Title: Can the FAST and ROSIER adult stroke recognition tools be applied to confirmed childhood arterial ischemic stroke?

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Author's response to reviews: see over
RESPONSE TO EDITOR AND REVIEWERS

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Editorial comments
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Reviewer: rebecca ichord
Reviewer's report:
DISCRETIONARY REVISIONS:
1) Methods: … They have not reported which clinicians’ documentation accurately depicted the child’s deficit – neurologist vs non-neurologist. As the larger problem driving this type of study is to define methods that front-line (non-neurologist) providers can use to identify cases, it would be of great interest to know how the ROSIER scale performed in this cohort when applied to the signs and symptoms documented by ED providers. This may be difficult to do in a retrospective study, but it does get to the fundamental issue of how well front line providers can identify children with stroke. Nonetheless, as this study is a valuable first pass at evaluating the utility of a stroke screening instrument, it would be useful to know if there is a significant discrepancy between neurologist’s and non-neurologist’s capacity to detect and document the presence of these very basic signs and symptoms which are the basis for screening. 
  >>We agree with the reviewer that ideally we would have assessed the performance of the scales based on findings by the ED physicians and separately by the attending neurologists. This was not possible due to the retrospective methodology. We add to methodology that the first emergency department notes and the first neurologists or neurosurgeons notes were used and we add in limitations (last para discussion) and that it would be important to assess for any discrepancy between the two. We are currently undertaking a prospective study where we will be able to separately assess ED and neurologist assessment. Preliminary data for the first 98 children recruited to this study were presented at the 2010 Child Neurology Annual Scientific Meeting. Reference: Chua ZK, Yock Corales A, Mosley I, Babl F, Mackay M. Distinguishing between arterial ischaemic stroke and non-strokes in children presenting with brain attacks to a paediatric emergency department. Annals of Neurology 2010;Supp14: S140

2) Results: What is the effect of assigning a negative score on the ROSIER to
seizures? The ROSIER scale assigns a -1 for a history of seizure. Children with stroke are known to have a higher incidence of seizure at stroke onset compared to adults. One might expect therefore that incorporating this item in the ROSIER scale in children might actually decrease its sensitivity. It would be interesting to know how the analysis would be affected if this item were removed from the scoring.

>>The authors thank the reviewer for highlighting this important difference between children and adults. In our study 8 (16%) patients had seizures. Of these 8 patients, 3 had a ROSIER of <1, one child with Moyamoya and two with posterior circulation stroke. This suggests that ROSIER appears to be largely positive due to other neurological signs and symptoms in stroke patients with seizures. When recalculating the ROSIER score with seizures removed there was no change in the number with a score of <1 (i.e. 9 patients). However the numbers of patients are too small to draw the conclusion that removing seizures would not make a difference.

We have incorporated a sentence to this effect in the relevant results section (last para) and in discussion, para 4.

3) Results: What is the effect of age? One might wonder how well the instrument performs in very young children, as compared to older children/teens. Signs and symptoms are often more difficult to assess in young infants compared to older children. Was there a difference in the presentation (and thus the performance of the FAST and ROSIER screens) in children < 2 years compared with > 2 years? The sample size might be too small for firm conclusions, but it would be interesting to know if there was an age effect.

>>There were only 9 patients less than 2 years of age. Of these 7 were ROSIER positive, 2 had a ROSIER of <1. The negative ROSIER patients included one with a posterior circulations stroke. Once again the numbers are too small for statistical comparisons/firm conclusions but ROSIER seems to perform similarly when compared to older children. We have also added this information to the relevant results section (last para) and discussion, para 4.

MINOR ESSENTIAL REVISIONS:
4).Discussion: On page 6, the authors state that the FAST and ROSIER screens had good specificity in the diagnosis of stroke in this cohort. This would seem to be an erroneous statement.

>>Changed to sensitivity

5). Results:

a. “Prior relevant medical history” – appears on pg 5, second paragraph. This is not defined. Please clarify – does this mean previously diagnosed conditions that have a known risk of stroke?

