Reviewer's report

Title: Genetic Risk Factors for Cerebrovascular Disease in Children with Sickle Cell Disease: Design of a Case-Control Association Study and Genomewide Screen

Authors:

Gaye T Adams (gayetadams@hotmail.com)
Dr Harold Snieder (hsnieder@mcg.edu)
Virgil C McKie (vmckie@mcg.edu)
Betsy A Clair (bclair@mcg.edu)
Donald Brambilla (donb@neri.org)
Robert J Adams (rjadams@mcg.edu)
Ferdane Kutlar (fkutlar@mcg.edu)
Dr Abdullah Kutlar (akutlar@mcg.edu)

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Reviewer: James Meschia

Level of interest: A paper of considerable general medical or scientific interest

Advice on publication: Accept after discretionary revisions

This paper is a detailed description of a planned case control study of genes that may modify the risk of cerebrovascular disease in pediatric patients with sickle cell disease. Patients will derive from the STOP and STOP II clinical trials. Twenty candidate genes will be tested, including genes involved in coagulation and platelet activation. A genomewide association study is also planned.

The paper is generally well written. The topic is timely, and the STOP investigators have a tremendous resource for studying the genetics of sickle stroke. I have no compulsory revisions, but I have some discretionary revisions:

1. Some of the terms for stroke are nonstandard. For example, in line 4 of the abstract, the term 'infarctive stroke' should be replaced by 'ischemic stroke.'

2. Patients were randomized in the Stroke Prevention Trial in Sickle Cell Anemia and not 'to' the trial (see p. 2, line 10).

3. Acronyms should be defined the first time they appear in the manuscript. In the abstract, many acronyms are undefined (TNF alpha, MALDI-TOF, VCAM-1, etc.). In fact, there are so many acronyms, that a table of abbreviations might be the best way to define them.

4. There is far too much generic background about sickle cell disease. Material that can be found in any general medical text should be avoided (e.g. the first paragraph on page 4). It just dilutes the message.

5. In line 17, page 4, it is said that in sickle cell patients under age 20 years, stroke is predominantly 'thrombotic.' Are we really sure that the ischemic stroke cases are related to thrombosis? Could it not also be that the ischemic stroke cases are mostly due to non-thrombotic vascular occlusion from red cell clumping?
6. The statement "...only a few genetic risk factors are known to influence stroke risk;" (page 4, line 20) should be supported with at least one reference.

7. The normal cerebral blood flow velocity for sickle cell children is reported as "140 cm/sec" (p. 5, line 6), but should there not be a range of normal values? As a point of reference, it might be helpful to also state what the age related normal range is for non-sickle children.

8. The ages should come with units. Examples: "2-16" (line 9, page 5 and line 21, page 5) should read "2-5 years." It is important not to be ambiguous.

9. The term "abnormals" (page 6, line 11) needs to be clarified.

10. It is stated that "TCD remains the only proven indicator of cerebrovascular disease and stroke risk in HbSS [p. 7, lines 24-25]" However, there is some evidence that silent stroke as seen on brain magnetic resonance imaging is also an indicator of stroke risk.

11. The statement "...results obtained in smaller studies [p. 8 line 2]" should be supported by one or more references.

12. Line 5 on page 8 states "Currently, 18 of the 130..." It would be better to give a date rather than use the vague statement "Currently".

13. The demographics of the patient population should be described in more detail. How many centers were involved in STOP and how many centers are now involved in STOP II? Where are these centers located (e.g. US, US and Canada, etc.)?

14. I suggest that the Human Studies material be placed in its own subsection at the end of the methods section (paragraph 3 on page 9).

15. The matching variables are not precisely defined prospectively, but it appears that the authors are writing in some 'wiggle room' into the protocol (see paragraph 2, page 9). The matching variables should be clearly stated.

16. Information about the company and company location (city, state) should be provided parenthetically for every key piece of equipment, reagent, or software. For example, instead of saying "Sequenom's MassARRAY system [p.10, line 7]" one could say "MassARRAY system (Sequenome; city, state)." This is common practice in journals like the Journal of Biochemistry, and it fosters independent confirmation of published findings.

17. "NTP [page 10, line 16]" is not defined.

18. The statement "more accurate compared to hybridization-based methods of SNP detection [p. 11, line 13]" should be supported by one or more references.

19. There should be some discussion of the clinical implications of finding risk modifier genes of modest effect. How sensitive and specific is TCD for identifying high-risk individuals? How would 'positive' results of the proposed study be integrated into a rational screening program for preventing HbSS associated cerebrovascular disease? How effective are genetic screening programs for diseases with well-established genetic risk factors like breast cancer? Would the same level of effectiveness be anticipated in the sickle cell population?

20. It would appear that the right half of table 2 is supposed to be an extension of the bottom part of the left half of the table. In its current form, the table is confusing.
Competing interests:

None declared.