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REVIEW ARTICLE

Radiological evaluation of odontogenic keratocysts in patients with nevoid basal cell carcinoma syndrome: A review

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KEYWORDS

Radiological Evaluation; Odontogenic Keratocysts; Nevoid Basal Cell Carcinoma

Abstract *Background:* Nevoid Basal Cell Carcinoma Syndrome (NBCCS) is an autosomal dominant syndrome that has various expressions in each patient. Generally; NBCCS is followed by multiple nevoid basal cell carcinoma of the skin, orbital anomalies, skeletal anomalies, central nervous system anomalies and multiple odontogenic keratocysts (OK). NBCCS is usually diagnosed between the ages of 5–30 years, with multiple basal cell carcinomas of the skin and OKs in the jaws as the initial findings. The purpose of this paper is to describe and compare the radiographic findings of the OKs in NBCCS patients in the literature with additional cases.

Materials and Methods: In this study, we evaluated the OKs of the patients with NBCCS in PubMed Database with 5 additional cases from our database. A total of 305 articles were found and the articles in English with full-text access were evaluated.

Results: Despite all limitations for a fair discussion; we would like to state that among 59 cases that specified whether a 3D or 2D imaging modality was used, 29 cases were only interpreted with 2D data which should be avoided in OK evaluation.

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Discussion: According to the World Health Organization's Classification of Head and Neck Tumours Book which was published in 2017, OKs in NBCCS has a higher chance to have small satellite cystic lesions which increase their recurrence possibility post-operatively, thus, a thorough clinical and 3D radiographic evaluation should be performed both to NBCCS patients and non-syndromic OK patients to avoid any recurrence.

Conclusion: High recurrence rates of OKs should be reminded all the time. Radiographic examinations with 3D imaging modalities should be done in patients with NBCCS in order to provide a concise diagnosis and optimum treatment.

