Author’s response to reviews

Title: TITLE: CHARGE SYNDROME: Genetic aspects and Dental Challenges, A Review and Case Presentation.

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Version: 1 Date: 13 Sep 2019

Author’s response to reviews:

10 September 2019

Rebuttal Letter

Head and Face Medicine

Manuscript No:

The Editor

Dear Sir/Madam

The authors have amended the manuscript in accordance with the comments made by the reviewers. We hope that these meet with approval.

In response to reviewer 1’s comments, the following have been amended- suggestions highlighted in yellow
The purpose of this article was to review the diagnosis, the genetic aspects and dental challenges of CHARGE syndrome. The review is comprehensive and represents a useful synopsis. Although interesting, a major review would be necessary before it could be considered for publication. Please, find below some comments that you might consider useful to strengthen your case report.

POINTS [references missing] The authors should observe that most of the sentences in the introduction (and discussion) have no references. The references of most sentences in the introduction and discussion section were not supplied.

Thank you for bringing this matter to our attention. As per request, the missing references have been supplied, both in the text and the bibliography.
SPECIFIC POINTS Major points: Introduction:

1) The genetic concerns are well described. The authors comment about the role of neural crest cells, however did not explore the role of neural crest cells in the establishment of pharyngeal arches and face and tooth development. It could be added a reference about the role, since the title of the paper includes dental aspects of the syndrome. Pertaining to this point, the authors are of the opinion that including the role of neural crest cells, may place too much emphasis on the embryological development which is not the focus of this article.

2) Case presentation: The authors cited that the patient is currently being managed by a multidisciplinary team which includes; occupational therapist, speech/feeding therapist, dietician, ophthalmologist, ENT surgeon, pulmonologist, neurodevelopmental paediatrician and medical geneticist. And about the dental assistance: Is she managed by a dental team? The point has been addressed in line 136 of the revised manuscript.

3) The authors cited that the child was co-operative and was able to open her mouth and permitted to obtain pictures. However, they declare that no bitewing radiographs were taken because it was not possible to place the film into her small mouth. It looks a little contradictory to me. I could understand if no bitewing radiographs were taken because the child was caries-free and, so, the radiographic exam was not indicated or necessary (AAPD guidelines, 2018).

4) The description of dental assessment is too short and some important information is missing: total tooth number (the only information is about the incisor fusion), tooth absence, alteration of tooth morphology, late eruption. I would like to add that the authors did not inform any concern about clinical tooth diagnosis: tooth hypoplasia presence, caries experience, crossbite... To discuss the challenges in dental care, it is important to relate the most possible dental clinical information of the patient. Please, supply more information, including information about occlusion development. Additional clinical information was added and extends from line 149-165.

5) Additionally, the authors should include if the patient was using some regular medication, since some drugs could modify oral mucosa health and alter salivary flow. The patient did not receive any chronic medication but was recalled monthly to evaluate the patency of the PEG. Furthermore, the patient received antibiotic prophylaxis before any invasive procedure. Lines 132-134

6) In relation to treatment: Why patient received fluoride application? Could the authors discuss this treatment decision based on the needs of the patient, including the risks and benefits? Point addressed in lines 174-178

7) The authors cited that all intraoral examinations were tolerated well. Which were the intraoral examinations parameters and results? These were visual examinations; no probes or suctioning could be done.
It should be necessary a deeper description of the dental clinical record, since the title of paper indicated tooth challenges to be resolved… The authors have described all the dental changes observed in this particular patient and discussed possible dental management implications of CHARGE in general.

Discussion: 8) The authors described a section "Dental anomalies found in CS", but the information about the dental anomalies is lack in case report description (as I have already commented above - only information is the incisor fusion). Please, insert the information about dental records in "Facial and dental assessment" to be able to use it in the discussion. This is addressed in the case report from line 152-165. No additional features were seen. The authors would like to highlight that the main focus of the paper is on dental management challenges and not on oral manifestations.

And about the follow up? Please, clarify.

