Case Report

Studying the multiple faces of nevoid basal-cell carcinoma syndrome: A case series

Shikha Saxena, Krishna Sireesha Sundaragiri, Akshay Bhargava, Bharat Sankhla

Department of Oral Pathology and Microbiology, RUHS College of Dental Sciences (Government Dental College and Hospital), Jaipur, Rajasthan, India

Abstract

Nevoid basal-cell carcinoma syndrome (NBCCS) or Gorlin–Goltz syndrome is an autosomal dominant-inherited condition that exhibits high penetrance and variable expressivity; however, this disorder can arise spontaneously. In 1960, Gorlin and Goltz described the syndrome as a condition, comprising the principle triad of multiple basal cell carcinoma, odontogenic keratocysts, and skeletal anomalies. The diagnostic findings of NBCCS in four patients were studied and compared with other reports in the Indian population. Early diagnosis of this syndrome is important for counseling of patients to prevent the life-long complications of this syndrome which includes the malignancy, oro-maxillofacial deformation, and destruction; this may be reduced if the diagnosis and treatment are made feasible at the earliest.

Keywords: Abnormalities, basal cell nevus syndrome, India, multiple, odontogenic cysts

Address for correspondence: Dr. Shikha Saxena, Department of Oral Pathology and Microbiology, RUHS College of Dental Sciences (Government Dental College and Hospital), Jaipur - 302 015, Rajasthan, India.
E-mail: drshikhasaxena29@gmail.com

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INTRODUCTION

Nevoid basal-cell carcinoma syndrome (NBCCS) is a rare inherited autosomal-dominant disorder. It was first described by Gorlin and Goltz in their article "Multiple nevoid basal-cell epithelioma, jaw cysts, and bifid rib. A syndrome," published in the *New England Journal of Medicine* in 1960.[1] Kimonis *et al*., (1997) in their study of 105 patients used the modified diagnostic criteria by Rayner *et al*., which also included calcification of falx cerebri or palmer and planter pits.[2]

This syndrome has numerous names as basal cell nevus syndrome (BCNS), multiple NBCCS, multiple basal cell carcinoma (BCC) syndrome, multiple basalioma syndrome, jaw cyst basal cell tumor-skeletal anomalies syndrome, fifth phacomatosis, hereditary cutaneomandibular polyoncosis, and epitheliomatose multiple generalisee.[3] The existence of this syndrome dates back to dynastic Egyptian times. Although the prevalence of this syndrome varies with different ethnic groups, it is estimated to be 1 in 57,000–1 in 164,000.[4] However, in India, only a few cases of NBCCs have been reported.

There is no specific laboratory test to diagnose NBCCS, and the diagnosis is made clinically using the specific criteria as defined by Evans *et al*., 1993; Shanley *et al*., 1994; Kimonis *et al*., 1997; and Kimonis *et al*., 2004. Recently, the diagnostic criteria were suggested by the First International Colloquium on BCNS. It was decided that a suspected diagnosis of BCNS/NBCCS could be reasonably considered based

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on the findings of less stringent criteria of: (i) one major criterion and molecular confirmation, (ii) two major criteria, or (iii) one major and two minor criteria.[5]

NBCCS is inherited as an autosomal dominant trait with a high level of penetrance and variable expression, which can manifest itself spontaneously. The mutations in tumor-suppressor gene called Patched (PTCH 1), located in the 9q22.3–q31 chromosome, has been identified as the cause of this syndrome. The oncogenic potential in NBCCS is explained by Knudson's oncogenic theory or 2-hit hypothesis, which states that normal cells require 2 mutagenic hits to produce a cancer. Patients with NBCCS have a germ line defect in 1 of the 2 copies of the patched gene, which is insufficient to cause cancer. If a second injury or if loss of the normal remaining allele occurs at the same locus (the second hit), the cell may become malignant. This explains why patients suffering from NBCCS show an important variability in their phenotype.[6]

The purpose of this present article is to describe, in detail, the clinical, radiological and histopathological findings in four cases of NBCCS from North India diagnosed in our department, to discuss the role of gene mutation analysis and diagnostic criteria in multiple syndromic odontogenic keratocysts (OKCs).

