signals measured by TCD were more commonly detected in patients with high D-Dimer levels. Treatment with anticoagulation was also noted to decrease D-Dimer levels [78]. This correlation between embolic signal and D-Dimer level may suggest that anticoagulation has the potential to attenuate cancer-induced hypercoagulability leading to stroke. Further, these data suggest that tracking D-Dimer levels may be a method to measure the risk of cancer-induced embolism and/or effect of anticoagulation in these patients.

Based upon these limited data, if we assume that anticoagulation is superior for the prevention of hypercoagulability-induced stroke, we must then consider which form of anticoagulation is most appropriate in cancer patients. There is data that low molecular weight heparin (LMWH) prevents VTE in cancer patients; however, whether the results can be extrapolated to arterial stroke is unclear. The results of trials with LMWH are summarized in Table 2. The CLOT study established the use of LMWH in patients with cancer and DVT. The probability of recurrent VTE was much lower in the dalteparin group at six months versus those treated with warfarin [79]. Similar results were seen with tinzaparin and semuloparin [80,81]. Enoxaparin has not been shown to be superior to warfarin, although the studies were often small and may not have been adequately powered [62]. A study evaluating antithrombotic prophylaxis with nadroparin versus placebo did include a subgroup analysis of patients with stroke [82]. Although there was a reduced rate of stroke in the nadroparin group, (3 of 769 patients) versus placebo group (3 of 381 patients) the total number of strokes was too small to draw concrete conclusions. The newer oral anticoagulants dabigatran (a direct thrombin inhibitor) and rivaroxiban (a direct factor Xa inhibitor), have proven effective in DVT treatment, [83] but remain to be studied in cancer subgroups.

Though there may be benefit to anticoagulation for stroke prevention in patients with cancer, there is also inherent risk. Large clinical trials show that systemic anticoagulation increases the rate of hemorrhage in ischemic stroke patients [84,85]. Developing a method for the selection of high-risk patients who may benefit the most using clinical (stroke severity), serologic (D-Dimer), and radiographic characteristics (presence of prior stroke), may be the optimal approach to deciding in whom to initiate therapy. In the VTE literature, there is a risk score for cancer patients used to guide which patients should be anticoagulated for primary prevention of DVT/VTE [86]. The score includes high-risk characteristics such as: type of cancer, platelet count, leukocyte count, D-Dimer, body mass index (BMI) and P-selectin. P-selectin is an adhesion molecule on endothelial

<table>
<thead>
<tr>
<th>Study</th>
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<th>Intervention</th>
<th>Outcome</th>
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<tr>
<td>ENOXACAN II</td>
<td>Randomized, double blind, placebo controlled</td>
<td>332 patients undergoing planned curative open surgery for abdominal or pelvic cancer</td>
<td>Enoxaparin vs placebo for 21 days. All patients received enoxaparin for first 6 to 10 days.</td>
<td>Reduced the incidence of VTE detected by ultrasound</td>
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<tr>
<td>CLOT</td>
<td>Randomized, open-label clinical trial</td>
<td>(N=336 treatment, n=336 standard care) Patients with cancer and a DVT, PE or both</td>
<td>Dalteparin for 5 or 6 days followed by Dalteparin vs warfarin for 6 months</td>
<td>Recurrent VTE lower in with no major increase in bleeding</td>
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<tr>
<td>Altinbas et al.</td>
<td>Randomized placebo controlled</td>
<td>84 patients with squamous cell lung carcinoma receiving chemotherapy</td>
<td>Dalteparin vs placebo for 18 weeks</td>
<td>Dalteparin favorably improved survival</td>
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<tr>
<td>FAMOUS</td>
<td>Randomized placebo controlled</td>
<td>385 patients with advanced malignancy</td>
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<tr>
<td>MALT</td>
<td>Randomized placebo controlled trial</td>
<td>(N=148 treatment, n=154 control) Patients with metastatic or locally advanced solid tumors</td>
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<td>Nadroparin favorably improved survival</td>
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<tr>
<td>LITE</td>
<td>Randomized, open-label clinical trial</td>
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<td>Tinzaparin vs warfarin for 3 months</td>
<td>3 month outcomes were similar, at 12 months VTE was reduced in the Tinzaparin group</td>
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<td>PROSPECT</td>
<td>Phase Iib</td>
<td>540 patients with locally advanced or metastatic pancreatic cancer undergoing chemotherapy</td>
<td>Enoxaparin vs placebo</td>
<td>Safety analysis showed no increase in bleeding in treatment group</td>
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<tr>
<td>PROTECHT</td>
<td>Randomized, double blind placebo controlled</td>
<td>(N=779 treatment and n=387 placebo) patients with metastatic or locally advanced solid cancer receiving chemotherapy</td>
<td>Nadroparin vs placebo for duration of chemotherapy versus 4 months</td>
<td>Reduced rate of stroke in nadroparin group, but only six total strokes occurred, also was increase in bleeding complications</td>
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<tr>
<td>SAVE-ONCO</td>
<td>Randomized, double blind placebo controlled</td>
<td>(N=1608 treatment, n=1604 placebo) Patients with metastatic or locally advanced cancer receiving chemotherapy</td>
<td>Semuloparin vs placebo until chemotherapy regimen was changed</td>
<td>Semuloparin reduced the risk of VTE, without an apparent increased risk of bleeding</td>
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cells and platelets that was in deploratively shown to be a predictor of cancer associated VTE [87].

We suggest that patients with known cancer and cryptogenic, multiple embolic events (involving the brain and/or other organs), VTE, or the presence of adenocarcinoma represent a group with predisposition to hypercoagulability. (Generally, we do not consider lacunar stroke to be related to cancer-associated hypercoagulability since lacunar stroke occurs through different mechanisms.) [69,70] If any of the above conditions are present, in the absence of another obvious cause for embolic stroke, patients are likely to benefit from anticoagulation with LMWH. In a patient in whom we are uncertain about the contribution of the cancer, we will often perform a TEE to investigate for NBTE. If present, NBTE would bias towards anticoagulation with LMWH. The TEE with bubble study can also tell us about the presence of a PFO, which by itself would not require anticoagulation, unless a DVT was present. Anticoagulation should likely be continued until the cancer is in remission, the patient cannot tolerate it, or a bleeding complication occurs.

CONCLUSIONS/FUTURE DIRECTIONS

Stroke and cancer are intertwined by virtue of their relatively common occurrence within the general population. It cannot be stressed enough that cancer is not the most common etiology of stroke, and that even in patients with cancer; the traditional risk factors are most commonly the underlying cause. There are, however, cancer-specific mechanisms that may further increase one’s risk for stroke. These include: hypercoagulable states induced by tumor cells, NBTE, vessel compression, chemotherapy related hypercoagulability or post radiation effects, hyperviscosity, or vessel infiltration by cancer cells. To date, there are no clinical trials leading to guidelines for diagnosis or treatment of these conditions. The DVT/VTE literature provides some insight into treatment of a subgroup of “hypercoagulable” stroke patients who may benefit from treatment from LMWH, but specific stroke prevention studies have yet to be performed.

Occult cancer may be an important missed diagnosis in cryptogenic stroke. There is little data to suggest what should be done to screen for malignancy in patients with cryptogenic stroke. First steps may include: 1) identifying a subgroup of stroke patients who are most likely to benefit from aggressive malignancy surveillance, and 2) subsequently carrying out this screening as part of the inpatient evaluation. Early screening will allow for more rapid detection of potentially treatable cancers, and may inform decisions on treatment for secondary stroke prevention. Our suggested approach needs to be validated in systematic studies to determine which patients require more aggressive screening and what are the most accurate diagnostic tests. Our approach also requires an analysis of the cost benefit of such a workup, as admittedly only 3% of all strokes are attributable to cancer and many screening tests such as PET are resource intensive and costly [17].

Finally, treatment of a patient with stroke in the setting of cancer is complex and requires careful integration from both neurologic and oncologic experts. Although existing data suggests LMWH may be superior, the role for antiplatelet agents versus anticoagulation with warfarin versus anticoagulation with LMWH is still unclear and requires further study. Treatment with chemotherapy and radiation also requires careful consideration when deciding how to proceed with cancer therapy post-stroke. An interdisciplinary team, including physician experts, therapists, and social workers, is best equipped to deal with the treatment decisions that follow.

REFERENCES


Central


Isolated Pulmonary Edema without Myocardial Stunning in Brainstem Strokes

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Abstract

Introduction: Ischemic stroke has been associated with stunned myocardium and neurogenic pulmonary edema (NPE). We studied a population of patients with large vessel brainstem ischemic stroke to see if there was an increased risk of pulmonary edema associated with strokes in this region independent of myocardial stunning.

Hypothesis: Large vessel ischemic strokes of the brainstem are associated with neurogenic pulmonary edema and occur independently of myocardial stunning.

Methods: This is a retrospective case control study of 1,278 patient admissions. Two hundred ten patients were identified with large vessel ischemic stroke or transient ischemic attack (mean age 65 years, 55% female, 50% black). Infarction locations included: brainstem (N=22), right middle cerebral artery involving the insula (N=38), left middle cerebral artery involving the insula (N=37), and transient ischemic attack (N=113). Multivariate logistic regression models for presence of echocardiographic wall motion abnormalities, QTc-interval prolongation, elevated serum troponin, and pulmonary edema were developed to examine the relative contribution of stroke location and markers of cardiopulmonary dysfunction to each respective outcome, controlling for patient characteristics.

Results: Large vessel brainstem stroke was associated with pulmonary edema (adjusted OR 29.23, 95% CI 1.90-449.51) but not cardiac abnormalities. Large vessel left middle cerebral artery stroke was also associated with pulmonary edema (76.44, 6.93-843.54) as well as QTc-interval prolongation (4.55, 10.77-19.24). Large vessel right middle cerebral artery stroke was associated with pulmonary edema (10.88, 1.02-116.70) as well as elevated serum troponin (10.51, 1.71-64.82).

