ORIGINAL ARTICLE

Nevoid basal cell carcinoma syndrome: an analysis of four familial and two sporadic cases

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Abstract:

The nevoid basal cell carcinoma syndrome (NBCCS) is an autosomal dominant disorder with complete penetrance and variable expressivity. It is caused by mutations in the patched gene, mapped to chromosome 9q22.3-q31. Its characteristics include multiple basal cell carcinomas, odontogenic keratocysts, vertebral and rib anomalies, and intracranial calcifications. Here, we describe the features of 4 familial and 2 sporadic cases of the NBCCS.

Keywords: congenital malformations, nevoid basal cell carcinoma syndrome, odontogenic keratocyst, ptch, skeletal anomalies.

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INTRODUCTION

The nevoid basal cell carcinoma syndrome (NBCCS), also known as the Gorlin–Goltz syndrome, was characterized by these authors in 1960, although compatible features were described in mummies in approximately 1000 BC[1]. The first patient they described was a middle-aged woman with macrocephaly, kyphosis, several basal cell carcinomas (BCCs), and jaw cysts; in addition, she wore a prosthetic left eye because of congenital cataract[2]. The NBCCS is inherited as an autosomal dominant disease with complete penetrance and variable expressivity; its prevalence is approximately 1 per 57,000 individuals. It shows no gender preference, and ~50% of the cases represent new mutations in the patched gene (*PTCH*)[1-3]. *PTCH*, the human homolog of the *Drosophila* patched gene, is mapped to chromosome 9q22.3-q31[1]. *PTCH* acts as both a developmental and a tumor-suppressor gene, which is in accordance with the features of congenital malformations and tumors observed in the NBCCS.

The most common clinical findings of the NBCCS are multiple BCCs, odontogenic keratocysts (OKs), and skeletal anomalies (Table 1)[4]. BCCs occur in 80% of the Caucasian patients and 38% of black patients; the mean age of onset is 25 years. The number of BCCs may vary from a few to hundreds, and the most frequently affected sites are the face, back, and chest[1,5]. The histopathology of BCC is similar between ordinary and NBCCS cases. OKs also are found in 80% of the patients, usually when they are approximately 15 years old. The mandible is 3 times more affected than the maxilla, without racial preference[5]. The most common skeletal anomalies are lamellar calcification of the falx cerebri, macrocephaly, rib anomalies such as bifid, synostosed or hypoplastic ribs, kyphosis, and bifid spinous process[1].

Table 1. General findings in th NBCCS[4].

50% or greater frequency
Enlarged occipitofrontal circumference (macrocephaly, frontoparietal bossing)
Mul ple BCCs
OKs of the jaws
Epidermal cysts of the skin
High-arched palate
Palmar and/or plantar pits
Rib anomalies (splayed, fused, partiall missing, bi d, etc.)
Spina bi da occulta of the cervical or thoracic vertebrae
Calci ed falx cerebri
Calci ed diaphragma sellae (bridged sella, fused clinoids)
Hyperpneumati atio of the paranasal sinuses
15–49% frequency
Brain ventricular asymmetry
Calci catio of the tentorium cerebelli and petroclinoid ligament
Calci ed ovarian fib omas
Short fourth metacarpals
Kyphoscoliosis or other vertebral anomalies
Lumbarizatio of the sacrum
Narrow sloping shoulders
Prognathism
Pectus excavatum or carinatum
Pseudocystic l tic lesio of bones (hamartomas)
Strabismus (exotropia)
Syndactyly
Synophrys
14% or less but not random
Medulloblastoma
True ocular hypertelorism
Meningioma
Lymphomesenteric cysts
Cardiac fib omas
Fetal rhabdomyoma
Ovarian fib osarcoma
Marfanoid build
Anosmia
Agenesis of the corpus callosum
Cyst of the septum pellucidum
Cleft li and/or palate
Low-pitched female voice
Polydactyly, postaxial hands or feet
Sprengel deformity of the scapula
Vertebral body fusion
Congenital cataract, glaucoma, coloboma of the iris, retina optic nerve, medullated retinal nerve fib rs
Subcutaneous calci catio s of the skin (possibly underestim ted frequency)
Minor kidney malformatio s
Male hypogonadism
Mental retardatio

Diagnosis of the NBCCS is typically based on 2 major or 1 major and 2 minor criteria, as shown in Table 2[4,5]. The diagnosis may be difficult because of the variable expressivity, as different phenotypes may be observed even within the same family. The age of onset of the different features of the disease is also not uniform; some may occur very late, causing difficulty in diagnosis particularly in children[6,7]. Early diagnosis is important for better clinical management of the syndrome[3]. Treatment depends on the presence of specific anomalies and conditions and involves an interdisciplinary approach, with remarkable emphasis on dental and dermatological follow-up[5].

