Author's response to reviews

Title: Variation in the circle of Willis in a Sri Lankan Population

Authors:

K Ranil D. De Silva (ranilds@slt.net.lk)
Rukmal Silva (ranil@sjp.ac.lk)
Lal S Gunasekera (l_gunasekera@yahoo.com)
Rohan W Jayasekera (rohanwi@hotmail.com)
S Somaratne (ssoma@ou.ac.lk)

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Author's response to reviews: see over
Response to referees:

Referee 1
Major Compulsory Revisions
The authors call attention to (ab)normal variations of the cerebral arterial circle (CAC) on 225 human adult cadaver brains in Sri Lanka, taking into consideration that similar anatomical study, as authors mention, has not been published, yet. Personally, I encourage beginning of this research and any similarity in future, together with specification of types of the same and/or different age in a sample, with the same and/or different pathological processes.

My remarks and suggestions are as follows:
1. I propose a new title: "Types of the cerebral arterial circle (circle of Willis) in a Sri Lankan Population"
Done: in page1 & 3

2. The citation of authors should be corrected in all parts of the article and in Table 1. All references must be numbered consecutively, in square brackets (they should not be in superscript).
Done

3. In the section Methods: please give a more precise definition of the term “typical CAC” (count its vascular components). The authors should include scheme with 28 types; include figure of CAC (Type 1), where the way of measuring of caliber will be evaluated.
Done, Figure 1 attached

4. In the section Results: please revise Type 24. It should involve a figure with 16 inserts, i.e. types (except the first one). It should involve Table 1 in the section Results (move the sentence from Paragraph 1, line 4 in the section Discussion).
Done page11

5. The Table 1 should be completely revised (consult a statistician) including coordinate numeric data types, as well as the country of corresponding author - see Efekhtar et al. (2006), and El Khamlichi et al. (1985).
Done:
1. Table 1 contain data & % in page 21-22
2. Statistical analysis done in pages: 3, 4, 8, 9, 11, 13

6. Please also take into consideration to revise References: 4-6, 10, 12, 13, 14, 16, 19, 21, 23-26, 28, 31, 33, 34, 36, 37).
Sorry could not detect any mistakes in the References.

Referee 2
MANUSCRIPT REVIEW – “Variations in the circle of Willis in a Sri Lankan Population”.
The authors have studied the external diameters of CW (circle of Willis) arteries, obtaining the circles from 225 autopsies. Their theme is that (i) the normal pattern for a circle [that has relative bilateral symmetry, with all segments complete and no severely undersize vessels] IS ACTUALLY NOT VERY COMMON (also discussed by Stehbens 1972, “Pathology of the Cerebral Blood Vessels”, page 25, where reference is made to about 4700 CWs reported by many authors), (ii) that racial and or ethnic variations among CWs can be significantly different from Caucasian-dominant data and (iii) that certain
non-typical CW configurations may be associated with vascular pathologies, such as the incidence of aneurysm formation. The authors have already published a paper on intracranial aneurysms and variations in CWs in the same sub-population 2007.

1. The results are reported in a somewhat helpful way – including 6 columns of data from other researchers, 3 of which might be interpreted as from non-Caucasian populations (Japan, Morocco, Iran) in addition to their own data from Sri Lanka (225 autopsies). Three other studies are assumed to be Caucasian-dominated (Riggs and Rupp, USA, Fisher, 1965 USA, and Lazorthes et al. France 1979). However, only their own data are presented with percentages, leaving it to a reader to make essential calculations to see any obvious similarities or differences across their table. No statistical evaluations have been done on the data – a serious shortcoming to the manuscript in its present form.

**Done:**
3. Table 1 contain data & % in page 21-22
4. Statistical analysis done in pages: 3,4,8,9,11,13

2. The ABSTRACT is rather indigestible in the RESULTS component, with an exhaustive list of the alleged variations of CW in the Sri Lankan population that “appear” different from other populations. Perhaps only the more outstanding variations should be noted in the abstract.

**Done:** only the common variations are included in page 3

The CONCLUSIONS, both in the abstract and in the body of the manuscript are very sweeping and rather casual (e.g. “or a combination of any of the above”). A proper statistical assessment would provide a framework for drawing their conclusions, and would provide the evidence needed for the reader have confidence in the statements about population variations and ethnicity. [REQUIRED REVISION]

**Done:** Conclusion changed according to statistical analysis, page 13.

3. The METHODS are clear. A helpful and simple addition would be to include the diameter of the smallest detectable vessel, since some communicating arteries can be quite tiny, and sometimes absent. This reviewer (Methods, p 8) is unsure if a limitation on acceptable normal vessel of > 1 mm (outer diameter) might be too restrictive for communicating arteries. These vessels are generally smaller, and perhaps considered quite normal blood-carrying vessels at a size below 1 mm. The authors could clarify their definition of ‘normal’, in reference to the relatively small communicating arteries, confirming with definitions established in the field. [Possibly it is the uncertainty of ‘normal size’ that explains the high variation among classifications of normal CWs.] [SUGGESTED AS DISCRETIONARY REVISION]

**Done:** under methods “Arteries where the external diameter was less than 1 mm, were documented as < 1mm” page 8

4. This reviewer invites the authors to report on the compatibility of measurements among MR-angiography (possibly x-ray angiography), ultrasonography, and the cadaveric measurements used in their and many other studies (reports identified in their list of references – such as #5,6, 7,9 and 10. The reason is that data for the living patient are only accessible through
angiography, methods which record luminal diameters of vessels distended by
normal arterial blood pressure, versus the cadaveric studies which report on
external diameters of collapsed vessels with zero luminal pressures.