Conclusion: In a retrospective case control study, large vessel brainstem stroke was associated with the development of pulmonary edema independent of cardiac abnormalities associated with myocardial stunning, suggesting a separate brainstem pathophysiologic mechanism which directly affects the lungs but not the heart.

INTRODUCTION

Over 790,000 strokes occur annually in the United States, making it the fourth leading cause of death and the leading cause of disability in people over the age of 65 [1]. Pulmonary and cardiac complications after stroke are common. The association of ischemic stroke with electrocardiographic change and elevated cardiac enzymes has been known for decades [2-4]. The classic triads of findings for neurogenic myocardial stunning are transient left ventricular wall motion abnormalities, electrocardiographic abnormalities and elevation in myocardial enzymes in the serum in the absence of coronary artery disease [5]. The physiological mechanisms underlying these associations are not fully understood. They are thought to involve sympathetic hyperactivity and possibly anatomic inhibition due to insular cortical injury [6-8]. Localization of ischemic stroke to the insula and the parietal lobe has been associated with fatal arrhythmias in animal models and human studies [7-9].

Respiratory failure occurs in 5-10% of patients with acute ischemic stroke, most often secondary to aspiration and decreased airway protection. Pulmonary parenchymal disease has been observed as a direct consequence of centrally mediated injury due to neurogenic pulmonary edema (NPE) [9,10]. NPE has been noted as a complication of a variety of neurological syndromes, including basilar artery thrombosis and intracerebral
hemorrhage [9-11]. The anterior and posterior cerebrovascular distributions have both been implicated in NPE [9,11,12].

It is unknown how often acute pulmonary edema noted in the setting of ischemic stroke occurs independently or as a result of cardiac dysfunction. It is also unknown if there is a relationship of particular cerebrovascular distributions to particular patterns of cardiac and/or pulmonary dysfunction in ischemic stroke. Here we describe a retrospective review of patients treated at a tertiary stroke center for large vessel ischemic stroke, to explore the association of the cerebrovascular distribution of infarction to pulmonary edema and cardiac function derangements as measured by echocardiography, elevated cardiac enzymes and echocardiography. We hypothesized that we would find an association between large vessel ischemia in the brainstem and pulmonary edema occurring independently of cardiac abnormalities associated with myocardial stunning.

PATIENTS AND METHODS

A retrospective review was performed on all patients admitted or transferred to the cerebrovascular neurology service at Johns Hopkins Hospital from June 2009 through June 2011. Clinical data obtained included: age; gender; race; and medical history of diabetes, hypertension, hypercholesterolemia, smoking, arrhythmia, atrial fibrillation, coronary artery disease, heart failure, diabetes and prior stroke or transient ischemic attack (TIA). Past medical history was recorded as per documentation in the medical record at time of admission.

All patients > 17 years of age admitted to the Johns Hopkins Hospital cerebrovascular service were included, whether or not they died while admitted. Patients were included if they had a discharge diagnosis of TIA (control group) [13]; ischemic stroke of the right or left middle cerebral artery (RMCA or LMCA); or basilar artery ischemic stroke, stenosis or occlusion. All other patients were excluded, including those who had ischemic strokes in multiple cerebrovascular distributions. To ensure inclusion of patients with large vessel middle cerebral artery infarction, of those patients with discharge diagnosis of ischemic stroke of the RMCA or LMCA; only those patients with radiographic findings consistent with infarction of the insular cortex were included. To ensure inclusion of patients with large vessel brainstem infarctions, of those patients with discharge diagnosis of basilar artery ischemic stroke, stenosis or occlusion, only those with radiographic findings consistent with infarction within the midbrain, pons and/or medulla in the setting of basilar artery stenosis or occlusion were included.

Imaging and laboratory data included: echocardiogram reports; electrocardiogram (EKG) reports upon admission and 48 hours after admission; initial and peak serum troponin levels; chest radiographs during admission. Heart failure was defined as an ejection fraction of \( \leq 35\% \) as measured by echocardiogram [14]. Cardiac wall motion abnormalities were documented by cardiologist-based interpretation of echocardiogram. Troponinemia was defined as \( >0.06 \text{ ng/mL} \), per institutional clinical laboratory designation. Nonspecific ST segment abnormalities and arrhythmias were determined from the final cardiologist report of EKG. Corrected QT (QTc) interval prolongation was defined as \( >460 \text{ ms} \) per EKG report. The presence or absence of pulmonary edema was determined by review of chest radiographs within 96 hours of admission, when available. These were reviewed by physician reviewers blinded to patient diagnosis and study hypothesis (T. C. and D. V.) using previously established criteria [15].

STATISTICAL ANALYSIS

For continuous variables, medians with interquartile range (IQR) and means with standard deviations (SD) were calculated. For categorical variables, frequencies were measured. Group differences for continuous variables were tested by one-way analysis of variance with Bonferroni’s adjustment for multiple comparisons. The \( X^2 \) test for independence or Fisher’s exact test was used to examine group differences for categorical variables. Univariate analyses were performed to assess for significant risk factors for development of pulmonary edema. Multivariate logistic regression analyses were performed with outcomes of interest (i.e. pulmonary edema, echocardiographic wall motion abnormalities, presence of elevated serum troponin, and QTc-interval prolongation) serving as the dependent variables. When clinical data was missing, the documented diagnosis was used based on clinical examination or report of clinical data at time of admission.

For each multivariate logistic regression model, patient characteristics including age \( \geq 57 \) years [16], history of atrial fibrillation, history of coronary artery disease, history of diabetes mellitus, history of heart failure, history of hypertension, history of smoking, and stroke location were included as independent variables and controlled for. In addition, diagnostic results indicative of cardiopulmonary dysfunction including presence of wall motion abnormalities on echocardiogram, arrhythmia on admission EKG, QTc prolongation on admission EKG, presence of pulmonary edema, and elevated serum troponin were included and controlled for as independent variables except when the dependent variable of interest for a respective multiple logistic regression model. Collinearity diagnostics were performed to assess for intercorrelations among independent variables. The amount of variation in the dependent variable explained by each respective model was assessed using Cox & Snell R Square and the Nagelkerke R Square tests. Goodness-of-fit of each multivariate logistic regression model was assessed by Hosmer and Lemeshow’s test (H-L). Significance of regression coefficients to respective logistic regression models were assessed using Wald’s test. Two-tailed statistical significance was assessed at the \( p<0.05 \) level. All statistical analyses were performed using the SPSS (version 22, IBM, Armonk, NY) statistical package while figures were made using the Prism (version 5, GraphPad, San Diego, CA) statistical package.

RESULTS

Clinical characteristics

We completed a review of 1,278 patient records. There were 210 patients with large vessel ischemic stroke or TIA identified and included in our analysis. Of these patients, 55% were female, 50% were black, 75% had a history of hypertension and their average age was 63.5 years (SD 15.9). Twenty-two patients had brainstem stroke in the setting of basilar occlusion or stenosis, 38 patients had large vessel right middle cerebral artery (RMCA)
strokes involving the insula, 37 patients had large vessel left middle cerebral artery (LMCA) strokes involving the insula, and 113 TIA control patients were identified. The large vessel brainstem stroke group included two patients with isolated medullary infarct, ten patients with isolated pontine infarct, and ten with infarction of multiple brainstem structures. With the exception of history of atrial fibrillation \((\chi^2 (3, n=208) = 14.75, p=0.002)\) and history of heart failure \((\chi^2 (3, n=208) = 10.72, p=0.01)\), patient groups were similar in terms of age; gender; race; history of prior stroke or TIA, diabetes, smoking and hypercholesterolemia (Table 1).

**Pulmonary evaluation**

Chest radiographs were available for review for 65 TIA, 28 RMCA, 31 LMCA, 19 brainstem stroke patients. The presence of pulmonary edema was determined based on review of available chest radiographs within 96 hours of admission [15]. For all other patients, pulmonary edema was assessed based on review of available chest radiographs reports at time of admission.

The proportion of patients with pulmonary edema varied across the four groups \((\chi^2 (3, N=210) = 52.02, p=0.0001, Figure. 1A)\). A greater proportion of brainstem (0.50) and LMCA (0.43) stroke patients had pulmonary edema compared to both the TIA (0.02) and RMCA stroke (0.24) groups.

Of the potential predictors for presence of pulmonary edema after large vessel ischemic stroke, only patient age \(\geq 57\) years, patient history of atrial fibrillation, patient history of heart failure, stroke location and elevated serum troponin were predictive (Table 2). The multivariate logistic regression model for presence of pulmonary edema explained between 36.7% and 53.5% of the variance in development of pulmonary edema, correctly classifying 81.4% of cases compared to baseline prediction rate of 73.5%, and fit the observed data well \((H-L \chi^2 (8) = 5.50, p=0.70)\) without evidence of intercorrelations among the independent variables. As shown in Table 3, having a LMCA stroke \((adjusted OR 7.64, 95\% CI 2.17-42.78)\) and patient history of coronary artery disease \((8.44, 2.04-34.93)\) were predictive of the presence of wall motion abnormalities on echocardiogram during admission.

**Echocardiography**

Echocardiograms were performed on 83 TIA, 35 RMCA, 31 LMCA and 14 brainstem stroke patients. There was no difference in proportion of patients with an ejection fraction \(\leq 35\% \) \((\chi^2 (3, N=167) = 3.93, p=0.27)\). Similarly, there was no difference in proportion of patients with new diagnosis of heart failure or decreased ejection fraction from baseline across groups \((\chi^2 (3, N=167) = 5.15, p=0.16)\). However, the proportion of patients with cardiac wall motion abnormalities on echocardiogram by cardiologist interpretation varied across groups \((\chi^2 (3, N=163) = 9.04, p=0.03)\) with a greater proportion of patients with RMCA stroke (0.34) than TIA (0.13) and brainstem stroke (0.07). There was no difference in proportions between the RMCA and LMCA (0.26) stroke groups.