Contents

1. Introduction

Nevoid Basal Cell Carcinoma Syndrome (NBCCS) is an autosomal dominant syndrome that has different various expressions in each patient (Curatolo et al., 2013, Daneswari and Reddy 2013, Fini et al., 2013, Grundig et al., 2013, Haenen et al., 2013, Mohan et al., 2013, Pol et al., 2013, Rambocas and Murphy 2013, Saulite et al., 2013, Budincevic et al., 2014, De Craene et al., 2014, Friedrich 2014, Inani and Mernissi 2014, Keceli et al., 2014, Khan et al., 2014, Kulkarni et al., 2014, Larsen et al., 2014, Mehta et al., 2014, Mufaddel et al., 2014, Patankar et al., 2014, Shephard and Coleman 2014, Tarnoki et al., 2014, Abreu et al., 2015, Anchlia et al., 2015, Chandran et al., 2015, da Silva Pierro et al., 2015, Galati et al., 2015, Ganguly et al., 2015, Grechi et al., 2015, Hajalioghli et al., 2015, Lata et al., 2015, Lazaridou et al., 2015, Majdoub et al., 2015, Manjima et al., 2015, Ojevwe et al., 2015, Pickrell et al., 2015, Ramesh et al., 2015, Hubacek et al., 2016, Khaliq et al., 2016, Ozcan et al., 2016, Ponti et al., 2016, Ribeiro et al., 2016, Scalise et al., 2016, Tandon et al., 2016, Thomas et al., 2016, Virgone et al., 2016, Casari et al., 2017, da Paz Oliveira et al., 2017, Mendes-Abreu et al., 2017, Mendes-Bastos et al., 2017, Nilesh et al., 2017, Pennisi et al., 2017, Sereflican et al., 2017, Trento et al., 2017, Witmanowski et al., 2017, Zamarron et al., 2017, Aloosi et al., 2018, Demir and Kocak 2018, Figueira et al., 2018, Hasan and Akintola 2018, Hsu et al., 2018, Khodaverdi et al., 2018, Kumar et al., 2018, Kumar et al., 2018, Mo and Zhang 2018, Moreira et al., 2018, Santander et al., 2018, Veronese et al., 2018, Yap 2018, Al-Jarboua et al., 2019, Bartos et al., 2019, Boos Lima et al., 2019, Galdes et al., 2019, Kesireddy et al., 2019, Mishra et al., 2019, Monaco et al., 2019, Moramarco et al., 2019, Nilius et al., 2019, Ozlu et al., 2019, Sahu et al., 2019, Cesinaro et al., 2020, Lata and Kaur 2020, Narang et al., 2020, Osiecka et al., 2020, Russo et al., 2020, Silva et al., 2020, Tomasso et al., 2020, Gao et al., 2021, Miraglia et al., 2021, Piccerillo et al., 2021, Rafiq et al., 2021, Singh and Mishra 2021, Tefon Aribas et al., 2021, Yin and Shi 2021, Chen et al., 2022, de Lima et al., 2022, Igaz et al., 2022, Katayama et al., 2022, Kortuem et al., 2022, Loveridge-Easther and Weatherhead 2022, Miraglia et al., 2022, Pazdera et al., 2022, Pitak-Arnnop et al., 2022, Rao and Taksande 2022, Reaz et al., 2022, Russo et al., 2022, Russo et al., 2022, Song et al., 2022, Spadari et al., 2022, Ye et al., 2022). Generally; NBCCS is followed by multiple nevoid basal cell carcinoma of the skin, orbital anomalies, skeletal anomalies, central nervous system anomalies and multiple odontogenic keratocysts (OK). NBCCS is usually first diagnosed between the ages of 5–30 years, with multiple basal cell carcinomas of the skin and OKs in the jaws as the initial findings (Friedrich 2014, Mufaddel et al., 2014, Tarnoki et al., 2014, Anchlia et al., 2015, da Silva Pierro et al., 2015, Hajalioghli et al., 2015, Lata et al., 2015, Ozcan et al., 2016, Ponti et al., 2016, Nilesh et al., 2017, Kumar et al., 2018, Bartos et al., 2019, Moramarco et al., 2019, Silva et al., 2020, Rafiq et al., 2021, Yin and Shi 2021, Igaz et al., 2022, Miraglia et al., 2022). OKs in these cases are usually observed in more than one quadrant, earlier and with higher recurrence rates compared to the non-syndromic OKs. Skin lesions are usually observed on the face, neck and trunk as flattened, red or brown papules. In some cases, carcinomas will occur following the

occurrence of OKs. According to the literature, the frequency of NBCCS has been reported to be 1 in 50,000 to 150,000 in general population (Khodaverdi et al., 2018, Kumar et al., 2018, Santander et al., 2018, Al-Jarboua et al., 2019, Bartos et al., 2019, Boos Lima et al., 2019, Moramarco et al., 2019, Nilius et al., 2019, Sahu et al., 2019, Cesinaro et al., 2020, Lata and Kaur 2020, Silva et al., 2020, Gao et al., 2021, Rafiq et al., 2021, Singh and Mishra 2021, de Lima et al., 2022, Katayama et al., 2022, Pazdera et al., 2022, Pitak-Arnnop et al., 2022, Rao and Taksande 2022, Reaz et al., 2022, Spadari et al., 2022).

Skeletal pathologies of the NBCCS are bifid rib, as agenesis of the ribs, synostosis of the ribs, kyphoscoliosis, fusion of the spine, polydactyly, shortening of the metacarpals, temporal bossing, minor hypertelorism, and mild prognathism. Calcification of the falx cerebri and other parts of the dura occur early in life and they it may get diagnosed with the lateral cephalograms or skull projections that are used in dentistry (Al-Jarboua et al., 2019, Moramarco et al., 2019, Nilius et al., 2019, Tomasso et al., 2020, Rafiq et al., 2021, Tefon Aribas et al., 2021, Spadari et al., 2022). Some cases also reported the presences of bronchogenic cysts and hyaline membrane diseases; thus, following the diagnosis of NBCCS consultations to other departments are required (Badnjević et al., 2013, Alić et al., 2017, Yap 2018).

