Author's response to reviews

Title: Ethnic Differences in Ischemic Stroke Subtypes in Young-Onset Stroke: The Stroke Prevention in Young Adults Study

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Version: 5 Date: 21 August 2015

Author's response to reviews: see over
August 20, 2015

Editor-in-Chief, BMC Neurology

RE: Ethnic Differences in Ischemic Stroke Subtypes in Young-Onset Stroke: The Stroke Prevention in Young Adults Study

Dear Editor-in-Chief,

We are submitting a revised version of our manuscript entitled “Ethnic Differences in Ischemic Stroke Subtypes in Young-Onset Stroke: The Stroke Prevention in Young Adults Study” for your review. The Reviewers comments have been addressed sequentially as detailed below with the revisions included in the manuscript. We appreciate both yours and the Reviewers efforts regarding the review of our manuscript. Again, the manuscript is being submitted as original research article. We believe that the manuscript will be of interest to the general readership of BMC Neurology because it describes ethnic differences in ischemic stroke subtypes among young adults, inferring on differing workup and treatment.

The corresponding author is John W. Cole, M.D., Department of Neurology, Bressler Bldg., Room 12-006, University of Maryland at Baltimore, 655 W. Baltimore St., Baltimore, MD 21201. (Phone 410-328-6483, Fax 410-706-0816, Email jcole@som.umaryland.edu).

We certify that we have participated sufficiently in the conceptual design of this work, the analysis of the data, and the writing of the manuscript to take public responsibility for it. We have reviewed the final version of the manuscript and approve it for publication.

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The authors have no affiliation with or involvement in an organization or entity with a direct financial interest in the subject matter or the material discussed in the manuscript. All financial project support of this research is identified in the acknowledgement in the manuscript.

Thank you for considering our work.

Sincerely,

John W. Cole, M.D.
Associate Professor of Neurology
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Comments:

1. Ethnic differences in stroke subtype exist in the population as a whole; why chose a “young stroke” database to answer a question on ethnic differences? The young population has been included in the previous large epidemiological studies in this topic. In other words, the authors should outline a rationale to expect differences in the black and white disparity in younger compared to older patients, when building their case in the background section.

We appreciate the Reviewers comment and have modified the Background section as suggested describing our rationale for evaluating stroke subtype differences among blacks and whites in younger as compared to older patients. We further emphasized that early-onset stroke (<50 years of age) accounts for ~10% of all strokes and often causes affected individuals to endure a greater number of years of morbidity, lost years of productivity, and an increased familial burden. Such facts prompt efforts to better understand young-onset stroke, the specific groups at risk, and identify factors that can be optimized to minimize future risk.

2. “clarify mechanisms of stroke in young adults” is mentioned in the conclusion of the abstract. That is not a fair statement if the authors really only analyzed the traditional stroke mechanisms that exist in the older population, and do not mention frequencies of other mechanisms more commonly seen in the young such as dissections, hypercoagulability, reversible cerebral vasoconstriction, moyamoya disease et cetera. These should be mentioned.

We appreciate the Reviewers comment and have modified the abstract accordingly. Indeed, the focus of the study was to evaluate for ethnic differences in stroke subtypes as based on traditional risk factors, this fact has now been better emphasized throughout the manuscript. Further, the Reviewer correctly points out that our young stroke population does indeed include other mechanisms of stroke which were classified by TOAST as other known causes (n=71). While we have not listed the etiology of each case on an individual basis, we have now describe several etiologic categories in the manuscript, including dissection (EA n=17, AA n=8), hypercoagulability (EA n=13, AA n=11), hypertensive encephalopathy (EA n=1, AA n=3), autoimmune related (EA n=4, AA n=2), and other rarer causes (n=12). We have added this information to the Results section.

3. Why was age of 40 chosen as cutoff for dichotomizing the age variable?

We appreciate the Reviewers query. Forty was the mean age of our population. A sentence describing this fact and highlighting that this was the reasoning behind our age dichotomization is now included in the Methods section.

4. How did the authors address patients where workup revealed multiple mechanisms in the same patient?

We appreciate the reviewers query. Based on the presenting clinical picture, a patient may be assigned to one of these five categories with either probable or possible certainty. Under the TOAST criteria, those patients whose stroke may be a result of
multiple possible etiologies are included in the category of undetermined etiology. This fact is now described in the Methods section of the manuscript.

5. Why were only four modifiable risk factors chosen? Why was dislipidemia, or drug abuse not chosen? Also the methods section should specify how each risk factor was defined for the purpose of uniform data collection.

As now better described in the manuscript our goal was to evaluate stroke subtypes by ethnicity as related to the presence/absence of traditional stroke risk factors. The four traditional risk factors (HTN, smoking, DM and MI) were chosen as for this reason. The Methods section was modified to include additional details regarding the study population as a whole and how each risk factor was defined. Our analyses were limited based upon small numbers in several of the ethnically stratified subtype cells; as we now point out in the manuscript the risk factors of DM and MI were excluded because of low number of subjects (overall DM:155; MI:48) in the ethnically stratified subtype cells. Unfortunately due to our study design were unable to attain accurate lipid data among the controls, as such dyslipidemia could not be included in the analyses. Statements describing these limitations were added to the manuscript.

We appreciate the reviewer’s comment regarding drug abuse; we have 2 papers in progress that are specifically evaluating cocaine and marijuana and stroke risk in this same case population and our control population (not utilized in this study). Beyond cocaine and stimulants, drug associated stroke risk is uncertain. We included 8 individuals with acute cocaine use (within 24 hours) in our analyses, their subtypes are as follows: Cardioembolic n=1, Lacunar n=1, Other Determined n=1 and Cryptogenic n=5. We have added text in the Discussion section detailing this information.

6. Diabetes was present in 155 patients. I suspect that is a sufficient number to include in risk factor analysis. It would be important to include diabetes as a risk factor for both lacunar and atherosclerotic strokes.

Again, while we agree with the Reviewer that diabetes is an important traditional risk factor, unfortunately when stratified by ethnicity and stroke subtype our numbers were quite small precluding inclusion in the analyses. However, we now include a statement in the manuscript describing the distribution of diabetes cases by subtype and ethnicity; CE=21 (AA=16, EA=5), LA=13 (AA=4, EA=9), lacunar=43 (AA=26, EA=17), cryptogenic=75 (AA=49, EA=26).

7. Stroke is now the fifth (not fourth) leading cause of death.

We appreciate the Reviewer identifying this error and have modified the Background section accordingly.

8. The discussion section is long, and somewhat weak. It is wandering in its content. The authors should focus discussion and quote studies that primarily deal with the theme of the paper differences in stroke subtypes.
We appreciate the Reviewers comment and have worked to focus and strengthen the Discussion section.