The multivariate model for echocardiographic wall motion abnormalities explained between 31.4% and 45.8% of the variance in having cardiac wall motion abnormalities on echocardiogram, correctly classifying 83.3% of cases, compared to baseline prediction rate of 73.5%, and fit the observed data well \((H-L \chi^2 (8) = 9.20, p=0.33)\) without evidence of intercorrelations among the independent variables. Stroke location made no significant contribution to the model. Only patient history of heart failure \((adjusted OR 9.63, 95\% CI 2.17-42.78)\) and patient history of coronary artery disease \((8.44, 2.04-34.93)\) were predictive of the presence of wall motion abnormalities on echocardiogram during admission.

**Serum troponin**

Serum troponin levels were measured for 65 TIA control patients, 27 RMCA, 28 LMCA and 12 brainstem stroke patients and varied significantly across groups \((\chi^2 (3, N=210) = 20.43, p=0.0001)\). A smaller proportion of TIA patients (0.05) had elevated serum troponin levels than RMCA (0.41), LMCA (0.32) and brainstem (0.33) stroke patients.

The multivariate logistic regression model for presence of elevated serum troponin explained between 26.8% and 40.8% of the variance in having an elevated serum troponin, correctly classifying 84.3% of cases compared to baseline prediction rate of 77.5%, while fitting the data well \((H-L \chi^2 (8) = 4.71, p=0.79)\)

Table 1: Patient Characteristics. Means (SD) are presented for the continuous variable "age", and N(%) presented for all other categorical variables. Group differences for continuous variables were tested by one-way analysis of variance with Bonferroni’s adjustment for multiple comparisons, with p-value presented. The \(\chi^2\) test for independence was used to examine group differences for categorical variables with p-value presented.

<table>
<thead>
<tr>
<th></th>
<th>TIA (N=113)</th>
<th>RMCA (N=38)</th>
<th>LMCA (N=37)</th>
<th>Brainstem (N=22)</th>
<th>Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63 (23)</td>
<td>71 (24)</td>
<td>65 (33)</td>
<td>65 (12)</td>
<td>p=0.87</td>
</tr>
<tr>
<td>Female Sex</td>
<td>70 (62%)</td>
<td>21 (55%)</td>
<td>15 (41%)</td>
<td>10 (46%)</td>
<td>p=0.11</td>
</tr>
<tr>
<td>African American</td>
<td>57 (50%)</td>
<td>18 (47%)</td>
<td>16 (43%)</td>
<td>13 (59%)</td>
<td>p=0.68</td>
</tr>
<tr>
<td>History of Stroke or TIA</td>
<td>46 (41%)</td>
<td>12 (32%)</td>
<td>9 (25%)</td>
<td>7 (32%)</td>
<td>p=0.34</td>
</tr>
<tr>
<td>History Atrial Fibrillation</td>
<td>6 (5%)</td>
<td>10 (27%)</td>
<td>7 (19%)</td>
<td>2 (9%)</td>
<td>p=0.002</td>
</tr>
<tr>
<td>History of Heart Failure</td>
<td>8 (7%)</td>
<td>9 (24%)</td>
<td>8 (22%)</td>
<td>2 (9%)</td>
<td>p=0.01</td>
</tr>
<tr>
<td>History of Diabetes</td>
<td>30 (27%)</td>
<td>8 (22%)</td>
<td>9 (25%)</td>
<td>4 (16%)</td>
<td>p=0.22</td>
</tr>
<tr>
<td>History of Hypertension</td>
<td>84 (74%)</td>
<td>28 (76%)</td>
<td>26 (70%)</td>
<td>20 (91%)</td>
<td>p=0.33</td>
</tr>
<tr>
<td>History of Smoking</td>
<td>47 (42%)</td>
<td>18 (47%)</td>
<td>15 (41%)</td>
<td>11 (50%)</td>
<td>p=0.82</td>
</tr>
<tr>
<td>History of Hypercholesterolemia</td>
<td>47 (42%)</td>
<td>13 (35%)</td>
<td>11 (31%)</td>
<td>12 (55%)</td>
<td>p=0.29</td>
</tr>
</tbody>
</table>
without evidence of intercorrelations among the independent variables. Only having a RMCA stroke (adjusted OR 10.51, 95% CI 1.71-64.82) was predictive of having an elevated serum troponin level.

**Electrocardiography**

Electrocardiograms were performed on 106 TIA control, 37 RMCA, 36 LMCA and 22 brainstem stroke patients. The proportion of patients with prolonged QTc-intervals (>460ms) was different across groups (χ² (3, N=201) =14.92, p=0.002), with the proportion within both the RMCA (0.43) and LMCA (0.50) stroke groups being greater than for the TIA (0.20) and brainstem stroke (0.32) groups. The proportion of patients with prolonged PR-intervals (>200ms; χ² (3, N=178) =7.62, p=0.06), arrhythmia (χ² (3, N=201) =6.46, p=0.09), abnormal intraventricular conduction (χ² (3, N=201) =2.58, p=0.46), or any ST-segment abnormality (χ² (3, N=201) =0.91, p=0.62) did not vary across groups.

The multivariate logistic regression model for presence of a prolonged QTc-interval on admission EKG explained between 26.3% and 36.0% of the variance in having a prolonged QTc-interval, correctly classifying 73.5% of cases compared to baseline prediction rate of 63.7%, while fitting the data well (H-L χ² (8) =8.09,p=0.43) without evidence of intercorrelations among
Central Probasco et al. (2014)

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the independent variables. Only having a LMCA stroke (adjusted OR 4.55, 95% CI 10.77-19.24) was predictive of having QTc-interval prolongation.

Myocardial dysfunction

The proportion of patients with either wall motion abnormalities on echocardiogram, elevated serum troponin, arrhythmia on admission EKG and/or prolonged QTc-interval on admission EKG varied across groups ($\chi^2 (3, N=210) =16.87, p=0.001$). Both RMCA (0.68) and LMCA (0.60) stroke groups had proportions greater than brainstem stroke (0.55) and TIA (0.35) groups (Figure 1B).

DISCUSSION

In a limited retrospective case control study of patients treated at a single tertiary medical center, large vessel ischemic stroke of the midbrain, pons, and/or medulla was associated with the development of pulmonary edema independent of evidence of cardiac abnormalities typically associated with myocardial stunning. In contrast, both large vessel RMCA and LMCA strokes with involvement of respective insular cortex were associated with pulmonary edema as well as cardiac abnormalities associated with myocardial stunning [5]. This suggests separate brainstem pathophysiological mechanisms for pulmonary edema with effects on the lungs but not the heart.

Neurogenic pulmonary edema and cardiac derangements, including stunned myocardium, have long been associated with increased mortality in a variety of neurological diseases, from seizures and trauma to hemorrhagic and ischemic stroke [9,17]. Catecholamine surge in the setting of injury to the diencephalon and brainstem is thought to cause activation of both α- and β-adrenergic receptors within both the pulmonary venous bed and myocardium, and neurogenic pulmonary edema independent of myocardial dysfunction has been felt to be a relatively rare phenomenon [9,10]. Specifically, sympathetic activation has been suggested to play a primary role in precipitating raised hydrostatic pressure and elevated vascular permeability in the pulmonary venous bed, similar to that seen in acute respiratory distress syndrome (ARDS) [11,18-21]. Here we present findings which suggest that in ischemic stroke of the brainstem, pulmonary edema can occur in the absence of cardiac derangement and stunned myocardium.

The relationship of stroke location (i.e. whether of the anterior or posterior circulation, laterality) to the development of cardiac derangements and neurogenic pulmonary edema following stroke is an open question. Cortical involvement in the development of cardiac derangements (e.g. dysrhythmia, QTc prolongation, heart failure) following ischemic stroke has been proposed to rely on connectivity of cortical regions, such as the medial prefrontal cortex and insular cortex, with the hypothalamus, midbrain, pons and medulla [22]. The laterality of infarction, whether right hemispheric or left, has been of unclear significance to the development of cardiac derangements and sudden death [23-25]. Similarly, direct injury to the hypothalamus, nucleus tractus solitarius and area postrema and their respective sympathetic projections to the hypothalamus and spinal cord have been implicated in the generation of isolated neurogenic pulmonary edema [9]. In animal model experiments, severe hypertension and neurogenic pulmonary edema have been induced by lesions to the hypothalamus as well as by irritation of the tractus solitarius nuclei of the medulla while increased cardiac output, peripheral vascular resistance and hypertension have been induced by unilateral stimulation of the area postrema of the medulla [9,26,27]. In animal models using phenolamine, an alpha-adrenergic antagonist active at the postganglionic adrenergic receptors, pulmonary edema has been prevented [26,27]. Hexamethonium, a preganglionic nicotinic acetylcholine receptors blocker caused reduction of serum catecholamine levels, reversal of hypertension, preservation of cardiac function, and prevention of hemorrhagic pulmonary

Figure 1 Cardiopulmonary Response by Ischemic Stroke Location. A) Proportion of patients with pulmonary edema varied across stroke groups and was greatest for patients with large vessel brainstem stroke. B) Myocardial dysfunction was defined as a composite outcome of wall motion abnormalities on echocardiogram, elevated serum troponin, arrhythmia on admission EKG, and/or QTc-interval prolongation on admission EKG. Myocardial dysfunction also varied in proportion across stroke groups, and was greatest among patients with large vessel left middle cerebral artery or right cerebral artery strokes involving the insula relative to control and large vessel brainstem stroke patients. * designates p<0.05 and *** designates p<0.001 by Fisher’s exact test.
edema after pharmacological ablation of the nucleus tractus solitarius [28].

There are isolated case reports of treatment responsive neurogenic pulmonary edema treated with phenolamine to interrupt cyclical hemodynamic instability and hypoxic respiratory failure. This has been reported in the setting of progressively declining urine catecholamine levels [29]. Fulminant neurogenic pulmonary edema has also been treated with prone positioning in ventilated patients [11].

These experimental and clinical observations suggest cardiopulmonary compromise in the setting of central nervous system injury. This study suggests neurogenic pulmonary edema in ischemic stroke can occur in the setting of large vessel infarction of the brainstem. This occurs independently of concomitant cardiac involvement as indicated by elevated serum troponin levels, EKG changes, and altered wall motion on echocardiography. This pattern of pulmonary edema independent of cardiac involvement associated with large vessel brainstem infarcts was markedly different from patterns observed in large vessel cortical strokes involving the RMCA and LMCA which were also associated with objective signs of stunned myocardium.