Radiographic features of the OKs are well recognized and reported in the literature. The differential diagnosis of the OKs from the other odontogenic cysts relies on the non-expansive & minimal-expansive nature of it. As the benign odontogenic lesions tend to expand the cortical borders of the jaws, OKs tend to extend antero-posteriorly along the long-axis of the jaws. Differently in OKs in NBCCS, multiple OKs may develop and their sizes vary from 1 mm to a few centimeters in diameter (Hubacek et al., 2016, Zhu et al., 2019, Cardoso et al., 2020, Kim et al., 2020, Lee et al., 2020, Mustakim et al., 2022). If a lateral cephalogram was taken instead of an orthopantomograph, a hyperdense line of the falx cerebri calcification can also be visualized which is a major criterion in NBCCS diagnosis. In some cases, laminated falx cerebri calcification can be seen. Multifocal lesions may be confused with other hypodense multifocal lesions of the jaws and the skull such as multiple myeloma however as the rest of odontogenic cysts, OKs have hyperdense cortical borders at the periphery of the lesion. As OKs do not cause lesions, clinicians can also distinguish them from the giant cell lesions of the cherubism as they are bilateral expansive lesions that displace teeth in an anterior direction (Daneswari and Reddy 2013, Mohan et al., 2013, Friedrich 2014, Keceli et al., 2014, Khan et al., 2014, Mufaddel et al., 2014, Patankar et al., 2014, Shephard and Coleman 2014, Tarnoki et al., 2014, Abreu et al., 2015, Anchlia et al., 2015, Chandran et al., 2015, Lazaridou et al., 2015, Majdoub et al., 2015, Manjima et al., 2015, Pickrell et al., 2015, Hubacek et al., 2016, Ozcan et al., 2016, Ribeiro et al., 2016, Nilesh et al., 2017, Aloosi et al., 2018, Figueira et al., 2018, Santander et al., 2018, Cicciu et al., 2019, Silva et al., 2020, d'Apuzzo et al., 2022, Minervini et al., 2022, Pitak-Arnnop et al., 2022, Spadari et al., 2022).

Following the definitive diagnosis, another challenge generally raises difficulties for the oral health care providers as OKs in NCBCS have higher chance for recurrence that requires even more aggressive treatment options. In order to detect early recurrent OKs, it is crucial to follow the patient and evaluate the condition with a radiograph. OPGs may not be favorable for the screening of the patients in early follows-up and CT is generally suggested for the detection of early lesions. Genetic consultations are also suggested for the dentists in case of early and multifocal OKs are detected. Diagnosis of NBCCS is based upon the major and minor clinical and radiological criteria which should be confirmed by DNA analysis (Khan et al., 2014, Kulkarni et al., 2014, Anchlia et al., 2015, Mendes-Abreu et al., 2017, Santander et al., 2018, Monaco et al., 2019, Osiecka et al., 2020, Silva et al., 2020).

The purpose of this paper is to describe and compare the radiographic findings of the OKs in NBCCS patients in the literature with additional cases.

2. Materials and methods

In this study, we evaluated the OKs of the patients with Basal Cell Nevus Syndrome with the following queries in PubMed Database *((((((((((((((Basal Cell Nevus Syndrome) OR (Basal Cell Syndrome)) OR (Gorlin-Goltz Syndrome)) OR (Gorlin Goltz Syndrome)) OR (Gorlin Syndrome)) OR (Multiple Basal Cell Nevi)) OR (Multiple Basal Cell Nevi, Odontogenic Keratocysts, and Skeletal Anomalies)) OR (Fifth Phacomatosis)) OR (NBCCS)) OR (Nevoid Basal Cell Carcinoma Syndrome)) OR (Nevus Syndrome, Basal Cell)) OR (Nevoid Basal-Cell Carcinoma Syndrome)) OR (Gorlin and Goltz Syndrome)) OR (Gorlin's Basal Cell Nevus Syndrome)) OR (Nevoid Basal Cell Nevus Syndrome))AND ((((((Odontogenic Keratocyst) OR (Keratocyst)) OR (Keratocystic Odontogenic Tumour)) OR (Keratocystic Odontogenic Tumor)) OR (Odontogenic Cyst)) OR (Jaw Cyst))) AND ((((((((((((((Radiograph) OR (radiography)) OR (tomography)) OR (cone-beam computed tomography)) OR (cbct)) OR (cone beam computed tomography)) OR (computed tomography)) OR (MRI)) OR (magnetic resonance imaging)) OR (ultrasonography)) OR (ultrasound)) OR (Panoramic radiograph)) OR (OPG)) OR (orthopantomograph)) OR (orthopantomography))) AND (English [Language])*.

