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Kevin Conboy
University of North Dakota

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Kevin Conboy, PA-S, BS, NREMT-P
Department of Physician Assistant Studies, University of North Dakota School of Medicine & Health Sciences
Grand Forks, ND 58202-9037

UND School of Medicine & Health Sciences
University of North Dakota

Abstract

- Stroke is a leading cause of disability and morbidity and the fourth leading cause of death in the United States, and the second leading cause of death worldwide.
- Early restoration of blood flow is the most effective treatment of ischemic stroke by intravenous thrombolytic therapy within 3-4.5hrs of symptom onset.
- Patient outcomes have been shown to improve with earlier thrombolytics, each 15 minute increment increases survival by 3.0-4.0%.
- Non-contrast CT is the current standard for differentiation of stroke. It is beneficial due to speed of acquisition and its high sensitivity in ruling out hemorrhagic stroke.
- However, with almost half of the US population living more than an hour from a Primary Stroke Center, the need to differentiate early in rural hospitals is increasingly important.
- The purpose of this study is to determine if biological markers like GFAP compared to CT can accurately differentiate ischemic stroke, hemorrhagic stroke, and stroke mimic.
- This literature review explores the studies that compare current biological markers in ischemic, hemorrhagic stroke, and stroke mimic, and then compares their accuracy to that of neuro imaging.
- This panel of biological markers could minimize the duration to thrombolytic therapy in patients suffering from ischemic stroke by allowing early differentiation in the rural hospital setting.
- The findings indicate that the sensitivity and specificity of a panel of biological markers, clinical judgment, and clinical tools such as NIHSS stroke scale, can approach that of the non-contrast head CT in rural setting, improving time to care and stroke recovery.

Introduction

- Stroke is a leading causes of morbidity and disability in the United States.
  - **A stroke occurs every 40 sec**, every 4 min someone dies of a stroke.
  - A high associated cost of care, $33.6 billion in the US in 2011.
    - **Cost will increase to $184.1 billion by 2032**.
  - 87% are ischemic strokes (IS), 13% are intercrannial hemorrhage (ICH).
- Early restoration of blood flow is the most effective treatment of ischemic stroke by intravenous thrombolytic therapy within 3-4.5 hours of onset of symptoms.
  - Recombinant tissue plasminogen activator (TPA) is the thrombolytic of choice.
  - Benefits of TPA in ischemic stroke is time dependent.
    - A faster onset to TPA treatment time in 15 minute increments, lead to a 3-4% improved outcome per 15 minute increment.
- Differentiation of ischemic stroke and intracranial hemorrhage is crucial.
  - Administration of TPA in intracranial hemorrhage is fatal.
  - Non-contrast CT is the gold standard
    - It is beneficial due to speed of acquisition and its high sensitivity ranging from 90-100%.
    - However, CT has poor sensitivity for detecting acute ischemia.
- Only a small percent of rural patients receive TPA.
  - **Diagnostic uncertainty limits TPA's use** and increases delays in stroke care.
    - **Approximately 30% of patients who present with stroke like symptoms and are thought to be suffering from ischemic stroke are found to have stroke mimic etiologies** include metabolic disorders, migraine, seizure disorders, and brain mass lesions.
  - **40% of the population live in counties with hospitals that have administered TPA to less than 2.4% of IS patients.**
    - Not all patients can be seen by neurologist in 3-4.5 hrs.
    - This window is much smaller in actual practice due to nearly 50% of Americans living more than 60 minutes from stroke facilities.

Statement of the Problem

There is significant diagnostic uncertainty associated with ischemic stroke and almost half of the US population is living more than an hour from a Primary Stroke Center, the need to differentiate stroke early in rural setting to reduce symptom onset time to TPA administration and to decrease morbidity and mortality is increasingly important.

Research Question

In adult stroke patients, does a panel of neuro specific biomarkers compared to neuroimaging like CT, provide accurate differentiation of ischemic stroke, hemorrhagic stroke, and stroke mimic?

Literature Review

The literature review provided the following major points.

- Fiebach et al (2004) found that expert clinical imaging readers were able to identify ICH in all patients with 100% sensitivity and specificity. Fourth-year medical students were able to identify ICH with a sensitivity of 95.2% and specificity of 95.5%.
- Chalela et al (2007) found that MRI was able to differentiate IS from ICH and stroke mimic with a sensitivity of 83% and specificity of 96%. CT was able to differentiate IS from ICH and stroke mimic with a sensitivity of 13% and specificity of 98%.
- Foerch et al (2012) GFAP was able to diagnose ICH by using a cutoff value of 1.0mcg/L with the specificity of 100% and sensitivity of 60.5%.
- Allard et al (2004) found that APO C1 and C3 were able to rule out ICH with a sensitivity of 94% and specificities of 73% and 87% respectively ($p<0.001$).
- Laskowitz et al (2009) found that there bedside point of care triage stroke panel made up of BNP, D-dimer, MMP-9, and S100B was able to rule out IS with a sensitivity of 91% and specificity of 45%.
- Stamova et al (2010) found that RNA probes detected in plasma were able to diagnose IS with a specificity of 94.7% and a sensitivity of 92.9%.
- Glickman et al (2011) used the NIH stroke scale with biomarkers including CRP, MMP-9, and S100B, and were able to differentiate IS from stroke mimic with an area under the curve (AUC) of 0.95, 0.92, and 0.89 respectively ($p=0.0006$, $p=0.0015$, and $p=0.0005$).
- Vanni et al (2011) found that the Cincinnati pre-hospital stroke scale (CPSS) and the triage stroke panel failed to recognize approximately 25% of stroke patients. However when used together, revealed in AUC of 0.86 ($p<0.001$).
- Montaner et al (2012) found that using a panel of biomarkers including S100B, sRAGE, and MMP-9 were able to differentiate IS from ICH with and AUC of 0.76 ($p=0.003$) that improved to 0.81 ($p=0.003$) when including clinical data like age, gender, previous ICH, CAD, A-fib, dyslipidemia, and the NIHSS score on admission.