This study is limited by its retrospective case-control design of data from a single tertiary facility with inherent potential for selection and recall bias including incomplete clinical data available for review. This also includes the effect of lead-time bias for the onset of pulmonary edema and variability in treatment across cases [9,30] Ischemic stroke size may have varied between groups and was not controlled for in this study. The large confidence intervals for multivariate analyses likely reflect the small sample size of this study, warranting larger, prospective study. Prospective multi-center studies of the pulmonary and cardiac derangements associated with ischemic stroke would help to clarify the temporal relationship of infarction with cardiopulmonary derangements.

CONCLUSION

In patients with large vessel brainstem infarction, unlike in patients with large vessel RMCA and LMCA strokes involving the insula, pulmonary edema can occur independent of myocardial stunning as analyzed by separate and composite cardiac endpoints including cardiac dysfunction, elevations of troponin and abnormalities of electrical conduction. This suggests that neurogenic pulmonary edema can be caused by ischemia of brainstem structures independent of cardiac dysfunction. Confirmation of these findings in a prospective analysis assessing the region of cerebrovascular involvement as well as brainstem structural involvement and the risk of neurogenic and cardiogenic pulmonary edema are required.

ACKNOWLEDGEMENT

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CONFLICTS OF INTEREST

Dr. Probasco, Dr. Chang, and Dr. Victor have neither conflicts of interest nor disclosures to report. Dr. Nyquist reports no conflicts of interest and discloses support through grant RO1NS062059-01A1 from the National Institute of Neurological Disorders and Stroke (National Institutes of Health, Rockville, Maryland).

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Cite this article

The most elegant and useful solutions are simple. But oversimplification of a complicated topic is also problematic. Prognostication following cardiac arrest has become complex, requiring: a detailed cranial nerve examination, EEG, SSEPs to evaluate the N20 response, and expensive laboratory testing (e.g., neuron specific enolase). Over time, this has led to a more accurate, but less universally applicable assessment. Albaeni and colleagues propose a novel, three item score that is simple, fast, reproducible, and inexpensive, with a surprising degree of accuracy. Conversely, historically the prognosis and recovery of aphasia has been oversimplified into a single treatment algorithm, overlooking the subtleties that differentiate one syndrome from another. Tippett and colleagues highlight the heterogeneity of language disorders. The extent and precise location of pathway disruption may have significant repercussions on both choice of therapy and response.
Predicting Survival with Good Neurological Outcome Within 24 Hours Following Out of Hospital Cardiac Arrest: The Application and Validation of a Novel Clinical Score

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3Division of Cardiology, Johns Hopkins Bayview Medical Center, USA

Abstract

Background: Despite 50 years of research, prognostication post cardiac arrest traditionally occurs at 72 hours. We tested the accuracy of a novel bedside score within 24 hours of hospital admission, in predicting neurologically intact survival.

Methods: We studied 192 adults following non-traumatic out-of-hospital cardiac arrest. In a 50% random modeling sample, a model for survival to discharge with good neurological outcome was developed using univariate analysis and stepwise multivariate logistic regression for predictor selection. The diagnostic efficiency of this modeled score was assessed in the remaining 50% sample using receiver operating characteristic (ROC) analysis.

Results: In this study, 20% of patients survived to discharge with good neurological outcome. The final logistic regression model in the modeling sample retained three predictors: initial rhythm Ventricular Fibrillation, Return of Spontaneous Circulation ≤ 20 minutes from collapse, and Brainstem Reflex Score ≥ 3 within 24 hours. These variables were used to develop a three-point Out of Hospital Cardiac Arrest score. The area under the (ROC) curve was 0.84 [95% CI, 0.75-0.93] in the modeling sample and 0.92 [95% CI, 0.87-0.98] in the validation sample. A score ≥ 2 predicted good neurological outcome with a sensitivity of 79%, a specificity of 92%, and a negative predictive value of 93%. A score ≥1 had a sensitivity of 100% and a negative predictive value of 100%; however, the specificity was only 55%.

Conclusion: This study demonstrates that a score based on clinical and easily accessible variables within 24 hours can predict neurologically intact survival following cardiac arrest.

INTRODUCTION

Despite standardized care guidelines for cardiac arrest patients that are uniform in many countries, outcomes are varied but remain generally poor [1,2]. Anoxic brain injury continues to be the major cause of death in this patient population. One of the most important tasks for health care providers is to correctly identify those patients most likely to survive to hospital discharge so that precious medical resources can be appropriately allocated.

Efforts have been devoted in the last 50 years to improve survival following cardiopulmonary resuscitation (CPR) [2−4], with one of the most important interventions being therapeutic hypothermia [5,6]. Clinical trials have identified factors that are
associated with improved survival post arrest, and have put forward predictive tools for such patients [7]. However, many of these predictive tools were developed in the 80s and 90s, prior to the advent of therapies like hypothermia that emerged in 2002 and require heavy sedation and the use of paralytics [5]. No studies have commented on how such sedation affects CNS recovery. Clinicians continue to rely on predictive tools that were developed in the 80s, while the relevance and applicability of such data to care in 2014 is unclear. Although a 2012 study has reported on a complex predictive score of 11 items, for patients with in-hospital cardiac arrest [8], the relevance of this predictive index to the broad more common entity of out of hospital arrest is unclear, due to the obvious heterogeneity of the two populations (i.e. inpatient Vs. outpatient cardiac arrest).

We chose to develop and study a simple clinical tool that applies primarily to patients surviving out of hospital arrest, is not technology driven, and possesses the ease of clinical application in all hospitals regardless of resource availability. In addition, we sought a tool that would not only possess incremental accuracy in predicting survival but also survival with good neurological outcome.

METHODS

Study design and population

Following Institutional Review Board (IRB) approval, we retrospectively studied 210 patients with non-traumatic out-of-hospital cardiac arrest who survived to hospital admission at a teaching university hospital between 2004 and 2010. All patients were older than 18 years of age. Resuscitation was delivered by emergency medical service (EMS) personnel and the emergency department staff according to the American Heart Association (AHA) guidelines as temporally relevant [2,9]. Data were collected using Utstein guidelines [10,11]. Cardiac arrest was defined as the absence of a palpable central pulse, apnea, and unresponsiveness. Resuscitation was defined as the act of attempting to maintain or restore life by establishing or maintaining airway, breathing and circulation through CPR, defibrillation and other related emergency care techniques [10,11]. Return of spontaneous circulation (ROSC) was defined as a period of 30 seconds or more of restored spontaneous circulation [10,11]. Down time (time from collapse to CPR), time from CPR to return of spontaneous circulation (ROSC), and time from collapse to ROSC were collected from EMS and emergency staff documents. In case of unwitnessed arrest, the time of first detection for cardiac arrest was used as a substitute for the time of collapse. Neurological outcome at discharge was assessed according to Glasgow-Pittsburgh Cerebral Performance Categories scale (CPC) : CPC 1 is conscious and normal; CPC 2 conscious with moderate cerebral disability; CPC 3 conscious with severe cerebral disability; CPC 4 coma or vegetative state; and CPC 5 death [11]. Patients with CPC 1 or 2 were considered to have a good neurologic outcome while those with CPC 3, 4 or 5 were considered to have a bad neurologic outcome.

Regional EMS Service

The study hospital is located in Maryland, and serves a mixed urban community where EMS has a 2-tiered response with first responders being AED equipped. The hospital serves a population of more than one million, of which 71% are Caucasian.

Usual ICU Care

The decision to initiate therapeutic hypothermia was made by an intensive care unit attending based on institutional guidelines. All patients treated with hypothermia received a standardized protocol of sedation with Fentanyl/Midazolam, and paralytics (Vecuronium). All therapies were continued for 24 hours following which passive rewarming occurred. Paralytics were then stopped and the use of sedation was only for patient comfort per Joint Commission on Accreditation of Healthcare Organizations (JCAHO) guidelines [12]. For all other post arrest patients (i.e. those not receiving hypothermia), sedation was based on clinical needs and was primarily for patient comfort and was determined by the Richmond Agitation-Sedation Scale (RAAS) [13,14].

Routine ICU care included a four hourly neurological assessment of the patient that involves assessment of Glasgow Coma Scale (GCS), pupillary reflexes, corneal reflexes gag/cough reflexes, oculocephalic reflexes and spontaneous breathing. Routine care also included stopping all sedation each morning to perform accurate neurologic assessments and spontaneous breathing trials (sedation holiday). Neurological assessments were usually performed by the nurses but also repeated separately by the resident physicians, the ICU attending physician and often the consulting neurologist. In case of discrepancy between observers, the report of the attending/neurologist was selected to reflect the status of the patient.

Brainstem Reflex Score (BRS)

The brainstem reflex score (BRS) was clinically reported in 2006 and was derived from five brainstem reflexes (1-Pupillary reflex, 2-Corneal reflex, 3-Cough/Gag reflex, 4-Oculocephalic reflex (Doll’s eye), 5-Spontaneous breathing). Each reflex was given equal impact and assigned one point giving BRS a range from 0 (worst) to 5 (best) [15].

Timing of neurological score assessment

Sequential BRS scores were recorded for all patients during 24 hours and the highest score for each patient, while off sedation, was used in the study whether therapeutic hypothermia was applied or not. For patients undergoing hypothermia therapy, the optimal 24-hour BRS score was primarily the BRS score prior to initiation of paralytics and hypothermia.

Study variables and model development

The goal was to develop a score that predicts survival with good neurologic outcome after out-of-hospital cardiac arrest, using variables accepted to be associated with improved survival. Many studies have confirmed that an initial rhythm of VT/VF, bystander CPR and duration to ROSC were associated with improved outcomes [16–21]. Hence these and other variables were tested in univariate analysis including: initial rhythm VT/VF [1, 16–18], return of spontaneous circulation (ROSC) less than or equal to 20 minutes from collapse [16,19], the presence of bystander CPR [16,20,21], Brainstem Reflex Score (BRS) within 24 hours post arrest more or equal to 3 [15,22], the use...
of therapeutic hypothermia [5,6], down time less or equal to 5 minutes [23,24], age less than 75 years [25,26], the use of more than three doses of epinephrine during CPR [27], witnessed arrest [1], location of arrest [28], and gender [29].