Noted parameters were age, gender, number of OKs, localization of the OKs, diameters of each OK, presence of malocclusion, unilocular/multilocular distribution, bimaxillary/unimaxillary distribution, presence of a neighboring impacted tooth/teeth, imaging modality, presence of inheritance, presence of cleft palate, presence of frontal bossing, presence of hypertelorism, presence of maxillary sinus involvement, presence of falx cerebri calcification, presence of bifid ribs.

Five new cases which were reported by us which were also evaluated according to the parameters that were mentioned above.

3. Results

A total of 305 articles were found and the articles in English with full-text access were evaluated (Supplemental Table 1).

Age: Mean age was 32.9 (min 6, max 86), for the patients with NBCCS who had OKs that were reported. 5 authors did not specify the age of their patients.

Gender: Among the papers that specified the gender of the patient, 45 females and 48 males were reported to have

Table 1 List of abbreviations.

Abbreviation	Full Name
NBCCS	Nevoid Basal Cell Carcinoma Syndrome
OK	Odontogenic keratocyst
OPG	Orthopantomography
CT	Computed Tomography
CBCT	Cone-beam Computed Tomography
MRI	Magnetic Resonance Imaging
BCC	Basal Cell Carcinoma
NBCC	Nevoid Basal Cell Carcinoma
2D	Two Dimension
3D	Three Dimension

NBCSS. Four patients were reported without any statements of the gender.

Number of OKs: Considered as one of the major criteria of NBCSS, studies that specified the absence/presence of OKs, all cases had at least 1 OK. However only 25 cases were reported with specified number of OKs and 81 lesions were present in those cases.

Localization of the OKs: While majority of the studies did not specify the exact localizations of the OKs, the most common localizations were mandibular posterior site and mandibular ramus.

Presence of malocclusion: Among 27 cases which were evaluated in means of malocclusion, only one case was reported without any malocclusion and 26 cases were reported with malocclusion.

Unilocular/multilocular distribution: Among 30 cases which were evaluated in means of unilocular/multilocular morphology, 20 OKs had unilocular radiographic appearance.

Bimaxillary/unimaxillary distribution: Among 56 cases which were evaluated in means of bimaxillary/unimaxillary distribution. There were 28 cases with bimaxillary distribution and also 28 cases with unimaxillary distribution.

Presence of a neighboring impacted tooth/teeth: Among 25 cases which reported a presence of neighboring impacted tooth/teeth, only 1 case had an OK without any neighboring impacted tooth and 24 cases were reported with a neighboring impacted tooth.

Imaging modality: Among 91 cases, 30 cases were evaluated with CT/CBCT, 3 cases were evaluated with both CT and MRI, and 51 cases were evaluated with OPG. OPG was the most common imaging methods followed by CT/CBCT.

Presence of genetic inheritance: 19 cases were reported to be have genetic inheritance and 9 cases were reported to be free of any genetic inheritances.

Presence of cleft palate: Only 3 cases were reported with the presence of a cleft palate.

Presence of frontal bossing: Considered as one of the minor criteria of NBCCS, among 48 cases that reported the presence/absence of a frontal bossing, 14 cases reported the absence and 34 cases reported the presence of a frontal bossing.

Presence of hypertelorism: 12 cases were reported to have hypertelorism while 18 cases were reported to no hypertelorism.

