Reviewer’s report

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

Version: 0 Date: 26 Jun 2019

Reviewer: Lisiane Bernardi

Reviewer’s report:

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.

GENERAL 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. Please, kindly check and provide all references in the text and in the references section.

For example:
CHARGE syndrome (CS) is a rare genetic condition (OMIM #214800) with an incidence of 1: 12-15,000.1 This condition has a variable phenotypic expression. Historically, the diagnosis of CHARGE syndrome was based on the presence of specific clinical criteria. [REFERENCE MISSING] The genetic aetiology of CS has since been elucidated and attributed to pathogenic variation in the CHD7 gene (OMIM 608892) at chromosome locus 8q12. 2 The CHD7 gene is involved in control of gene expression, particularly chromatin remodelling. [REFERENCE MISSING] Changes in the CHD7 gene sequence which lead to absent or reduced protein result in disrupted chromatin remodelling, ultimately leading to the multi-organ abnormalities found in CS. [REFERENCE MISSING] CHD7 seems to be particularly important in controlling the function of neural crest cells, which are pluripotent cells with migratory potential. [REFERENCE MISSING] The neural crest has multiple vertebrate derivatives, including the craniofacial skeleton, the central nervous system (CNS) and associated sensory organs, and parts of the heart. [REFERENCE MISSING] The induction of the neural crest is determined by signalling molecules such as BMP, WNT, FGF and retinoic acid. [REFERENCE MISSING]
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.

Case presentation:
2) 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?
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.
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.
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?
7) The authors cited that all intraoral examinations were tolerated well. Which were the intraoral examinations parameters and results? It should be necessary a deeper description of the dental clinical record, since the title of paper indicated tooth challenges to be resolved...

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.
9) And about the follow up? Please, clarify.

Minor points:
10)Table 1 is not correct formatted and it is confused. Please review.
11)List of abbreviations in incomplete (I do not know if it is necessary)
Level of interest
Please indicate how interesting you found the manuscript:

An article of importance in its field

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