Patient group allocation

Of 210 eligible patients, 18 were excluded for missing data. The remaining 192 patients were randomly divided into two samples: a modeling sample of 96 patients and a validation sample of 96 patients.

Data analysis

All variables used were categorical and continuous variables were dichotomized. We tabulated descriptive statistics for both the modeling and validation samples.

In the modeling sample, we worked to generate a predictive score. Univariate analyses were performed on all eleven variables of interest to explore association with survival to discharge with good neurological outcome (cerebral performance category of 1 or 2) using Chi square test. Variables that had a statistically significant association (p<0.05) with neurologically intact survival in univariate analyses were then included through a forward stepwise selection in a multivariable logistic regression model.

Beta-coefficients of multivariate logistic regression were used to inform the building of a simplified prediction score. Variables were given an equal weight of one score point if the 95% confidence intervals of the beta coefficients overlapped. The diagnostic efficiency of the score was assessed using the receiver operating characteristic curve (ROC) analysis in the validation sample [30]. Hosmer-Lemeshow goodness of fit test was used to assess the fitness of the developed model, and sensitivity analysis was performed to evaluate model performance with regards to ACLS guidelines changes, therapeutic hypothermia, and care withdrawal. The sensitivity, specificity; positive and negative predictive values of the score at different thresholds were assessed in the validation sample.

RESULTS

Patient demographics

During the study period, 210 consecutive patients were admitted to the ICU with OHCA and 192 were analyzed after meeting inclusion criteria. The modeling and validation samples were comparable in terms of major comorbidities (Table 1). The mean age was 64 years (SD±15), 52% were male, 72% Caucasian, and 27% African American. Coronary artery disease was present in 41% of patients and congestive heart failure in 35%.

Cardiac arrest characteristics are shown in Table 2. The initial rhythm was Ventricular Fibrillation or Tachycardia in 42 patients (22%); 46 patients (24%) survived to hospital discharge, of those 38/46 (83%) survived to discharge with good neurological outcome; ROSC occurred within 20 minutes from collapse in 76 patients (39 %). Brainstem reflex score was ≥3 within 24 hours from admission in 44 patients (23%), and therapeutic hypothermia was used in 88 patients (46 %). Out of these 88 patients, 24 patients had VF/VT and 64 had PEA/Asystole as their initial arrest rhythm.

Univariate and multivariate analyses

Eleven variables were tested in univariate analysis to generate the prediction equation. Five variables emerged as being predictive of survival with good neurologic outcome; 4 of which were associated with improved likelihood of neurologically intact survival, (initial rhythm of VF/VT, ROSC≤20 minutes from arrest, BRS≥3 within 24 hours of arrest, and down time ≤ 5 minutes) while the use of 3 or more doses of epinephrine during CPR worsened outcome (Table 3). The five variables were
Table 2: Cardiac Arrest Characteristics in the Development and Validation Samples.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients N=192</th>
<th>Development Sample N=96</th>
<th>Validation Sample N=96</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witnessed arrest, n (%)</td>
<td>139 (72)</td>
<td>65 (68)</td>
<td>74 (77)</td>
<td>0.14</td>
</tr>
<tr>
<td>Bystander CPR, n (%)</td>
<td>60 (31)</td>
<td>28 (29)</td>
<td>32 (33)</td>
<td>0.53</td>
</tr>
<tr>
<td>Initial Rhythm VF/VT, n (%)</td>
<td>42 (22)</td>
<td>20 (21)</td>
<td>22 (23)</td>
<td>0.72</td>
</tr>
<tr>
<td>ROSC ≤ 20 minutes, n (%)</td>
<td>76 (39)</td>
<td>41 (42)</td>
<td>35 (36)</td>
<td>0.37</td>
</tr>
<tr>
<td>Use of ≥3 doses of epinephrine, n (%)</td>
<td>106 (55)</td>
<td>51 (53)</td>
<td>55 (57)</td>
<td>0.56</td>
</tr>
<tr>
<td>Hypothermia therapy, n (%)</td>
<td>88 (46)</td>
<td>46 (48)</td>
<td>42 (44)</td>
<td>0.56</td>
</tr>
<tr>
<td>BRS at 24 hours ≥ 3, n (%)</td>
<td>44 (23)</td>
<td>19 (20)</td>
<td>25 (26)</td>
<td>0.30</td>
</tr>
<tr>
<td>Survival to Hospital discharge with good neurological outcome (CPC=1, 2), n (%)</td>
<td>38 (20)</td>
<td>19 (20)</td>
<td>19 (20)</td>
<td>1.00</td>
</tr>
<tr>
<td>Down time ≤ 5 minutes, n (%)</td>
<td>103 (54)</td>
<td>47 (49)</td>
<td>56 (58)</td>
<td>0.19</td>
</tr>
<tr>
<td>Arrest Location, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Private</td>
<td>126 (66)</td>
<td>63 (66)</td>
<td>63 (66)</td>
<td></td>
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<tr>
<td>Public</td>
<td>16 (8.3)</td>
<td>11 (11.4)</td>
<td>5 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>50 (26)</td>
<td>22 (23)</td>
<td>28 (29)</td>
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</table>

Table 3: Results of Univariate Analysis in the Development Sample.

<table>
<thead>
<tr>
<th>Study Variables</th>
<th>N</th>
<th>Survivors with Good Neurological Outcome (CPC 1 or 2), n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witnessed arrest</td>
<td></td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>Yes</td>
<td>65</td>
<td>16 (25)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>31</td>
<td>3 (10)</td>
<td></td>
</tr>
<tr>
<td>Bystander CPR</td>
<td></td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>Yes</td>
<td>28</td>
<td>5 (18)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>68</td>
<td>14 (21)</td>
<td></td>
</tr>
<tr>
<td>Initial rhythm VF/VT</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Yes</td>
<td>20</td>
<td>8 (40)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>76</td>
<td>11 (14)</td>
<td></td>
</tr>
<tr>
<td>ROSC ≤ 20 minutes</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>41</td>
<td>16 (39)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>55</td>
<td>3 (5)</td>
<td></td>
</tr>
<tr>
<td>Use of ≥3 doses of epinephrine</td>
<td></td>
<td></td>
<td>0.009</td>
</tr>
<tr>
<td>Yes</td>
<td>51</td>
<td>5 (10)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>45</td>
<td>14 (31)</td>
<td></td>
</tr>
<tr>
<td>Hypothermia therapy</td>
<td></td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>Yes</td>
<td>46</td>
<td>11 (24)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>50</td>
<td>8 (16)</td>
<td></td>
</tr>
<tr>
<td>BRS within 24 hours ≥ 3</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>19</td>
<td>9 (47)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>77</td>
<td>10 (13)</td>
<td></td>
</tr>
<tr>
<td>Down time ≤ 5 minutes</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Yes</td>
<td>47</td>
<td>14 (30)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>49</td>
<td>5 (10)</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Yes</td>
<td>30</td>
<td>3 (10)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>66</td>
<td>16 (25)</td>
<td></td>
</tr>
</tbody>
</table>

Gender
- Male: 60 (10 [17])
- Female: 36 (9 [25])

Arrest Location
- Private: 63 (9 [14])
- Public: 11 (2 [18])
- Other: 22 (8 [36])

Subsequently included through a forward stepwise selection in developing a multivariable logistic regression model.

Multivariate analysis identified three predictive variables (key variables) that retained statistically significant association with survival with good neurologic outcome (P<0.05) (initial rhythm VF/VT, ROSC≤20 minutes, BRS≥ 3 within 24 hours) (Table 4).

Prediction score and validation
Regression coefficients of the 3 key variables were used to develop a score that would predict the probability of survival with good neurological outcome. Each variable was given an equal weight as previously mentioned to generate a prediction score from 0 to 3 with the presence or absence of any combinations of these 3 key variables (Table 5). Of the patients who had only one favorable predictor (OHCA score=1), only 12% survived with good neurological outcome. The presence of any two favorable predictors (OHCA score=2) increased the probability to 64%, and the presence of all three favorable predictors (OHCA score=3) in any patient further increased the probability to 86%.

The area under the curve for the modeling sample was 0.84 [95% confidence interval (0.75-0.93)]. In the validation sample the area under the curve was 0.92 [95% confidence interval...
Table 4: Beta Coefficient and Odds Ratio of Multivariable Logistic Regression Model.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Beta Coefficient</th>
<th>95% Confidence Interval</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial rhythm VF/VT</td>
<td>1.65</td>
<td>0.28-3.02</td>
<td>5.21</td>
<td>1.32-20.53</td>
<td>0.018</td>
</tr>
<tr>
<td>ROSCs 20 minutes</td>
<td>2</td>
<td>0.61-3.40</td>
<td>7.45</td>
<td>1.84-30.18</td>
<td>0.005</td>
</tr>
<tr>
<td>BRS ≥ 3 within 24 hours</td>
<td>1.63</td>
<td>0.27-2.99</td>
<td>5.11</td>
<td>1.31-19.91</td>
<td>0.019</td>
</tr>
</tbody>
</table>


Table 5: OHCA Score at Different Thresholds (95% CI).

<table>
<thead>
<tr>
<th>OHCA Score</th>
<th>Probability of Survival</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
<td>100%</td>
<td>0%</td>
<td>22% (10-34)</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>12%</td>
<td>100%</td>
<td>55% [48-62]</td>
<td>39% (28-50)</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>64%</td>
<td>79% [66-92]</td>
<td>92% [88-96]</td>
<td>72% [65-79]</td>
<td>93% [89-97]</td>
</tr>
<tr>
<td>3</td>
<td>86%</td>
<td>32% [17-47]</td>
<td>99% [98-100]</td>
<td>83% [77-89]</td>
<td>83% [77-89]</td>
</tr>
</tbody>
</table>

OHCA: out-of-hospital cardiac arrest, PPV: positive predictive value, NPV: negative predictive value.