Presence of maxillary sinus involvement: 16 cases were reported to have OKs which caused expansion or had a contact with the maxillary sinus while 4 cases were reported to have OKs which has no sinus involvements.

Presence of falx cerebri calcification: Considered as one of the important criteria of NBCCS, 7 cases were reported without falx cerebri calcifications and 56 cases were reported with falx cerebri.

Presence of bifid ribs: Rib anomalies are considered as one of the important criteria of NBCCS; however 15 cases were reported without bifid ribs and 33 cases were reported with bifid ribs.

4. Discussion

OKs are one of the main features of the patients with NBCCS and it was found that all cases of NBCCS had at least 1 OK in the jaws. Evans et al. and Kimonis et al. established the diagnostic criteria for the NBCCS in 1973 and according to their classification, presence of 2 major or 1 major and 2 minor criteria is necessary for the confirmation of BCNS (Evans et al., 1991, Kimonis et al., 1997). Following the modifications after the 1st International Colloquium of NBCCS criteria, presence of rib anomalies is changed as minor criterion and presence of medulloblastoma is changed as major criterion (Kimonis et al., 1997).

The major criteria for NBCCS were:

- 2 or more BCCs or one BCC before 20 years
- Presence of Odontogenic Keratocyst
- >3 cutaneous palmar or plantar pits
- 1st degree relative with NBCC.
- Presence of a medulloblastoma

The minor criteria for NBCCS were:

- Presence of macrocephaly following the height adjustment
- Presence of congenital orofacial defect such as frontal bossing, cleft palate and hypertelorism
- Presence of skeletal abnormalities such as syndactyly, pectus deformity or scapula defects
- Presence of a radiological abnormality such as fusion of the vertebras, hemivertebras, bridging of Sella turcica and morphological defects of the hands and feet.
- Presence of an ovarian fibroma
- Presence of bifid or fused ribs

In our review with 5 additional cases of us (Figs. 1-5), we realized that there is a lack of standardization in case reports and case series which complicates the possibility to draw conclusions and interpret the data of OKs of NBCCS patients. Among 91 case reports, 28 of them specified the number of OKs (30.76%), 53 of them noted the localization of OKs (58.24%), 12 of them specified the diameters of OKs (13.18%), 27 of them specified the presence of a malocclusion (29.67%), 28 of them specified the unilocular/multilocular appearance of OKs (30.76%), 25 of them specified the presence of an impacted tooth that is related to the lesion (27.47%), 59 of them specified whether a 3D or 2D imaging modality was used or not (64.83%), 28 of them specified the presence/absence of a genetical inheritance (30.76%), 3 of them specified the presence/absence of a cleft palate (3.29%), 56 of them specified the bimaxillary / unimaxillary involvement of OKs (61.53%), 48 of them specified the presence/absence of a frontal bossing (%52.74), 30 of them specified the presence/absence