[STRONGLY SUGGESTED REVISION]

Revised in page 5 para 1

5. The DISCUSSION lacks authority because of the lacking statistical
assessment. The table would be made much more reader-friendly by including
the percentages in the incidences of each anomalous CW configuration, rather
than just the absolute incidence (which the reader can readily calculate, of
course, with a calculator, but shouldn’t need to). [ESSENTIAL MINOR
REVISION] Upon consultation with statistical services at our medical school, this
referee is suggesting a Chi-square test would be a basic test of value in this
study, enabling a proper comparison among studies. The ethnicity (or racial
relevance) of the individual studies is not noted, and possibly not available. One
expects that the Iranian and Japanese studies are likely more homogeneous in
their racial/ethnic status. The Moroccan study is uncertain, and one might expect
that the two US studies, and the French study are Caucasian dominant. The
Fisher study is from Harvard, and likely mainly a white population. However, the
US studies may well have significant fractions of a negroid component in those
studies. [ESSENTIAL STATISTICAL REVISION]

5. Revised in Table 1 in page 21-22

6. Statistical analysis done in pages: 3,4,8,9,11,13

6. The conclusion that the “study reveals that there are marked variations in the
circle of Willis” may be valid, but lacks authority, not only from the statistical
perspective that needs to be explored, but also because of the lack of discussion
of assumptions that are implicit in their table 1 of comparisons. Are the methods
amongst the studies virtually the same, or are there differences that might affect
the cataloguing of anomalies, are measurements to the nearest mm or 0.1 mm?,
definitions of normal “circle”, etc. The references cited seem appropriate, and
helpful. The inclusion of Stehbens’s book on Cerebral Blood Vessels might be of
value, in part because of its comprehensiveness, but also because of its authority
in the field of cerebral vascular pathology. [DISCRETIONARY REVISION]
The authors make the point in the covering letter that this is the first study of CW
arteries in the Indian subcontinent. While the study represents a substantial
amount of work and care, the addition of 225 cadaveric measurements of CW
arteries to a large body of similar cadaveric studies already published makes it a
paper of modest scientific or medical impact in its present form.

Referee 3:
No response necessary.

Referee 4

General

In experimental animals, variations of the circle of Willis depend on the strain (1).
If this dependency holds true for humans, it will be clinically important. The
authors measured the size of brain vessels of Sri Lankan people and compared
the results with previous similar measurements for other races.
However, the methods and definition of hyoplasia differ among some of these
studies, which may hamper the validity of the comparison. Ideally, this
comparision should be made at a single institution where brains of different races can be obtained, while the second-best way is to establish standard methods for measuring brain vessels. If the same methods are used, results from several institutions from around the world can be utilized to compare the brain vessel size among different races.

I am afraid this manuscript lacks a detailed description and discussion of the methods employed in this study, and as well as those used in previous studies.

**Done:** Methodology re-written in page7 & 8

**Major compulsory revisions**

Page 7 The numbers of female and male brains should be specified.

**Done in page7**

Page 7 Methods: More detailed descriptions and a photograph of a representative case should be provided. These should help readers to understand better how the size of the vessels was measured.

**Done: Methodology re-written in page7 & 8**

**Figures (1&2) are included**

Page 9 Results: Most of the description on this page is also shown in the Table 1. I recommend the authors should avoid duplication and describe in this section only the most salient points of the results.

**Done: the common types are only included in page10.**

**Page 9 Results:** The mean and standard deviation of the sizes should be given for each segment, such as “right PCoA: 2.2 +/- 0.8mm”.

**This we did not include in our results as diameters of 225 components of CW 20 segments = 4500 data is beyond the scope of this manuscript.**

**Minor essential Revisions**

Page 7 Line 3 At “to the brain,. The”, comma is not necessary. **Done**

Page 7 Line 5 If “the circulus arteriosus” is the same as the circle of Willis, the authors should use “the circle of Willis” here. Use of synonyms may confuse some readers. **Done**

Page 19 Table1: Percentage should be displayed

**Done: Table 1 contain data & % in page 21-22**

**Discretionary Revisions**

Page 4 Conclusion: In this section, the authors should state whether the frequency of occurrence of variations of the circle of Willis of Sri Lankan people is different from that of other race or there are no significant differences.

**Done: Conclusion changed after performing statistic analysis page 13.**

Page 5 Lines 7-9 Brackets [ ] may be inappropriate.

Page 7 Line 13 Product name or product number of the micrometer-calibrator may be necessary. Similarly, the city name and country of the manufacturer may be required where the micrometer-calibrator was made.

Page7 Line 14 Please provide the initials of “the author”.

**Done:** first Author
Page 10 First Paragraph: This paragraph should be moved to the Results section.

Done

References:
(1) Strain-related differences in susceptibility to transient forebrain ischemia in SV-129 and C57black/6 mice.
Fujii M, Hara H et al.. Stroke. 1997 Sep;28(9):1805-10; discussion 1811.