Table 2. Diagnostic cri eria of the NBCCS[4,5].

Major criteria
1. More than 2 BCCs or one under the age of 20 years
2. OKs of the jaws proven by histology
3. Three or more palmar pits
4. Bilamellar calci catio of the falx cerebri
5. Bi d, fused, or markedly splayed ribs
6. First-degree relati e with the NBCCS
Minor criteria
Any one of the following features:
1. Macrocephaly determined a er adjustment for height
2. Congenital malformatio s such as cleft li or palate, frontal bossing, "coarse face," and moderate or severe hypertelorism
3. Other skeletal abnormali es such as Sprengel deformity, marked pectus deformity, and marked syndactyly
4. Radiological abnormaliti s such as bridging of the sella turcica; vertebral anomalies such as hemivertebrae, fusion or elongatio of the vertebral bodies; modeling defects of the hands and feet; and ame-shaped lucencies of the hands or feet
5. Ovarian fib oma
6. Medulloblastoma

Diagnosis is based on the presence of 2 major or 1 major and 2 minor criteria.

PATIENTS AND METHODS

This study describes the features of 4 families and 2 individuals sporadically affected by the NBCCS.

RESULTS

Family A

Family A included 3 affected members. A 26-year-old white woman (individual 1A) was referred by a dentist because of a sinus tract in the anterior region of the maxilla. According to the medical history, her left ovary had been removed 7 years ago because of cystic lesions. The extraoral examination revealed macrocephaly, frontal and parietal bossing, mild hypertelorism, and a cutaneous lesion suggestive of BCC on the left side of the nose (Figure 1A). The intraoral examination disclosed a partially edentulous mouth and a sinus tract on the anterior region of the maxilla. Radiographically, the maxilla showed absence of both lateral incisors, a periapical lesion associated with the left central incisor, and an impacted left third molar. The mandible presented 3 well-defined radiolucent lesions, 2 of which affected both mandibular rami and the third was associated with an impacted right canine and lateral incisor (Figure 1B). The 3 mandibular radiolucencies were confirmed as OKs and the cutaneous lesion as BCC (Figure 1C). Chest X-ray did not show any abnormality. The anteroposterior and lateral skull radiographs confirmed evident frontal and parietal bossing. Considering the occurrence of multiple OKs, BCC, mild hypertelorism, frontal and parietal bossing, and macrocephaly, she was diagnosed with the NBCCS.

The patient's brother, aged 19 years (individual 2A), also showed frontal bossing. He was very tall (1.92 m) and had a prosthetic left eye because of congenital microphthalmia. Panoramic radiography revealed failure of eruption of the left upper canine and lower third molars, and agenesis of both upper lateral incisors. He also presented a radiolucent mandibular lesion extending from the left third molar to the ascending ramus, which was histologically confirmed as an OK. Skull and chest X-rays showed frontal and parietal bossing, hyperaeration of the frontal sinuses, and bifid ribs (Figure 1D). In addition, clinical examination of his son, a 4-year-old white boy (individual 3A), revealed frontal bossing, syndactyly and oligodactyly of the left hand, and oligodactyly of the right foot (Figure 1E).

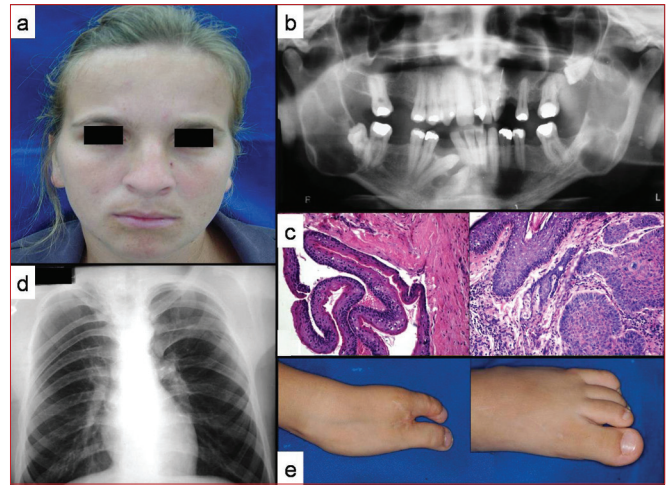

Figure 1. Clinicopathological features of family A. A. Cutaneous lesion on the left side of the nose of individual 1A, diagnosed as BCC. B. Panoramic radiograph revealing 4 well-defined radiolucent lesions in individual 1A; all 3 mandibular lesions were diagnosed as OKs. C. Histopathological features of an OK (right) and a BCC (left) in individual 1A (hematoxylin and eosin stain; magnification, ×200). D. Chest radiograph showing anomalies of the ribs in individual 2A. E. Syndactyly and oligodactyly of the left hand (right) and oligodactyly of the right foot (left) of individual 3A.