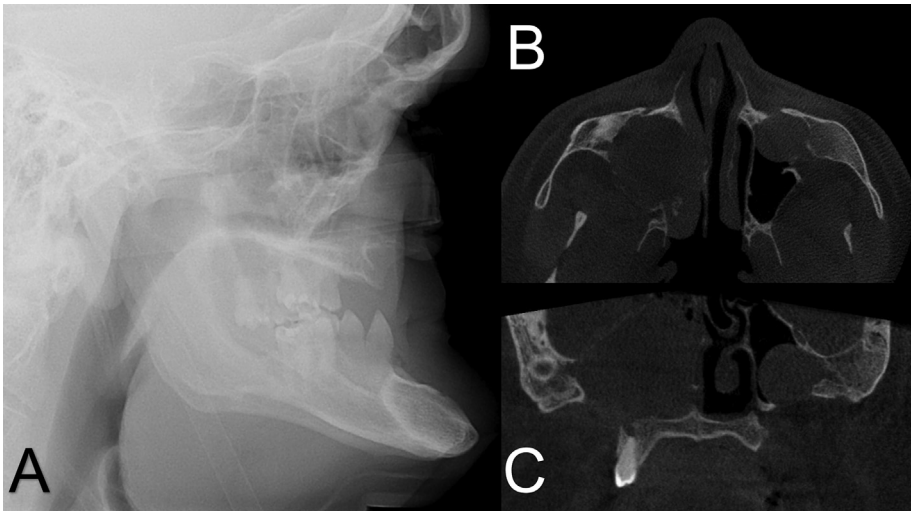

Fig. 1 Lateral skull radiograph (A), CBCT axial slice (B) and CBCT coronal slice (C) of a patient with NBCCS. Note the Class III malocclusion and bilateral OKs that are localized bilaterally at maxillary sinuses.

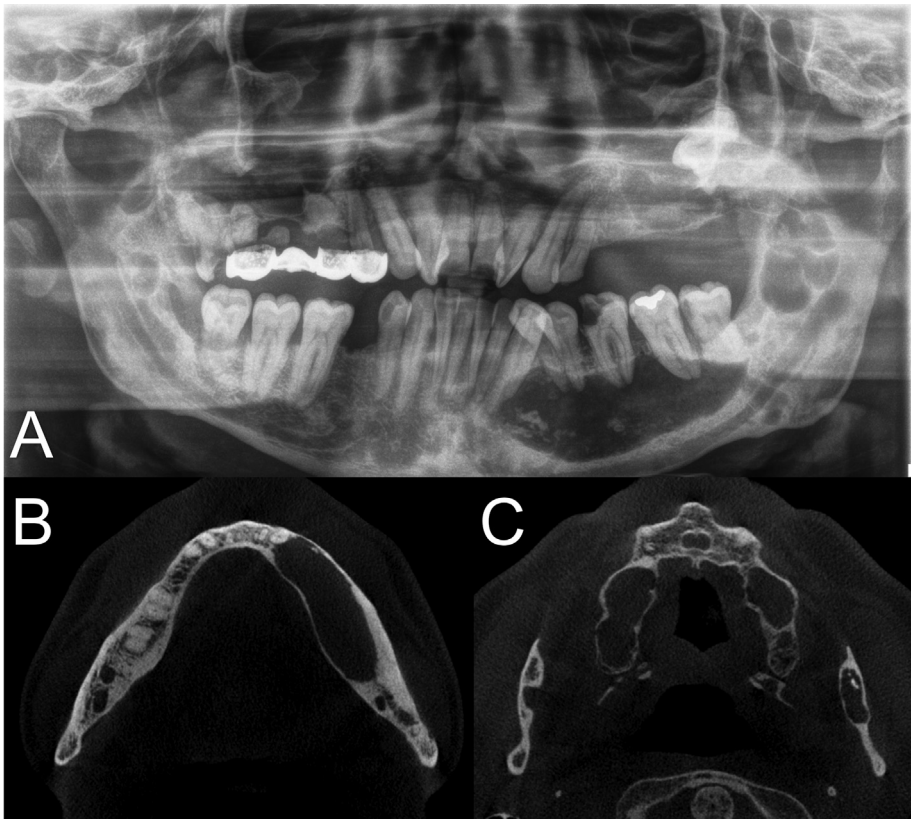

Fig. 2 OPG (A), CBCT axial slice (B,C) of a patient with NBCCS. Note the non-expansive cystic lesions at the CBCT slices and the maxillary left third molar that is impacted in the maxillary sinus due to a OK.

of hypertelorism (32.96%), 20 of them specified the whether the OKs had a maxillary sinus involvement (21.97%), 63 of them specified the presence/absence of falx cerebri calcification (69.23%), 48 of them specified the presence/absence of a bifid rib (52.74%).