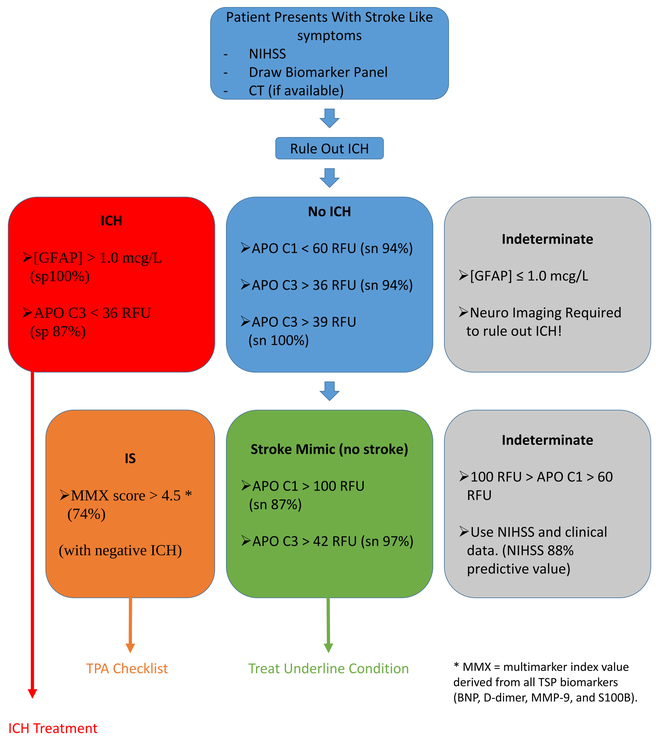
Discussion

Differentiating IS from ICH:
- Biomarkers:
  - GFAP can detect ICH with 100% specificity.
  - APO C1and C3 can rule out ICH with a sensitivity of 94% each.
  - The Triage Stroke Panel (TSP) using BNP, D-dimer, MMP-9, and S100B can rule out IS with a sensitivity of 91%.
- Neural Imaging:
  - CT can differentiate IS from ICH with 100% sensitivity and specificity.

Differentiating IS from stroke mimic:
- Biomarkers:
  - The TSP (BNP, D-dimer, MMP-9, and S100B) can rule out stroke with a sensitivity of 90%.
  - RNA probe set was able to detect IS with a specificity of 94.7% (compared to healthy controls).
  - CRP, MMP-9, and S100B with NIHSS were able to detect IS from stroke mimic patients with the following AUC: 95%, 92%, and 89%.
- Neural Imaging:
  - CT is not very accurate at ruling out IS when lesions are not present, sensitivity is only 16-26%.
  - MRI is moderately accurate at ruling out IS when lesions are not present with a sensitivity of 83%.

Proposed Stroke Biomarker Panel:
- GFAP, APO C1, APO C3, the expanded 97 RNA probe set, and the TSP biomarkers (BNP, D dimer, MMP-9, S100B)
  - Specific equipment and computers are needed to read the RNA probe set. The result turnaround time is greater than one day, therefore this biomarker would not be beneficial for the acute stroke setting.

Biomarker Stroke Diagnostic Algorithm



* MMX = multimarker index value derived from all TSP biomarkers (BNP, D-dimer, MMP-9, and S100B).

Applicability to Clinical Practice

- Differentiation of stroke etiology in the rural setting is the biggest application to clinical practice in a rural setting.
  - Will decreased time of symptom onset to TPA administration in IS
    - Will lower rates of diagnostic uncertainty of IS due to lack of experience and lack of neurology,
    - Will allow differentiation of IS and ICH in rural hospitals without CT scanners
    - Can be drawn in a point-of-care system, allowing rural EMS services to initiate differentiation during longer transport times.
    - When used with telemedicine would give neurologists another objective form of data to help analyze and direct care of patients.
- Can be used in all setting in addition to current diagnostic studies as to increase accuracy of ruling out stroke mimic.
  - Can be used with NIH stroke scale improving the 12-25% of stroke patients missed to less than 10% missed.
  - Can be used with Neuro imaging to increase CT's ability to differentiate IS from mimic from less than 50% to greater than 90%.

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