Family B

Family B comprised 4 sisters with the NBCCS. Individual 1B, a 20-year-old white woman, presented frontal bossing, mild hypertelorism, sebaceous hyperplasia on the nose, and a lesion suggestive of BCC on the right nasal ala. The intraoral examination disclosed a partially edentulous mouth. Radiographically, an impacted left upper third molar and 2 cystic lesions involving both mandibular rami were seen. On the basis of these clinical and histological characteristics, the patient was diagnosed with the NBCCS.

Individual 2B, a 24-year-old white woman, had mild hypertelorism and palmar pits (Figure 2). Panoramic radiography disclosed impacted third molars and 2 cystic lesions involving both mandibular rami. The lesions were also confirmed histologically as OKs.

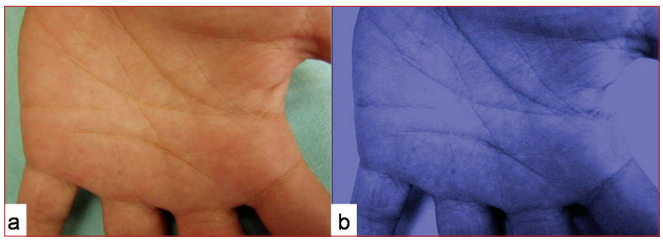

Figure 2. Clinical findings in individual 2B. A. Palmar pits under natural illumination. B. Palmar pits under fluorescent illumination.

Their sister, aged 26 years (individual 3B), had mild hypertelorism, frontal bossing, and palmar pits. Radiographic examination showed impacted upper and lower right third molars and 2 OKs in the mandible.

Individual 4B, a 28-year-old white woman, also had mild hypertelorism, frontal bossing, and palmar pits as well as various facial nevi. She also presented impacted upper third molars bilaterally, the left one showing microdontia, and 2 well-defined bilateral radiolucent lesions in the mandibular angle. The lesions were confirmed as OKs.

Family C

This family included 4 affected members. The mother, a 38-year-old Caucasian (individual 1C), presented 2 radiolucencies in the jaws. The patient reported previous surgical treatment for multiple BCCs of the face. Enlarged frontal and temporoparietal areas, strabismus, and palmoplantar dyskeratosis were observed. Radiographs revealed enlarged maxillary and frontal sinuses and 2 bilateral radiolucencies in the mandible, confirmed histologically as OKs.

Her daughter, a 16 year old (individual 2C), presented facial nevi, kyphoscoliosis, enlarged frontal and temporoparietal regions, auditory pavilion anomalies, hypertelorism, pectus excavatum, malocclusion, and ogival palate. Radiographs revealed 2 cysts bilaterally in the posterior region of the maxilla. The cysts were confirmed to be OKs.

The older son, a 13 year old (individual 3C), presented macrocephaly, hypertelorism, palmoplantar dyskeratosis, malocclusion, an OK in the mandible, and bifid ribs. The second boy, a 9 year old (individual 4C), showed pectus excavatum, enlarged frontal and temporoparietal areas, auditory pavilion anomalies, hypertelorism, malocclusion, and a single mandibular radiolucency confirmed histologically as an OK. Chest X-ray also revealed bifid and anomalous vertebrae.

Family D

The affected members of this family were a woman and her son. The proband, a 17-year-old white boy (individual 1D), was referred because of mandibular cysts. He had tall stature, macrocephaly, frontal and parietal bossing, hypertelorism, and a lesion suggestive of BCC on the left malar skin. Radiographs revealed hyperaeration of the frontal sinus, calcification of the falx cerebri, rib anomalies, and impacted left upper second and third molars. Two cysts were located in the mandible, one involving the right angle and the other between the left canine and the first premolar. Both cysts were revealed to be OKs and the malar lesion was confirmed as a BCC.