While 53 of the case reports, noted the localization of OKs, most of those papers did not specify the exact region of OKs. As it is seen on Supplemental Table 1, some authors described the localization of OKs (Table 1) as just "mandible" or "maxilla". Moreover, most of the parameters that are written above is not present in more than half of the case reports and case series, it is not appropriate to do statistical analysis as the results will be biased. Some studies solely concentrated to the histopathological, radiological or genetic features of the

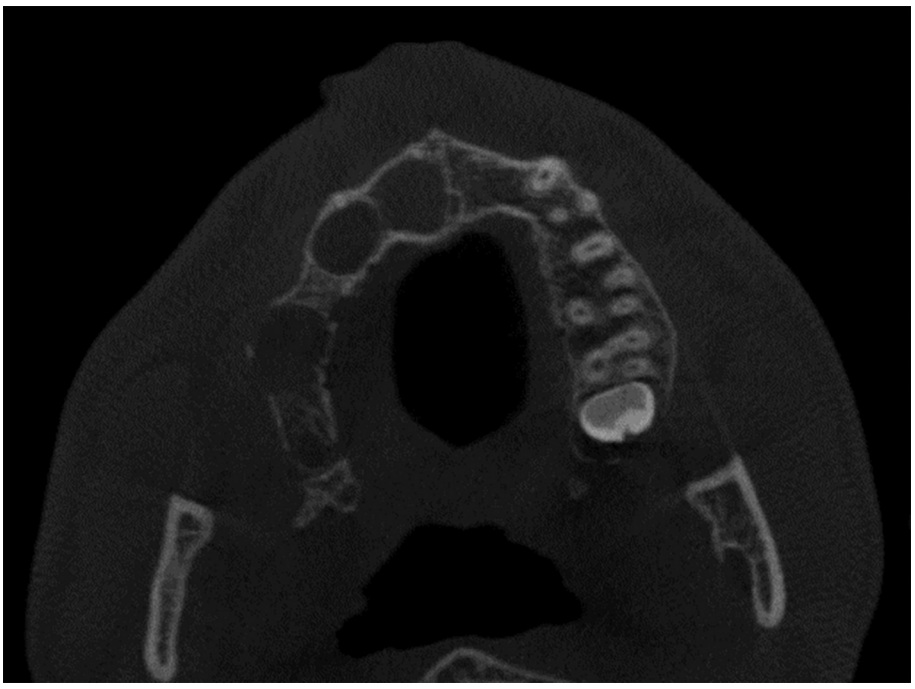

Fig. 3 CBCT axial slice of a patient with NBCCS. Note 3 lesions that are localized at the same quadrant that did not cause significant expansion.

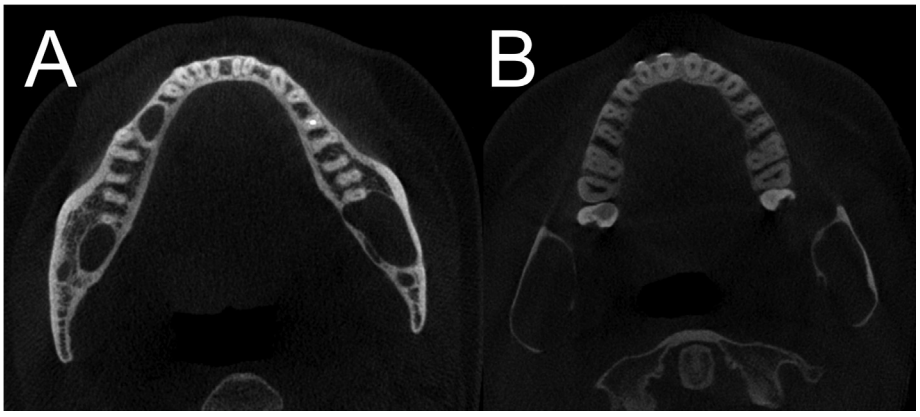

Fig. 4 CBCT axial slices of a patient with NBCSS. Note the non-expansive lesions at the body of the mandible and bilateral expansive lesions at the left and right ascending ramus of the mandible.