(0.87-0.98). The P value for goodness of fit was 0.26, suggesting that the developed model reflected the outcome experienced in the validation sample (Supplement Table 6). Sensitivity analysis showed that our model was not affected by heterogeneity of therapeutic hypothermia, care withdrawal, or changes in ACLS guidelines.

**OHCA score sensitivity and specificity**

Survival probability (with good neurological outcome), sensitivity, specificity, positive predictive value (PPV), and negative predictive values (NPV) at different score points for the validation sample are shown in Table 5. An OHCA score ≥ 2 predicted survival with good neurological outcome with a sensitivity of 79% [95% CI, 66-92%], a specificity of 92% [95% CI, 88-96%], a positive predictive value of 72% [95% CI, 65-79%], and a negative predictive value of 93% [95% CI, 89-97%]. Alternatively, OHCA score ≥ 1 predicted good neurological outcome with a sensitivity of 100% and a specificity of 55% [95% CI, 48-62%], a positive predictive value of 39% [95% CI, 28-50%] and a 100% negative predictive value.

**DISCUSSION**

This study shows that a clinically derived simple prediction tool comprised of 3 readily available variables (initial rhythm VF/VT, ROSC ≤20 minutes, and BRS ≥ 3 within 24 hours) can predict neurologically intact survival in out of hospital cardiac arrest patients.

For many acute or chronic disease entities where outcomes are varied, the field of medicine has developed and validated scoring systems to help identify patients more likely to have a good outcome or identify those at high risk for complications (e.g. atrial fibrillation, pancreatitis) [31,32]. In all such instances the purpose has been to better treat patients and also to better allocate precious health care resources. No score is absolute, but serves to guide clinical decision making.

The fundamental goal of resuscitation is to maintain vital organ perfusion with the quintessential goal being good neurological recovery. Despite great efforts and advances in optimizing the management of cardiac arrest victims, post cardiac arrest brain injury is common and often the major contributor to death [33]. Our study demonstrates a survival to discharge of 24% following admission post arrest. Of those discharged alive, 83% had a good neurological outcome (CPC 1, 2). These survival rates are directionally similar to those reported by McNally et al. who reported that of those discharged post arrest 72% had a good neurological outcome [1].

**Predictors of neurological outcome**

Efforts at prognosticating neurological recovery in cardiac arrest patients can be traced to the 1960s when the EEG was first used to predict outcome and was found to be a poor marker of recovery [34]. Several investigators have commented and reported on the poor outcome of patients who have absent pupillary light reflexes [7,22,35,36]. However, no single sign predicted a favorable outcome. Motor reflexes have also been invoked for predicting neurological survival. Although the presence of myoclonus on day 1 has been shown to be a poor prognosticator of outcome, the false positive rate can be as high as 8.8% [36]. Thus, clinicians are reticent to use this finding alone to prognosticate outcome given the likelihood that if one is using this criterion alone, one may erroneously miss a survivor nearly 10% of the time [36]. This has been the major criticism of relying on motor reflexes for prognostication.

In 1985 Levy et al. developed a clinical prediction tool to identify patients most likely to recover following cardiac arrest. Although many other tools and algorithms have been evaluated, the Levy paper remains the clinical corner stone for guiding clinical decision making in such patients [7]. The Levy study examined neurological recovery on admission, day one, day three, one and two weeks after arrest. It relied on the presence or absence of brainstem reflexes to predict survival. The data from this study showed that only two out of 57 patients in whom eye-closed coma lasts for three days regained independent function. Another study by Bell and Hodgson in 1974 reported the rarity of full recovery after coma lasting three days [37]. Thus evaluating neurological status at day three emerged as the recommended time for recovery assessment. Levy reported that if pupillary light reflexes were absent, no patient survived while those with
preserved pupillary light reflexes and spontaneous movements on day one recovered.

Multiple studies have evaluated the role of somatosensory evoked potentials in predicting outcome after cardiac arrest, and found that bilateral absence of N20 component after median nerve stimulation, can reliably predict death due to its low false positive rates. However, the usefulness of the presence of N20 response appeared to be limited due to low sensitivity and low positive predictive value [36,38,39].

Years later and after the advent of therapeutic hypothermia, these observations were broadly revalidated; however, the issue of how hypothermia and its attendant sedation affect brainstem reflexes was poorly addressed. In 2011, Bouwes et al. restudied the reliability of the neurological exam, median nerve sensory-evoked potentials (SEP), and neuron-specific enolase (NSE) in predicting outcome post hypothermia therapy. The study demonstrated that the absence of pupillary light reflex, corneal reflex at 72 hours or the bilateral absence of cortical N20 responses of the median nerve could reliably predict poor outcome [40]. However; Zandbergen et al. questioned the usefulness of SSEP as a diagnostic or predictive tool since it appeared to be subject to noise interference and inter observer variability [41]. In addition, our score is based on easily accessible variables that do not depend on technology that requires significant training for interpretation and performance and might not be available in all institutions.

Neurological assessment scores: limitations and shortfalls

Using the parameters discussed above in addition to key demographics, others have developed scores to predict survival after cardiac arrest. A prospective study by Geocadin et al. reported that survivors had a higher initial median Brainstem Reflex Score (BRS= 4) than those who died (BRS=2.5) [15]. The absence of light or corneal reflexes has also been associated with a poor prognosis [7,22].

A well-calibrated score by Adrie et al. that predicted survival with good neurological outcome was developed on prospectively collected data and was validated in multiple institutions. However, it was developed before the era of hypothermia and validated on populations after the introduction of hypothermia [42]. Another score by Okada et al. utilized five readily available variables on admission to predict survival with good neurological outcome. It was developed only on patients who were treated with hypothermia; thus, its usefulness in other post arrest patients is unknown [43]. Using the Get-with-the-Guilene-Resuscitation registry data base, a large prospective registry of in-hospital cardiac arrest, Chan et al. developed a complex score of eleven variables to predict survival with good neurological outcome after in-hospital cardiac arrest. Although the score was detailed, well calibrated, and developed on a large sample, it would be clinically unwieldy to use due to its inherent complexity. Such a score would be difficult to remember or implement in a busy ICU [8].

As a result, there was a need for a simple clinical score that is validated in cardiac arrest patients with and without therapeutic hypothermia, is capable of predicting neurologically intact survival with promising accuracy as early as the first 24 hours after cardiac arrest, and is easy to use and implement in a busy environment such as the intensive care unit.

Effect of sedation

Obviously when a paralytic is used, motor responses cannot be followed. Sedation on the other hand, to levels that are commonly used for patient comfort, should not impact brain stem reflexes deleteriously. However, it has been shown that obesity, and hypothermia delay the clearance of commonly used sedatives [44,45]; hence, the duration of effect may change but the magnitude of the effect should not be affected if sedation is appropriately titrated to a RASS score of negative 1 or 2 [13,14]. Several sedatives and drugs used nowadays sequester in fat and may thereby contribute to delayed awakening calling into question the “three day rule” as suggested by Levy et al. Also, hypothermia has been shown to decrease the metabolism of Fentanyl and Midazolam, commonly used for sedation post arrest and thus likely to affect the timing of neurological awakening [44,45]. This becomes extremely relevant since such drugs are almost universally used in post arrest patients. Therefore, the applicability of the Levy observations to clinical practice in 2014 is unclear.

Since a component of our score is assessment of brainstem reflexes, our study circumvents the limitations imposed by therapeutic hypothermia and sedation by calculating the best BRS score during the “sedation holiday” in the first 24 hours and before initiation of paralytics and therapeutic hypothermia in patients receiving this intervention.

Clinical relevance and implications

The goal of this study was to develop a score that was incremental, simple, easy to use in daily clinical practice, and able to accurately estimate survival with good neurological outcome (CPC 1,2) post arrest. The score consisted of three easily accessible variables (ROSC≤20 minutes, BRS≥3 within 24 hours of arrest, initial rhythm VF/VT) and was found to be incremental in its association with neurologically intact survival. If the score was ≥2, the sensitivity and specificity were high enough to predict survival with good neurological outcome. Additionally a score <2 had a high negative predictive value (93-100%) with an extremely low likelihood of survival. No patient scored zero and survived to hospital discharge with good outcome in the validation sample, and only one did in the development sample.

The incremental nature of our score suggests that if all 3 variables are present during the first 24 hours after arrest, continued intensive care, while factoring in other clinical variables, would be more likely to be rewarded with a good probability of neurologically intact survival.

Study limitations

Several limitations of this study should be considered. First, this study reflects a single institution experience where the score was internally validated on a sample size that is robust for most resuscitation studies (210 patients with 46 survivors of whom 38 had good neurological outcomes). The original Levy study comprised 210 patients and the Adrie study 340 patients. Second, this score is not intended to recommend further treatment;
however, if validated in a large prospectively collected data it has the potential to be a useful tool in the hands of physicians to help guide aggressiveness of care and optimize the appropriate use of resources. Furthermore, prospective validation of such a score may help families in making decisions that are consistent with their values and goals of care. Third, withdrawal of care in patients with poor prognosis has the potential of introducing a bias to the outcome examined in this population; however, when the model was tested in patients who did not have withdrawal of care, all three variables forming the score continued to be significant predictors of neurologically intact survival. Also, when we further tested the difference between those variables’ beta coefficient, the difference was not significant (P value = 0.94) indicating that even in this subpopulation, all three variables can still be given an equal weight in building the final simple score from 0 to 3. Thus such bias did not have a significant effect on the predictive accuracy of the score. Fourth, despite the importance of SSEPs in predicting survival, this technique was not used in this study as our score relies on readily available clinical variables that can be measured at any institution without the need for sophisticated technology. Finally, the impact of percutaneous coronary intervention (PCI) on survival after out-of-hospital cardiac arrest was recently established in multiple studies [46,47]; however, it did not become a popular therapeutic tool until 2012 which is a time period beyond the analysis of this study and hence was not factored into the analytical design.