>>We now explain and enumerate the relevant medical history in the corresponding results section (prior stroke, head neck trauma, sickle cell disease etc).

b. Table 1 lists several items under Complaints, which are of uncertain meaning. Please clarify/define: “sudden onset”, “woke from sleep”, "worsening symptoms"

>>We followed broadly the (limited) definitions in Hand, Stroke 2006 [ref 16]. Overall, however, due to the retrospective methodology, we accepted any statement of “sudden” or “immediate” as “sudden onset”, noted “after waking” or similar as “woke from sleep” (as documented in the ED record by ED physicians or the medical
record by neurologists) and any statement as to deterioration in neurological symptoms as “worsening symptoms”. We added this to the limitation section (last para, discussion).

c. Table 2 lists “possible aetiology” as one of the classification subtypes. This does not appear as a subtype in the Wraige paper. Please clarify what this means.

>> The Paediatric Stroke Classification (Wraige et al 2005) has a category “Multiple probable/possible aetiologies” in Table 1. The patient in our study had a prothrombotic disorder. This is listed as one example of a possible diagnosis in the footnotes to Table 1 in the Wraige 2005 paper. We believe our patient is best categorised under this subtype (category 7) and for consistency with the Wraige paper we have changed our patient to “Probable/Possible diagnosis” and added a footnote to table 2. However we are happy to change the classification if required by the reviewer but only other options are Subtype 6 or 8 (Other undetermined aetiology or Undetermined aetiology).

d. Table 1 also shows a substantial occurrence of patients with “no lateralizing symptoms”, i.e. 38%. This is puzzling and begs an explanation.

>> This refers to patients with no lateralising symptoms and collectively includes patients with visual disturbances 5/18 (27% of the total of patients with NLS and 10% of the total 47 patients), headache/vomiting 8/18 (44% of the total of patients with NLS and 17% of the total 47 patients), altered conscious state in 5/18 (27% of the total of patients with NLS and 10% of the total 47 patients); and seizures in 4/18 (22% of the total of patients with NLS and 8.5% of the total 47 patients). We have added a footnote to table 1 to make this clearer to the reader.

Reviewer: Mubeen Rafay

However, a control group consisting of children with similar presentation but different neurologic diagnosis (the so called stroke mimics) were not included. Considering that stroke mimics are a frequent occurrence in a pediatric emergency compared to ischemic stroke, a comparison group can be easily included in the analysis and will add significant weight to the results of this study. Although the application of these tools will greatly improve diagnosis and delays in stroke diagnosis in children, lack of a comparison group does not allow calculation of the negative and positive predictive values which are important in determining the significance and value of these tools in screening children with ischemic stroke presentations. A case control study will be the most suitable study design to study the utility of these tools in children in clinical practice.

>> While we agree with the reviewer that ideally we would have a control/comparison group of stroke mimics, the retrospective study methodology does not allow the inclusion of a stroke mimic group. We chose a well defined group of children, identified from our institutional stroke data base, in order to describe the scope of symptoms and signs in radiologically confirmed stroke and to test the sensitivity of adult recognition tools. It would be difficult to retrospectively identify a group of stroke mimics from the large number of possible diagnosis which could be stroke mimics. There are no data at this time as to what final diagnoses or searchable emergency department discharge diagnosis represent stroke mimics. In addition the level of documentation in these patients may be different to the stroke group.
However, we currently undertaking such a study at this time by prospectively tracking all strokes and stoke mimics. Preliminary data for the first 98 children were presented at the 2010 Child Neurology Annual Scientific Meeting. Reference: Chua ZK, Yock Corales A, Mosley I, Babl F, Mackay M. Distinguishing between arterial ischaemic stroke and non-strokes in children presenting with brain attacks to a paediatric emergency department. Annals of Neurology 2010;Supp14: S140. This ongoing study will hopefully allow the calculation of specificity, NPV and PPV.

In addition, it would be beneficial to use appropriate statistical analytical methods including calculation of negative and positive predictive values.

>>Without a stroke-negative group NPV and PPV cannot be calculated.