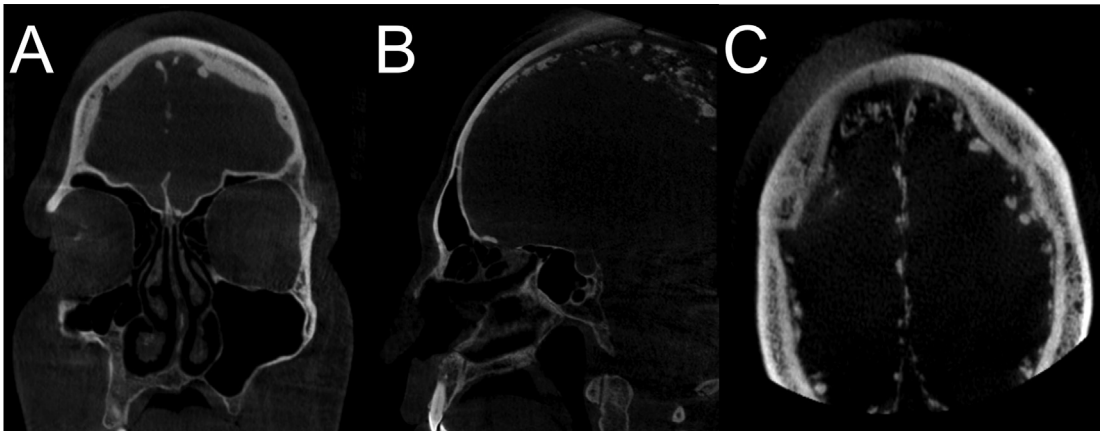

Fig. 5 CBCT coronal (A), sagittal (B), axial (C) slices of a patient with NBCCS. Note the falx cerebri calcifications at all slices.

NBCCS patient's and only 13.18% of the OKs were evaluated in means of diameters; hence, we could not discuss the potential sizes of OKs in those patients.

Although OKs which extended to the processus condylaris were reported in the literature none of the articles reported any TMJ disorder that can be related to the presence of OKs (Ferrillo et al., 2022, Minervini et al., 2022, Minervini et al., 2022, Minervini et al., 2022).

Despite all limitations for a fair discussion; we would like to state that among 59 cases that specified whether a 3D or 2D imaging modality was used, 29 cases were only interpreted with 2D data which should be avoided in OK evaluation. According to the World Health Organization's Classification of Head and Neck Tumours Book which was published in 2017, OKs in NBCCS has a higher chance to have small satellite cystic lesions which increase their recurrence possibility post-operatively, thus, a thorough clinical and 3D radiographic evaluation should be performed both to NBCCS patients and non-syndromic OK patients to avoid any recurrence. Last but not least, 24 out of 25 cases had a neighboring impacted tooth/teeth around the OKs.

5. Conclusion

NBCCS is a syndrome which is characterized by the presence of multiple OKs that can be diagnosed in the early stages of life. The diagnosis of OKs is crucial since they are the most common early finding of the NBCCS and the initial treatment generally relies on them. In this review with additional cases, we aimed to interpret the features of OKs in NBCCS patients; however, it was found out that the lack of standardization in case reporting is a major limitation. Majority of the cases were examined solely by clinical examination and OPG which might cause misdiagnosis for the early OKs as OKs are generally non-expansive lesions that do not cause symptoms. Clinicians must remember that CBCT is precise in examining initial intraosseous lesions with its superior voxel isotropy and spatial resolution. The high recurrence rates of OKs should be reminded all the time and 3D evaluation of OKs should be done in order to provide the optimum treatment.

6. Data availability statement

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The data are not publicly available due to privacy/ethical restrictions.

7. Ethics approval statement

This study was approved by the Near East University Ethical Committee.

Informed consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients for being included in the study.

9. Author contribution statement

G.Ü., G.M. and M.C. designed the work and acquired the data. R.A.A.A., M.R.A.H, A.A.K, and B.K. were responsible of the data analysis. G.Ü. and M.C. drafted the work and R.A.A.A and M.R.A.H contributed to the critical revision of article. All authors approved the article with an online meeting. No funding was received. All authors agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sdentj.2023.05.023.

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