CONCLUSION

Physicians continue to struggle with correctly prognosticating survival post cardiac arrest. The field of resuscitation medicine continues to use 1985 data to guide such decisions despite many therapeutic advents that directly call into question the validity of these observations. Multiple scores in recent years were developed to address the issue of prognostication but all were complex scores that employed clinical, laboratory and procedural inputs. We have identified an easy to use incremental clinical score that has the potential to guide treatment and better triage resources. Further testing of this score in different databases is justified to establish validation in a larger cohort.

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Review Article

Aphasia: Current Concepts in Theory and Practice

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Abstract

Recent advances in neuroimaging contribute to new insights regarding brain-behavior relationships and expand understanding of the functional neuroanatomy of language. Modern concepts of the functional neuroanatomy of language invoke rich and complex models of language comprehension and expression, such as dual stream networks. Increasingly, aphasia is seen as a disruption of cognitive processes underlying language. Rehabilitation of aphasia incorporates evidence based and person-centered approaches. Novel techniques, such as methods of delivering cortical brain stimulation to modulate cortical excitability, such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation, are just beginning to be explored. In this review, we discuss the historical context of the foundations of neuroscientific approaches to language. We sample the emergent theoretical models of the neural substrates of language and cognitive processes underlying aphasia that contribute to more refined and nuanced concepts of language. Current concepts of aphasia rehabilitation are reviewed, including the promising role of cortical stimulation as an adjunct to behavioral therapy and changes in therapeutic approaches based on principles of neuroplasticity and evidence-based/person-centered practice to optimize functional outcomes.

ABBREVIATIONS

CNS: Central Nervous System; rTMS: Repetitive Transcranial Magnetic Stimulation; tDCS: Transcranial Direct Current Stimulation; ICF: International Classification of Functioning, Disability, and Health; WHO: World Health Organization; LPAA: Life Participation Approach to Aphasia

INTRODUCTION

Communication through language is central to the human experience. The essential role of linguistic interaction in daily function drives interpersonal connections key to health-related quality of life. Interest in the study of language, and its rehabilitation, is fueled by the considerable impact of aphasia on both public and personal health, and by societal costs. Recent estimates are that there are more than 795,000 strokes per year in the US [1]—the major source of aphasia incidence. Between 1997 and 2006, the number of individuals with aphasia grew by approximately 100,000 per year [2]. Aphasia is present in 21-38% of acute strokes and associates with higher mortality, morbidity, and healthcare resources consumed [3]. Costs for stroke-related healthcare exceeded $25 billion in 2007 [1]. On an individual level, reintegration into school, work, and family life may be unattainable given human dependence on the spoken word. Social isolation is a devastating and all too common consequence of aphasia [4].

Norman Geschwind wrote that “every behavior has an anatomy” [5]. Language is no exception. Though complex in its underpinnings, the study of the structural and physiological basis of aphasia has been a major focus of neurological investigation since the mid-nineteenth century. However, we are now witnessing a revolution in the understanding of language and its disorders. Recent advances in neuroimaging contribute to a combined understanding of the structural and functional correlates of language. In fact, in the morphometry and the dynamic functioning measured with neuroimaging have emerged highly refined models of the neurobiological organization of language. Extensive research has focused on the functional neuroanatomy of language, with current models modifying the neurological model of language and promoting a dorsal-ventral stream framework [6-9]. Similarly, advances in the study of treatment of aphasia have resulted in adaptation of evidence based and person-centered approaches to rehabilitation [10] as well as methods of delivering cortical brain stimulation to...
modulate cortical excitability, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) [11,12].

In this review, we discuss the historical context of the foundations of neuroscientific approaches to language. We sample the emergent theoretical models of the neural substrates of language and cognitive processes underlying aphasia that contribute to more refined and nuanced concepts of language. Current concepts of aphasia rehabilitation are reviewed, including the promising role of cortical stimulation as an adjunct to behavioral therapy and changes in therapeutic approaches based on principles of neuroplasticity and evidence-based/person-center approach to optimize functional outcomes.

HISTORICAL BACKGROUND

The study of aphasia and its associated lesions in the late nineteenth century by Dax [13], Broca [14,15], and Wernicke [16] led to many insights about the neural organization of the language functions. The most reliable finding was that individuals who had language impairments were later found to have damage to the left hemisphere at autopsy. Damage to the left posterior inferior frontal cortex, was often found in those whose spoken output was limited or poorly articulated [15]; damage to the more posterior regions in the left temporal lobe was found in those whose spoken output was well articulated but meaningless [17]. These early observations established that language functions are localized in the left cerebral hemisphere and provided the groundwork for Geschwind’s seminal work on aphasia classification and associated lesion sites. These classic aphasia classifications, such as Broca’s, Wernicke’s, global, conduction, anomic, and transcortical aphasias, are vascular syndromes consisting of frequently associated deficits that reflect damage or dysfunction of regions of neural tissue supplied by a particular artery [19]. The characteristics of the classic aphasias are reviewed in detail by Damasio [20], Goodglass [21], and Hills [19]. These syndromes are clinically useful in predicting areas of ischemia and patterns of recovery, and in selecting rehabilitation approaches [19,22,23].

Early accounts employed thoughtful correlations of site-of-lesion and manifested behavior. Thus, from the context of brain pathology, localization of normal function can be extrapolated [24]. It is important to note that individual variability in the shape of the brain as well as the patterns of sulci and gyri renders only approximate localization of function [25,26].

Beginning in the 1980’s, advances in neuroimaging, including PET, functional MRI, and magnetoencephalography, expanded understanding of the functional neuroanatomy of language by specifying the anatomical and functional correlates of central nervous system (CNS) stations that support overall language function. Safe, noninvasive imaging of the brain reveals that areas in both hemispheres of the brain are activated specifically during language tasks, although the left hemisphere shows more activation in the majority of neurologically normal adults [27-30], and that more distant areas of the cortex, such as inferior and anterior temporal cortex [31] and the basal ganglia and thalamus [32], are also activated during language tasks. In addition, there is increasing understanding of the complexity of language tasks, including underlying cognitive processes and representations that are needed to accomplish even basic tasks such as naming [33,34]. Recognition that focal neurodegenerative disease can cause primary progressive aphasia allows investigation of language deficits caused by cerebral atrophy of regions of the brain not typically damaged by stroke [35]. This approach to characterizing aphasia by disruption of specific cognitive processes is important for developing theories of how language is represented and processed [19]. Brain/language relationships are further elucidated by technologies which introduce temporary dysfunction or suppress overactive areas associated with CNS insult, such as inhibitory rTMS [36].

Contemporary paradigms of neural substrates of language

A principal concept of the functional neuroanatomy of language holds that the processing needed to interpret the complex and multidimensional information in language, and its context, requires an intricate division of bio-encoding labor. One compelling model characterizes a dual stream: a ventral stream for mapping sound onto meaning, and a dorsal stream for mapping sound onto motoric productions and articulation [6-9]. The brain computes a transform between thought and an acoustic signal transmitted across parallel, ascending pathways of the auditory brain stem and cortex [37] and executes parallel processing to synthesize input via interconnected neural networks [38]. Support for this complex neural circuitry is found in studies of the neocortex which show that there are vertically oriented columns of neurons perpendicular to the cortex [39].

A dual stream model of vision processing is well established. Studies of the primates’ visual cortex show that cells within a column respond similarly to an external stimulus [40]. In the original account, vision processing is divided into two streams: a ventral stream projecting to inferior temporal areas to process object identity (the “what” pathway) and a dorsal stream projecting to parietal areas to process object locations relative to the observer and other objects in the environment (the “where” pathway) [41]. Subsequently, the function of the dorsal stream is expanded to include integration of visual input and motor responses (the “how” stream) which facilitate reaching and grasping in visual space [42].

The dual stream model of afferent information processing is similarly applied to auditory processing in which the ventral stream processes “what” and the dorsal stream processes “where” [43], changes in the auditory signal over time [44], and auditory-motor integration in which a sequence of sounds are heard and then spoken, the latter much like that in the visual domain [4,45].

The dual stream model is extended to explain cortical organization of language. In this neuroanatomical model, proposed by Hickok, speech processing is defined as any task involving aurally presented speech; speech perception refers to any sub-lexical task; and speech recognition refers to the transformation of acoustic signals into a representation which accesses mental lexicon [7]. Speech perception involves auditory-responsive areas in the superior temporal gyrus bilaterally, left more so than right. The processing system then diverges into
two streams: a ventral stream which maps sound onto meaning, and a dorsal stream which maps sound onto articulatory-based representations to yield production. The ventral stream is thus a sound-meaning interface responsible for processing speech signals for comprehension. In the dorsal stream, acoustic speech signals are translated into articulatory representations, essential for speech development and production, involving auditory-motor integration. The dual streams are also thought to be bi-directional; the ventral stream mediates the relationship between sound and meaning for perception and production, and the dorsal system can also map motor speech representations onto auditory speech representations [46].

More recently, roles for the ventral and dorsal streams in forward prediction are proposed. The role of forward prediction in speech perception is obvious; perception is dramatically improved when one knows what to listen for as cued by awareness of speaker, time, place, circumstance, and myriad additional contextual factors. Forward prediction from the motor system (dorsal stream) on speech perception is less clear. For example, transcranial magnetic stimulation studies show that damage to the motor system does not result in deficits in speech perception as would be expected if motor prediction is critical. An alternative hypothesis is that ventral stream forward prediction enhances speech recognition [46].

The ventral stream projects ventro-laterally and involves cortex in the superior temporal sulcus and the posterior inferior temporal lobe. The dorsal stream projects dorso-posteriorly toward the parietal lobe and ultimately to frontal regions [6,7,45]. In contrast to prior models, speech processing is bilaterally organized, thus the ventral stream incorporates parallel processing, explaining why there are not substantial speech recognition deficits following unilateral temporal lobe damage [7]. The dorsal stream is strongly left dominant, accounting for speech production deficits that are seen with dorsal temporal and frontal lesions [47]. In addition, functional neuroimaging studies support bilateral organization of speech recognition as well as a neural circuit for auditory-motor interaction. For example, neurophysiologic recordings of normal subjects listening to speech stimuli uniformly show bilateral activation in the superior temporal gyrus [6]. Imaging studies show that the left superior posterior temporal region, located within the planum temporale, is activated during speaking, naming, and humming [7, 47].