CASE REPORT

We report a series of four cases of syndromic multiple OKCs reported to the Department of Oral Medicine, RUHS College of Dental Sciences, Jaipur, India. Written patients' consent was obtained for history, biopsy, and subsequent surgery. The diagnostic protocol suggested by Lo Muzio was followed [Table 1].[3]

Any relevant past history or family history of cysts/tumors was carefully noted for each patient. After extraoral and intraoral clinical examinations, orthopantomogram (OPG), computed tomography (CT), and radiological evaluation of skull bones, chest, maxilla-mandible, spine were carried out for all patients. Examination for palmar/planter pits and measurement for head circumference and interpapillary distance was done in all patients. The patients were referred to dermatology (for cutaneous abnormalities), neurology (cranial abnormalities), ophthalmology (for ocular abnormalities), cardiology, surgery, and ear, nose, and throat departments for a multisystem evaluation.

The processing and histopathological examination of each biopsy specimen was done in the department of oral pathology.

Table 1: Diagnostic protocols in nevoid basal cell carcinoma syndrome[3]

Family history
Past medical and dental history
Clinical examinations
Oral
Skin
Central nervous system
Head circumference
Interpupillary distance
Eyes
Genitourinary system
Cardiovascular system
Respiratory system
Skeletal system
Genetic testing
X-ray
Chest
AP and lateral skull
Panoramic radiograph
Cervical and thoracic spine - AP and lateral
Hands (for pseudocysts)
Pelvic (female)
Ovarian ultrasound (female) for ovarian fibroma
Echocardiogram (children) for cardiac fibroma

The diagnosis of NBCCS was made based on the presence of major and minor criteria suggested by the First International Colloquium on BCNS [Table 2].[5,7] The first-degree relatives of all patients (parents, offspring, and siblings) were called for the oral clinical examination and radiological examination as per the diagnostic protocol to rule out undiagnosed and asymptomatic NBCCS. The details of clinical and radiological manifestations of NBCCS in each case are summarized in Tables 3 and 4, respectively.

A total of 4 cases comprising 2 male patients and 2 female patients in the age range of 9–33 years are presented. None of the cases had any first-degree relatives with minor or major criteria of NBCCS.

First case is a 9-year-old girl, who complained of retained deciduous teeth with swelling and discharge on the left maxillary anterior region. Radiograph revealed multiple cystic lesion (one maxillary and one mandibular), which were diagnosed with OKCs. Further clinical examination revealed palmar plantar pits, hypertelorism, rib anomalies, dermal nodules, and flattened nasal ridge. Thus, the diagnosis of NBCC was made [Figure 1].

Second case presented with synchronous multiple OKC[4] along with palmar, plantar pits, falx cerebral calcification, rib anomalies, and coarse facies with hypertelorism. The patient also showed the feature of kyphoscoliosis [Figure 2].

Third and fourth case presented with synchronous multiple OKCs, palmar pits, fused eyebrows, coarse facies, fused eyebrows, and flattened nasal bridges. Third case

presented with brown pigmented patch on the left side of the face [Figure 3]. Fourth case presented with elongated phalanges [Figure 4].

The most common symptom in all cases was the presence of intraoral and extraoral swelling. The duration of the swellings ranged from 1 to 18 months. All the cases had multiple cystic lesions in the jaws as seen in OPG. The number of cysts ranged from 2 to 5 per patient, the most common site being the mandibular retromolar region. Tables 3 and 4 list the clinical and radiological details of all the patients.

The CT examination supplemented the conventional radiographic findings and was helpful in the preoperative assessment of size and extent of lesions, especially those involving the maxillary antrum. They also showed perforation of cortices and additional small cysts not seen on OPG as in case 5 where maxillary cyst in relation to left third molar was seen in CT.

