

Peer Review File

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Reviewer A

The authors have performed a review on cardiovascular diseases in patients with TS. The subject is interesting, however some points should be addressed.

The abstract

The conclusion in the abstract is not informative and should be modified. Results of the search are not presented in the abstract.

The paper

In the introduction the authors mention that many guidelines have been published but they do not mention the references at the end of the sentence.

Reply: Removed statement about many reviews as there have actually not been that many. Last major guideline is from the AHA in 2018 and is the only guideline worth mentioning for cardiovascular screening and management at this time.

The authors mention a literature review. What are the dates chosen for this literature search?

Reply: Dates of the search added

Line 29 the authors mention discussion but where are the results?

Reply: Results of the literature search were added

Line 49 The authors mention surgical issues concerning coarctation but they do not describe aortic coarctation in the previous paragraph.

Reply: A brief description of coarctation of the aorta as well as bicuspid aortic valve, being the 2 most common lesions found in TS, were added

How many patients have been reported with chylothorax? What is the prevalence as compared with patients without Turner syndrome?

Reply: The prevalence of developing Chylothorax after aortic arch repair compared to the general population was added

Line 63: the authors report Turner patients with HLHS. This syndrome is however quite rare and this should be mentioned.

Reply: The low, but significant, prevalence of HLHS among TS patients was reported

Line 81: the authors mention that renal defects may explain hypertension. However, although TS patients may have kidney abnormalities, most of them do not alter kidney function and therefore do not induce hypertension.

Reply: The current AHA guidelines specifically state "Hypertension may be the result of renal anomalies that are frequently seen in TS or may be idiopathic." This will not be changed aside from adding modification that the hypertension may be idiopathic

The authors should describe the norms of aortic diameter considering body surface area. They should mention several recent studies reporting the evolution of aortic diameters. The study by Lin et al. is an old study.

Reply: More updated literature was added regarding aortic diameter

A lifelong follow-up of aortic diameter should be mentioned in the paper.

The authors should mention that bicuspid valve may be missed during infancy and that echography should check at adolescence the presence of an aortic bicuspid valve (ref Donadille B et al. EJE)

The authors should mention recent reference testing QT abnormalities in patients with TS.

Reply: An entire section has been added that further addresses the ECG changes seen in TS, emphasizing the QT issues.

Many references are old references and new references should be mentioned in the paper.

Reply: Several older references have been removed in place of newer references that are more relevant

Reviewer B

This article is a good review of Turner's cardiovascular complications. However, English is hard to read, and it should be better to have a professional English revision.

There are some comments:

-Pg 2, lines 34-7 This phrase has a concept error. The lymphedema causes the neck webbing, so the physiopathology should be similar and not a cause-effect.

Reply: The phrasing of this was improved upon.

-Pg 3-4, lines 65-68, the Norwood operation and the Glenn procedure should be quickly described.

Reply: A brief description of the purpose of the single ventricle palliative pathway was added. Individual descriptions of each complex surgery are felt to be beyond the purview of this review

-Pg 5 line 93. Though hypertension and congenital cardiac malformations are risk factors for aneurism dissections, they are not essential. The authors should better discuss this possibility.

Reply: The underlying pathology of intima-media abnormalities of the aorta were added as the most likely source of aortic aneurysm and dissection.

-Pg 5, line 99: it has been described the aortic dissection in younger than 18 yo.

Reply: The true age range of aortic dissection was added, including as young as 4 yo.

-Pg 6, line 127: some authors advise also using beta-blockers or ACEi in these cases.

Reply: We added recommendations to use beta blockers and ACEi as are used in Marfan Patients as they have been shown to reduce the rate of aortic dilation in that population

-Pg 7, line 133: "If the patient does NOT have a BAV ...", in fact, " If the patient does have a BAV"...

Reply: Our statement was in fact correct. This was not changed. Please read closer

-Pg 7, line 143: the 2017 consensus should also be cited here.

Reply: Don't feel this is necessary give more recent 2018 AHA guidelines that all Cardiologist should follow over prior, outdated consensus.

-Pg 8, line 158: corrected QT should better be calculated by Hodges' formula than Bazett's formula.

Reply: The argument for using other formulas is presented, but there is no consensus on this, and Bazett remains the only formula used clinically. The literature does not support broad use of the Hodges formula. In fact, it can be argued that the Framingham formula is really the best at correcting at high heart rates.

Finally, a good general physician or endocrinologist with experience in Turner syndrome can make the cardiac evaluation and only send the patient to a cardiology specialist if necessary.

Reply: I respectfully disagree with this sentiment and will not be adding anything of this nature to the manuscript.