A spatio-temporal language processing model is proposed to resolve theoretical inconsistencies in the dual stream approach [48]. For example, as stated earlier, one interpretation of the roles of the dual streams is that the ventral stream maps sound to meaning and the dorsal stream maps sound to articulation. Alternatively, the dorsal stream is thought to process complex syntax whereas the ventral stream is thought to process simple syntax [49].

These divergent proposals are unified in a spatio-temporal model based on the Extended Argument Dependency model which assumes a cascaded architecture of language processing [50]. In this model, parallel systems process linguistic information that is both dependent and independent of temporal aspects of linguistic data flow. Ventral and dorsal streams are asserted to be engaged in sentence comprehension, with time-independent processing associated with the ventral stream and time-dependent processing associated with the dorsal stream. The dorsal stream analyzes sequences of segments in time or space and integrates sensorimotor input to support production; the ventral stream extracts meaning independently of the temporal or special sequences of linguistic elements [51].

In addition, a novel dual lexicon framework, which builds on the dual stream model, is suggested to explain how and where words are stored in the brain. Two lexica are proposed to provide an interface between linguistic subunits. The ventral lexicon is an interface between phonetic and semantic representations. This area is not a store of semantic knowledge, but instead retains morphologically organized representations of words to link acoustic phonetic representations to semantic content. The dorsal lexicon is an interface between phonetic and articulatory representations and houses articulatory organized-word form representations, a concept not previously endorsed [52].

Cognitive processes underlying aphasia

Increasingly, aphasia is seen as a disruption of cognitive processes underlying language tasks, such as sentence comprehension and naming. Cognitive representations are distributed across regions of the brain and activation of these various areas is needed to evoke semantic representations. For example, the semantic representation of a horse includes features of how it moves (middle temporal visual area and middle superior temporal area), what it eats, and how it is used by humans [19]. Damage to specific areas of the brain may account for specific patterns of impairments, such as selective naming deficits. Examples include the inability of an individual with visual agnosia to name an item on visual confrontation, but demonstrate preserved naming in response to a verbal description, and the inability of an individual with optic aphasia to activate a semantic representation given a structural description despite full access to semantics given tactile cues.

Modality-independent lexical access is also proposed as a mechanism to explain anomia commonly seen in several aphasia subtypes. Individuals with anomia have intact semantic representations, but cannot access phonological and/or orthographic representations. Responses on convergent and divergent naming tasks can include both semantic and phonemic errors despite intact error awareness.

Treatment

Aphasia treatment is progressively more informed by advances in understanding of the neurobiology of recovery and learning. For example, tDCS is designed to facilitate synaptic plasticity [53]. rTMS can modify cortical excitability, increasing or decreasing activity in targeted areas of the cortex. Protocols employing rTMS improve naming in individuals with nonfluent aphasia. The mechanism proposed to explain this treatment effect is suppression of over-active right hemisphere homologues [54,55]. The promise of these methods relies on a full understanding of the anatomy of the neural networks underlying language and variables that influence potential timing and extent of structure-function reorganization.

The multi-dimensionality of cortical reorganization and
modifiability can be observed in the neuroplasticity producing clinical recovery observed in response to stimulation [56]. Plasticity studies reveal the functional importance of the “use it or lose it” principle and indicate that beneficial behavioral and neural changes can be effected through intense and repetitive practice [57]. Importantly, findings of recent investigations of aphasia therapy emphasize that intense treatment for short periods is more effective than a similar number of therapy sessions over longer periods [58]. The rationale for early intervention in aphasia is also based on these neuroplasticity principles such that therapy capitalizes on spontaneous recovery in the immediate post stroke period [59].

While prosthetic stimulation offers a potentially important adjunctive approach, behavioral therapy remains the mainstay for treatment of aphasia. Behavioral therapy is both restitutive and compensatory. Current practice standards dictate that therapy must be evidence-based and person-centered. Evidence-based practice refers to an approach in which current, high-quality research evidence is integrated with practitioner expertise and client preferences and values [60]. The hierarchy and generalizability of evidence are evaluated [61,62] and an individual’s life circumstances, preferences, coping mechanisms, and concomitant medical, sensory, behavioral, and psychological issues are considered when making treatment decisions. Because supportive, evidenced-based client-specific research can be difficult to identify, clinicians are advised to combine multiple, available studies of sufficiently good design, expert consensus, and clinical knowledge of anatomy and physiology to make reasonable judgments about the appropriateness and effectiveness of a specific treatment technique [63].

Principles of neuroplasticity support early and intense therapy, however, questions remain regarding specific intervention strategies given the variable nature of aphasia. Historically, clinicians base therapy largely on assessment data. Therapy tasks are developed to target specific domains, such as auditory comprehension at sentence level or word retrieval at a single word level. This approach follows a medical model which emphasizes impairment of function, and is therapist-, rather than patient/person-, centered [64]. This circumscribed approach suffers from multiple limitations. Clearly, increased ability to name pictured objects in a treatment task does not necessarily translate to a relevant outcome, such as improvement in functional communication [65,66]. In addition, in their consumer perspective, Dyke and Dyke [67] cite specific examples of the ways that impersonal approaches diminished the effectiveness of rehabilitation therapies, and how linking therapy “to the person that (General Dyke) was and is, rather than to a generic set of tools and techniques” (p. 150) maximizes outcome.

Application of principles governing brain organization and reorganization may contribute to the development of more meaningful therapy goals. For example, practice on a confrontation naming task may facilitate the ability to convey communicative intentions to listeners as a result of the adaptive property of the brain. Treatment goals may also be reframed based on the dual stream model of language organization. For example, in those with Broca’s aphasia, therapy may be directed at translating sound to motor speech productions to produce simple sentences as disruption of the dorsal stream would be expected; and in those with Wernicke’s aphasia, therapy may be directed at processing speech for comprehension or meaning in sentences as disruption of the ventral stream would be expected. Further investigation is warranted regarding how the segregation of language functions described by this model suggests particular approaches that promote “use” most effectively. One suggestion is that ventral stream could be accessed by instructing patients to process the meaning of a target word during a repetition task in the treatment of conduction aphasia [68].

Given the limitations of medical/clinician-centered models of therapy, a social model of therapy has emerged which encompasses the authentic involvement of users (patients), creation of engaging experiences, user control, and accountability [10]. Person-centered practice “involves valuing the individual needs and rights of patients, understanding patients’ illness and health care experiences, and embracing them within effective relationships which enable patients to participate in clinical reasoning” [69, p. 68]. This practice is consistent with the conceptual framework for contemporary models of health care of the International Classification of Functioning, Disability, and Health (ICF) of the World Health Organization (WHO) [70].

The ICF is structured around the broad components of body structures and functions, activities (related to tasks and actions by individuals) and participation (involvement in life situations), and additional information regarding personal and environmental factors. Language, cognition, voice, and swallowing are body functions, and interpersonal interactions reflect the activity/participation component of the ICF, relevant to speech-language pathology. Family support and availability of communication partners are examples of environmental factors; premorbid personalities, such as reticence versus extroversion, are factors germane to cognitive/communicative intervention. This framework encourages patient-centered care, focusing on development of goals which address individual needs and circumstances. Therapy is a collaborative process. Patients, families, and caregiver identify goals which are important to them. Clinicians conduct formal assessment, and then negotiation occurs between patients and therapists to define a treatment plan. This is in contrast to therapist-controlled approaches; a genuine patient-centered approach allows patients, their families, and caregivers to lead the goal setting process rather than the clinician [64].

A critical approach to monitoring treatment effect requires that clinicians document goals and outcomes for any relevant component (e.g., body structure/function, activity, participation). Outcomes of treatment can then be measured for the specific modality that was treated, and/or at the activity/participation level consistent with the ICF framework. For example, an activity level goal may be “demonstrating the ability to speak in sentences” and the participation level outcomes are “engaging in a parent-teacher conference” and “giving a professional oral presentation” [71]. The Quality of Communication Life Scale, which examines the impact of communication disorders on various aspects of quality of life, including relationships with others, communication interactions, and participation in activities, captures components of the ICF health outcomes [72].
A specific example of a patient-centered approach is the Life Participation Approach to Aphasia (LPAA) [73]. "The LLPA places the life concerns of those affected by aphasia at the center of all decision making...and empowers the consumer to select and participate in the recovery process and to collaborate on the design of interventions that aim for a more rapid return to active life" (p. 279). Specific tasks can also be adapted to conform to a patient-centered approach. For example, the Activity Card Sort (ACS) [74] can be tailored to elicit information from individuals with aphasia about their level of engagement in meaningful activities as well as hindrances to participation, allowing clinicians to obtain qualitative information about interests, level of involvement, and priorities which could then be used to shape the direction of therapy [75]. The value of considering multiple sources of information, as well as daily life functioning and communication contexts, as part of the evaluative process, is echoed by the Academy of Neurologic Communication Disorders and Sciences Practice Guidelines Group [76]. Challenges abound in the implementation of evidence-based, patient-centered care which incorporates path-breaking discoveries in the functional neuroanatomy of language. These include how to involve individuals with aphasia in goal setting, how to reconcile clinician and patient-targeted goals when discrepancies arise, and how to modify and supplement traditional modes of treatment to optimize outcomes. Evidence is preliminary, but promising, which shows the effectiveness of methods to deliver cortical neuroimaging, development of new theories of language function, knowledge base, persistence, and creativity.

Treatments. Addressing these issues requires a sound clinical mechanism associated with language recovery after these novel brain stimulation; further research is indicated to establish the which shows the effectiveness of methods to deliver cortical optimize outcomes. Evidence is preliminary, but promising,
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