All the biopsied cysts were reported as OKCs [Figure 5]. All the patients then underwent enucleation of the smaller OKCs and the larger OKCs were first marsupialized and subsequently enucleated followed by aggressive curettage and application of Carnoy solution. There has been no recurrence in healed lesions, and no new lesions have been detected in any of the cases in a follow-up ranging from 9 to 18 months.

Comparing the findings of the present case series with other reports in the Indian literature, none of our patients had BCCs, syndactyly or polydactyly, pectus deformity, bridging of sella turcica as opposed to these findings in some earlier reports in the Indian population. As all the patients reported in this series were from Western India, this suggests wide variation in syndrome manifestations within the same ethnic and racial population. Cleft lip and palate had been reported in only two Indian patients with NBCCS previously. The features such as palmar/plantar pits, bifid/fused ribs, calcification of falx cerebri, frontal bossing, fused eyebrows, and hypertelorism were frequently seen.

On comparing the diagnostic findings of our case series with that of Lata *et al*.[8] who studied case series in Northern Indian population, multiple OKC was observed in 100% cases in both the studies. We observed palmar and plantar pits in 100% of the cases, while Lata *et al*. also observed it in 80% cases. Ectopic calcification of falx cerebri in Lata *et al*. case series was reported as 60% while we observed it in

Table 2: Diagnostic criteria for nevoid basal-cell carcinoma syndrome based on the consensus statement from the first international colloquium on nevoid basal-cell carcinoma syndrome[7]

Diagnostic criteria for NBCCS
Major criteria
BCC before 20 years old or excessive numbers of BCC out of proportion to prior sun exposure and skin type
OKCs of the jaw before 20 years of age
Palmar or plantar pitting
Lamellar calcification of the falx cerebri
MED
First-degree relative with NBCCS
Minor criteria
Rib anomalies
Skeletal malformations and radiologic changes (i.e., vertebral anomalies, kyphoscoliosis, short fourth metacarpals, and postaxial polydactyly)
Macrocephaly
Cleft lip/palate
Ovarian/cardiac fibroma
Lymphomesentric cysts
Ocular abnormalities (i.e., strabismus, hypertelorism, congenital cataracts, glaucoma, and coloboma)

BCC: Basal-cell carcinoma, OKC: Odontogenic keratocysts, NBCCS: Nevoid basal-cell carcinoma syndrome, MED: Medulloblastoma

Table 3: Clinical and radiological findings in the present case series of Indian patients with nevoid basal cell carcinoma syndrome

Case number	Age/sex	Major criteria	Minor criteria	Additional features
1	9/female	Synchronous multiple OKC (2) Palmar pits Planter pits	Bifid rib Hypertelorism	Frontal bossing Flattened nasal bridge Dermal nodules Retained deciduous maxillary incisors
2	26/male	Synchronous multiple OKC (4) Palmar pits Planter pits Falx cerebral calcification	Hypertelorism Bifid rib Coarse facies	Frontal bossing Depressed nasal bridge Kyphoscoliosis Nevus on the face
3	33/male	Synchronous multiple OKC (5) Palmar pits	Hypertelorism Coarse facies	Fused eyebrows Flattened nasal bridge Malocclusion Brown-pigmented patch on the left side of face below eyes
4	28/female	Synchronous multiple OKC (3) Palmar pits	Hypertelorism	Fused eyebrows Flattened nasal bridge Malocclusion Elongated phalanges

OKC: Odontogenic keratocysts

Table 4: Relevant patient data with radiographic findings in the present case series (patient 1 to patient 4)