Lines 179-184

Minor points:

Table 1 is not correctly formatted and it is confusing. Please review.
Reviewed Table 1

List of abbreviations in incomplete (I do not know if it is necessary)
List of abbreviations was removed from the manuscript

In response to Reviewer 2’s comments

In this case report, the authors present a child with a very rare genetic defect (CHARGE syndrome) and describe - apart from the general health effects - in particular the development of the skull and face as well as oral health. Overall, the manuscript therefore fits in thematically with "Head & Face Medicine". Although the disease is very rare, the manuscript is of interest to the reader for comprehensive information about this disease from a dental point of view.

Unfortunately, there are some typos that need to be corrected. Typos are corrected

Also, the references are inconsistent and not in the required form, necessary for "Head & Face Medicine". Some of the references are incomplete, thus, the references need to be revised. References have been revised
In response to Reviewer 3’s comments – suggestions highlighted in green

1) The first line of Background section: the incidence might be 1:12000-15000, but not 1:12-15000. Thank you for your comment. This has been addressed in line 51.

2) Differential diagnosis of similar syndromes might be involved, such as Abruzzo-Erickson syndrome, Kallmann syndrome. This point was addressed in line 78-80

3) Could you please provide image of occlusion wear? Unfortunately, no further intra-oral pictures could be obtained due to limited mouth opening and difficulty in keeping the mouth open

4) Could you please provide some indexes of dental plaque and caries? Although the patient allowed us to view her teeth with a mirror, she did not tolerate any other dental instruments such as probes in her mouth. She was caries-free.

5) How about some treatments to bruxism or occlusion wear? And does it necessary to take some protections to the TMJ? Thank you for highlighting our omission, the preventative measures lines 179-184

6) The sequential therapy plan to CHARGE syndrome might be added, such as treatments of maxillofacial surgery, Periodontology, Prosthodontics and Orthodontics. Future treatment discussed on lines 179-184. The child is four years old. Recall visits have been organized for every six months. At this time a future treatment plan cannot definitively be developed.

In response to Reviewer 4’s comments – suggestions in pink

1) However, there are plenty of statements and affirmations without its corresponding citation. Thank you for your valuable input. This point has been addressed. Much gratitude

2) Consider avoiding acronyms when used as the first time in the text. Point noted and addressed. Thank you

3) Case presentation: The authors state after the description that "based on the clinical and investigation findings, the patient met criteria for the diagnosis of CHARGE syndrome. However, in the first paragraph division of molecular biology and human genetics at the university has already confirmed that diagnosis. It is not clear if the investigators performed the diagnosis or if they only describe an already diagnosed patient. This was a history of how the diagnosis of CHARGE was made."
4) Please re-order the text accordingly and clarify. Dental treatment is poorly described, consider to improve description. Examples: Initial treatment planning, fluoride description, and timing, …
This has been addressed from lines 167 to 179. The authors would like to highlight that the focus of the paper is dental management implications. Thank you

5) The is a lack of discussion with the available published data comparing with patients features.
This was addressed in lines 200-205

6) The authors state that "health care professional…should be mindful of the specific dental anomalies associated…that can influence dental care" However, no specific dental anomalies are described or presented in the case presentation section. Besides regarding the last part, no description of what can influence and in which way dental care in these patients. …health care professional…should be mindful of the specific dental anomalies associated…that can influence dental care – should read “the oral health care professional…. should be mindful of several systemic anomalies associated with…… that can influence dental care. – Corrected line 196-198

7) Please try to avoid using words such as "obviously " in the manuscript.
Noted and corrected thank you

8) How was "the patient ability to taste preservation" tested?
Feedback from parents and clinical geneticists.

9) Relation of bruxism description and differences with child bruxism
The authors are unclear as to what is required

10) Figures Although a consent form seems to be signed for picture publication, some effort should be made to ensure and respect patients protection taking into account is an under-age patient by masking unnecessary exposure.
    The authors feel that a complete picture/image of the craniofacial region highlights the clinical manifestations of the disorder.

11) Missing some intraoral pictures, that will give a better description of present specific features related to the aim.
    Intra-oral pictures could not be obtained as the patient did not tolerate intra-oral mirrors and her mouth was too small.

12) Conclusion This paragraph reflects the findings, but it can be summarized accordingly.
    The authors feel that the conclusion is adequately summarized

Thank you for your most insightful input

Yours truly,

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Dr TS Roberts (PhD)