Reviewer's report

Title: High prevalence of cardiovascular risk factors in children and adolescents with Williams-Beuren syndrome

Version: 2
Date: 18 August 2014
Reviewer: R. Thomas Thomas Collins II

Reviewer's report:

Major Compulsory Revisions

1. In lines 19-20 of the Background, the authors state that the atherosclerotic risk factors they are studying (high blood pressure, hypercholesterolemia, etc) are important in the prevention of progression of elastin arteriopathy. This is completely unfounded. There is no evidence that risk factors for atherosclerotic disease have any effect on elastin arteriopathy. While the intellectual conclusion could be reached that the two could compound arterial stenoses and subsequent "downstream" effects, no one has adequately study such an outcome. Further, such a synergistic mechanism is different from the statement the authors are making—that being that atherosclerotic disease risk factors worsen elastin arteriopathy. The authors make the same statement on page 12, in line 2 and 3. While it makes the results of the work seem that much more important, it is not based on any available data, at least to my knowledge. If the authors have such data available, it would be imperative to include it in the manuscript. Otherwise, it is imperative that this sentiment be removed. This sentiment is seen in other places in the manuscript (lines 1-3 of page 12, 13-15 of page 13, & 7-9 of page 14). This must be changed.

2. The first paragraph of the Methods section actually describes results and should be moved to the Results section. Additionally, beginning in line 6 of the first paragraph of the Methods the data reported should either be placed into a table, which would be most helpful, or it should be stated that all of the patients had SVAS in addition to the secondary abnormalities. This is to say the reiteration of SVAS with each group is cumbersome.

3. In line 15, the authors state that “no patient showed significant SVAS,” and follow with their definition of “significant” SVAS being >50 mmHg. I suspect the authors would be hard-pressed to find a group of cardiologists who would say that a gradient of 40 mmHg is not significant. A gradient of 50 mmHg or greater may be one upon which intervention may be undertaken, but hemodynamic changes occur below 50 mmHg and would therefore be considered as “significant.”

4. In the line beginning in line 7, the authors state “long-term exposure to these risk factors may increase the incidence of CV events in adulthood.” Other investigators have shown a clear translation of CV risk factors in childhood into
adulthood. Gerald Berenson and colleagues have published a wealth of data from the Bogalusa Heart Study demonstrating that these risk factors indeed propagate. The authors would benefit from reviewing the large body of literature on this topic. The same sort of statement is made in lines 8-10 of page 15, in the Conclusion. If we know, in normal populations, risk factors in childhood translate to adulthood, risk factors in adulthood increase CV risk, and risk factors in childhood increase adulthood CV risk, then why would we not expect the same thing to occur in WS? It makes no sense to think that WS would be immune to this pathophysiologic process and subsequent outcome.

Minor Essential Revisions

1. In the first sentence of the Background, the authors state that Williams et al described the disorder as being "a congenital developmental disorder involving both the connective tissue and the central nervous system..." This is an incorrect attribution. Williams et al described four patients with supravalvular aortic stenosis, mental retardation, and characteristic facial features. They did not describe the disorder as congenital. They made no statement as to the disorder being of a developmental nature. They did not specifically address that it involved the central nervous system outside of the cognitive component. While such could be inferred, it was not so described. Therefore, this is an incorrect attribution. The verbiage used by the authors is somewhat similar to that used by Kaplan et al in their paper in the Journal of Childhood Neurology 2001. The first statement should be changed to reflect that WS is as the authors describe and that it was first reported by Williams et al, but the two should not be tied as they presently are.

2. In the second paragraph of the Methods section, the authors describe the methods used for diagnosis of WS. Was FISH testing for other deletions on 7q11.23 used? If not, the authors should the statement should be made that “the diagnosis of WS was made using FISH to demonstrate ELN homozygosity or deletion.” The first line of page 5, references Figure 1. A figure should only be included in the Methods section if it delineates clearly the methodology used to undertake the study. The use of the figure included suggests more testing was used than that which is described.

3. Table 1, while outlining a large number of data, contains so much information as to be of little use. A given reader will look at the table and decide there is too much contained therein to even review. In reality, it seems to me the table could be completely deleted without significant loss to the manuscript.

4. The paragraph in the Results section beginning on line 11 and continuing through line 15 is completely reiterative of the data in Table 2. This should be deleted.

5. Lines 2-9 on page 8 are reiterative of Table 2. Here again these data could be removed from the manuscript and a reference made to Table 2.

6. In line 5 of page 8, the authors state HOMA-IR was 40%. In Table 2, this
number is 43%. Consistency should be maintained. It is either 40% or 43% and should be the same in both places.

7. Line 12 of page 8 is reiterative in the same manner as comments 4 & 5 above.

8. In line 1 of page 11, the authors state that loss of elastin function “causes the formation of CV lesions.” The authors need to clarify what they are trying to say here. The elastin concentration is decreased due to haploinsufficiency in ELN. The function of the elastin protein is decreased, but function is not completely lost. Further, this varies for different patients, as it is known that 20% of patients with WS, all of whom have ELN haploinsufficiency, do not have cardiovascular lesions. A number of patients with WS have VSDs and other non-arterial lesions. There is no evidence these lesions are “caused” by ELN haploinsufficiency. Therefore, the statement the authors make is not entirely correct. It would be better stated that decreased elastin function is known to be the etiology of the vascular lesions found in WS.

9. In line 9-11 of page 13, the authors state that the arterial lesions in WS “should be considered as generalized elastin arteriopathy.” For those who care for patients with WS and study the disease process, it is considered to be a generalized elastin arteriopathy. The statement in the manuscript should be altered to reflect it is known to be such and the data presented validate such an understanding.

Discretionary Revisions

1. In line 17 of the abstract, the word "since" should be changed perhaps to "during" or "from." This occurs elsewhere in the manuscript as well.

2. The lengthy paragraph on page 5 describing the methods used for testing repeats the statement “measured using commercially available kits.” This is tedious. There should be one single sentence stating, “All biochemical measurements were made using commercially available kits.”

3. The authors should consider creating a table containing the lipid profile data. This would be much more helpful than the information contained in the Results section and repeated in Table 2.

4. In lines 7-9 of page 10, it would be more concise to state, “There were no differences in any of the study measurements between the hypertensive and non-hypertensive groups.”

5. The sentence beginning on line 3 of page 11 is reiterative of the sentence immediately preceding it.

6. In line 3 of page 14, consider changing the statement to “children has been reported to be 7% and 1%....”

Level of interest: An article of importance in its field
Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.