Case number	Duration of lesion	OKC	Site	Radiographic features	Other findings	Recurrence	Follow up
1	18 months	2	Left anterior maxilla Anterior mandible	Unilocular radiolucency extending from 61 to 24 Unilocular radiolucency extending from 75 to 85	Root resorption of 61, 62, 63, 73, 74, 75 Impacted 21, 22, 23, 33, 34, 35, 42, 43, 44, 45	-	12 months
2	3 months	4	Right posterior maxilla Left posterior maxilla in relation to 28 Left anterior mandible Right angle and ramus of mandible	Unilocular radiolucency extending from 16 to 18 Unilocular radiolucency irt 28 Multilocular radiolucency extending from mesial root of 36 to 44 Multilocular radiolucency extending from 45 to ramus with impacted 48	Missing 18, 22, 23 Impacted 28, 33, 48	-	9 months
3	1 month	5	Left anterior maxilla Left posterior maxilla Left body and ramus of mandible Right anterior mandible Right ramus of mandible	Unilocular radiolucent lesion Left anterior maxilla with impacted 23 Left posterior maxilla with impacted 28 extending in maxillary sinus Left body and ramus of mandible with impacted 38 Right anterior mandible with impacted 43 Right ramus of mandible	Impacted 23, 28, 32, 33, 38, 43 Over retained 63, 72, 73 Missing 44, 45, 48	-	18 months
4	2 months	3	Right posterior maxilla Left posterior maxilla Right angle and ramus of mandible	Unilocular radiolucent lesion Right posterior maxilla with scalloped margins irt roots of 16, 17 Left posterior maxilla with scalloped margins irt roots of 26, 27 Right posterior mandible extending from roots of 44 to ramus	Missing 18, 28, 37	-	12 months

OKC: Odontogenic keratocysts

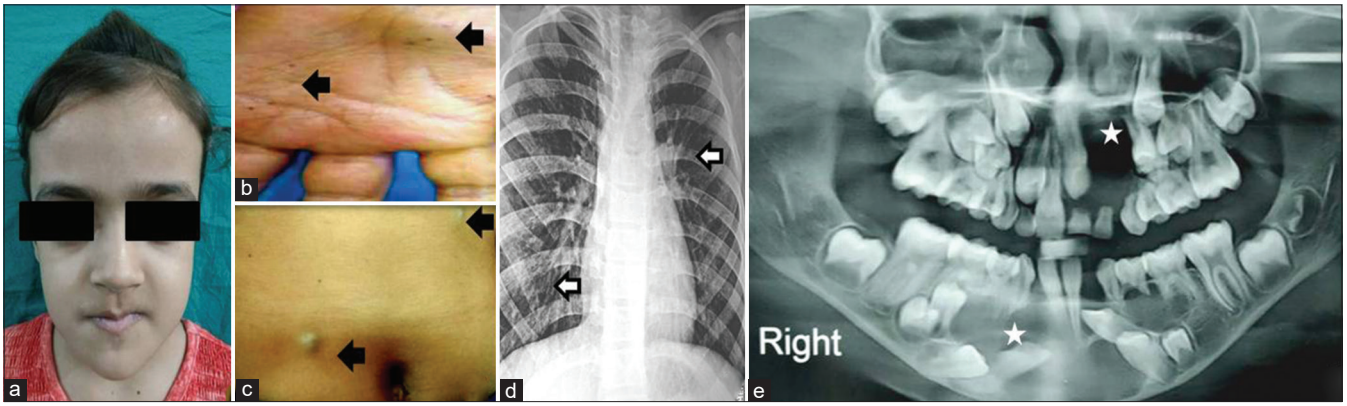

Figure 1: Case 1 is a 9-year-old girl showing (a) extraoral clinical photographs with hypertelorism (b) Palmar pits (c) Dermal nodules (d) Bifid rib (e) orthopantomogram revealing multiple radiolucent lesions (white asterisk)

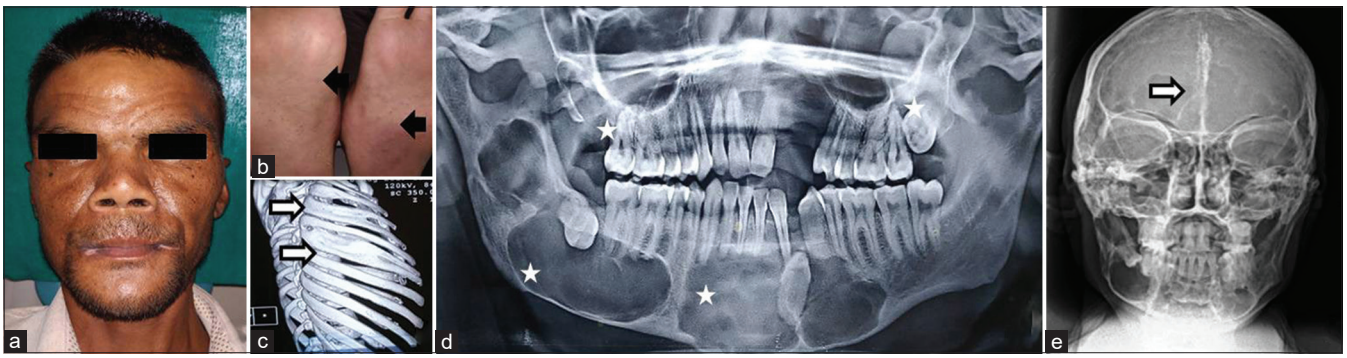

Figure 2: Case 2 is of a 26-year-old male showing (a) extraoral clinical photographs with hypertelorism and depressed nasal bridge, multiple nevus, (b) plantar pits, (c) bifid ribs (d) orthopantomogram with multiple radiolucent lesions (white asterisk)

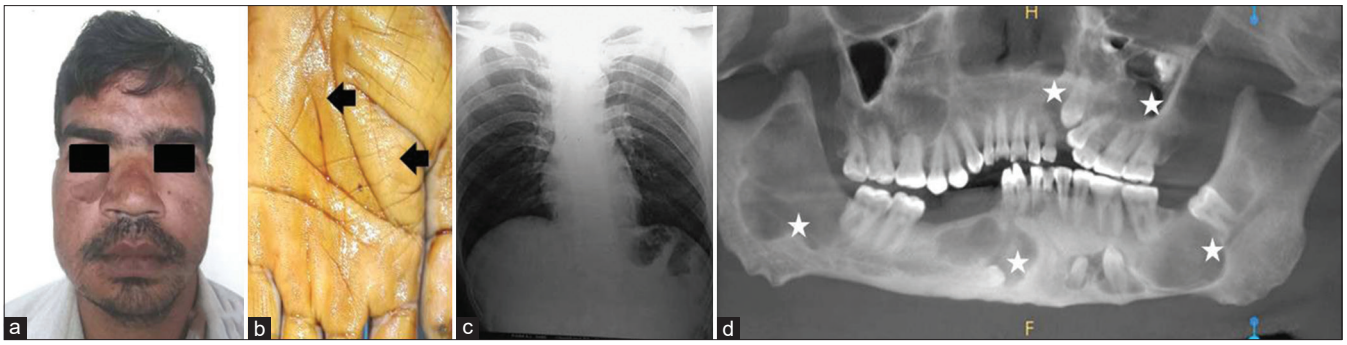

Figure 3: Case 3 is of a 33-year-old male showing (a) extraoral clinical photographs with hypertelorism, depressed nasal bridge, multiple nevus (b) plantar pits (c) no rib anomaly (d) orthopantomogram with multiple radiolucent lesions (white asterisk)

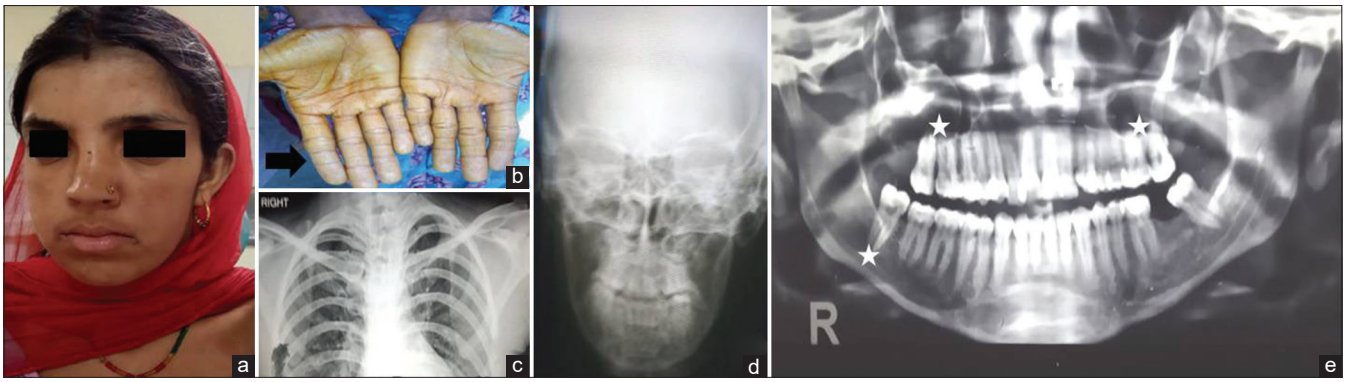

Figure 4: Case 4 is of a 28-year-old female showing (a) extraoral clinical photograph (b) palmar pits and elongated phalanges (c) no rib anomaly (d) PA skull X-ray (e) orthopantomogram with multiple radiolucent lesions (white asterisk)

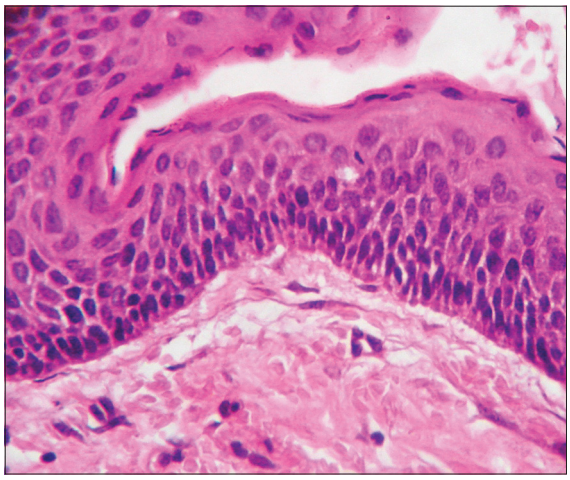

Figure 5: H and E stained section of odontogenic keratocyst (×400)

25% cases. Rib anomalies were found to be in 50% patients. Only one of our patients (25%) showed kyphoscoliosis. Hypertelorism in their study was 80%, whereas in our study is 100%. Frontal bossing was seen in 50% cases. Lata *et al*. observed ovarian fibroma in 20% patients. Our study included two female patients, but none of them showed any evidence of ovarian fibroma.

On comparison of diagnostic findings of this syndrome in Indian patients with other parts of the world, the incidence of bifid or fused ribs was found to be higher in Indian patients. Medulloblastoma (MED) has not been found in any Indian patient in contrast to other studies conducted worldwide. Multiple unerupted teeth were present in all the cases.

All the four patients have been kept on regular periodic follow-ups, and no recurrence of OKC's or new syndromic manifestations have been found in any patient until date.

DISCUSSION

NBCCS is a rare inherited multisystem disorder that is a result of mutations in the PTCH gene. Many different signs and symptoms may be associated with NBCCS [Table 5].[3]

Multiple OKCs are the most consistent and representative signs of NBCCS in the first and second decades of life. OKCs account for 10%–20% of odontogenic cysts and are the third most common cyst of the jaws,[9] but the simultaneous occurrence of multiple cysts in both the maxilla and mandible of a patient is rare.[7] About 10% of patients have multiple OKCs (either metachronous or synchronous), and half of these patients have NBCCS.[9] Other rarely reported syndromes with which multiple OKCs

Table 5: Disorders reported in nevoid basal carcinoma syndrome[3]

Skin	Central nervous system	Stomatologic system	Ocular system
Cutaneous dyskeratosis Erythematous-squamous spots degenerating in NBCC Nodular or patch lesions Palmo-plantar pits Multiple basal cell carcinomas Benign dermal cysts Multiple nevi	Ectopic calcification Falx cerebri Tentorium cerebelli Spotted meningeal calcification Complete or partial bony bridging of the sella turcica Meningioma Multiform glioblastoma Moderate mental retardation MED Grand mal Congenital hydrocephalus Huntington's chorea	Odontogenic keratocysts Dental ectopy, heterotopy Impacted teeth internal strabismus Dental agenesis malocclusion Maxillary fibrosarcoma Ameloblastoma Odontogenic myxoma Spindle cell carcinoma Cleft palate and lip Mandibular prognathism High-arched palate Squamous cell carcinoma Skeletal open bite Idiopathic pseudocyst Hyperplasia of the mandibular coronoid processes	Cataract, coloboma, microphthalmia Chalazions Rotatory nistagmus Exophthalmus Hypertelorism Congenital blindness
Musculo-skeletal system	**Cardio-vascular system**	**Genito-urinary system**	**Auditory system**
Congenital skeletal anomalies Bifid, fused, splayed, or missing ribs bifid wedges fused vertebra Scoliosis Frontal, temporal and parietal bossing Polydactyly Sindactyly Short fourth metarcapal Sprengel shoulder Polyostotic bone cysts	Cardiac fibroma (interventricular septum) Absent internal carotid artery	Males: Middle ear anomalies hypogonadism Cryptorchidism Females: Ovarian calcifications Ovarian cysts Ovarian fibroma Hypogonadism	Middle ear anomalies Otosclerosis Conductive Hearing loss Posteriorly angulated ears
Respiratory system	**Gastroenteric system**	**Biochemical findings**	
Bronchogenic cysts Hyaline membrane disease	Linfomesentery cysts Gastric polyps	High levels of CAMP High levels of AP	

MED: Medulloblastoma, NBCC: Nevoid basal cell carcinoma

have been described are orofacial digital syndrome,[10] Ehler-danlos syndrome,[11] Noonan syndrome[12] and Simpson-Golabi-Behmel syndrome.[13]

The OKCs seen in NBCCS are multiple, ranging in number from 1 to 30 with an average of 5, occur at an early age, usually in the first decade of life, and have a higher rate of recurrence. The literature reports wide variation in the incidence of OKCs in NBCCS patients ranging from 62%[14] to 100%.[15] This association has been found to be 100% in our case series. The NBCC cases visiting the dental surgeon will be that with multiple OKC, so stating that 100% cases of NBCC present with multiple OKCs can be an over exaggerated statement leading to an increased prevalence rate of OKC in NBCC.

However, at the same time, multiple OKCs should not be treated as isolated cases. While planning the treatment, all associated characteristics should be taken into consideration. Recognition of the syndrome is important since the jaw cysts by virtue of their continued development in the multiple regions of the mandible and maxilla, pose problems in management.

A multidisciplinary approach (dentists, oral and maxillofacial surgeons, dermatologists and neurologists) is required for the diagnosis and management of this syndrome. In this syndrome, management is about adequate treatment of cysts and removal of tumors.

CONCLUSION

The diagnosis of NBCCS may be difficult because of the variability of expressivity and because of different ages of onset for the different traits of this disorder. Early diagnosis of NBCCS is crucial for the affected children and their families, considering the risk of developing malignancies such as MED and aggressive skin cancers. A negative family history could hamper the early clinical recognition of patients with NBCCS. However, it may be diagnosed during early childhood if the clinician is well aware of clinical signs of the disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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