The patient's mother, aged 42 years (individual 2D), reported excision of 237 histologically proven BCCs: 133 of the thorax, 62 of the head and neck, and 42 of the limbs. The patient also reported removal of the left ovary. Radiographs showed bone defects in the mandible because of previous surgeries to remove OKs. In addition, the left upper second and third molars were impacted.

Sporadic case I

A 17-year-old white girl (individual S1) presented with a mandibular fistula. The extraoral examination revealed a prominent forehead, macrocephaly, and slight progmatism. Intraorally, the patient had several retained and incorrectly positioned teeth, missing upper central incisors, and a purulent secretion in the mandibular left molar region. Radiographic examination disclosed cysts in the maxilla involving the left and right premolar and molar regions. In addition, a remarkably large cystic lesion involved the left side of the mandible (Figure 3). Chest X-ray revealed rib anomalies. The patient was followed for 7 years. The retained teeth were extracted, the OKs enucleated, and several BCCs that appeared were removed.

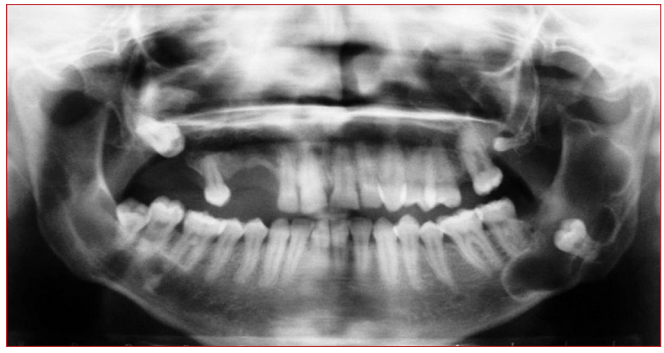

Figure 3. Radiographic findings in sporadic case I. Cysts involving the maxilla and mandible bilaterally were observed. Notice the remarkable large cystic lesion in the left side of the mandible.

Sporadic case II

A 19-year-old white boy (individual S2) was referred to a dental service because of severe malocclusion. The medical history revealed treatment for cleft lip and palate in infancy. Physical examination showed macrocephaly, frontal bossing, and hypertelorism. Intraorally, the patient had full cross bite and absence of some teeth. Radiogra-

phs disclosed a large cyst in the left side of the mandible, which proved to be an OK. Bifid ribs were also detected through chest X-rays.

DISCUSSION

The NBCCS is an autosomal dominant disorder characterized by both cancer predisposition and developmental anomalies. Mutated *PTCH* encodes a transmembrane glycoprotein that acts as an antagonist to members of the Hedgehog family. These intercellular signaling molecules are involved in the formation of multiple embryonic structures and control of cell proliferation[8,9]. The features of the NBCCS could arise through a two-hit mechanism, where developmental abnormalities are heterozygous for *PTCH* whereas tumors, such as BCC, result from loss of heterozygosity[9].

The clinical diagnosis of the syndrome is based on the criteria defined by Kimonis et al.[5]. A hallmark of this syndrome is the variability in expression, with different phenotypes observed even within the same family, as illustrated by the cases presented here. In addition, because the onset of the different features occurs at diverse ages, the diagnosis may be very difficult, especially in children[6]. Therefore, the NBCCS is usually diagnosed in adulthood, as in the various cases described here. The 4-year-old boy of family A (individual 3A) certainly has the syndrome, but without the family history, this diagnosis would be unlikely.

In family A, some interesting characteristics were observed. First, microphthalmia was observed in the proband's brother. The role of *PTCH* in eye development is well established, and ocular alterations have been described in the NBCCS with a frequency of 15% to 25%[10-12]. Congenital cataract, vitreoretinal anomalies, coloboma, and internal strabismus are among the most common, and microphthalmia is unusual[2]. Other remarkable features were syndactyly and oligodactyly of the left hand and oligodactyly of the right foot of individual 3A. Syndactyly and polydactyly have been described as NBCCS features by many authors[1,6,13]. Nevertheless, as far as we know, this is the first described case of oligodactyly related to the syndrome.

Recently reclassified as keratocystic odontogenic tumor, the OK is a benign, aggressive cystic lesion of the jaws[14]. Favoring the neoplastic nature of OK, various studies showed the expression of bcl-2, p53, p63, and Ki-67[14,15]. OKs have show loss of heterozygosity for *PTCH*, which is also indicative of its neoplastic nature, explaining the close relationship with the NBCCS[3]. Nevertheless, most oral pathologists still prefer the term "OK," as used inon this work. Frequency of OK in NBCCS patients is approximatelyabout 80%[1]. OKs were the most regular findings in the present series, and were observed in almost all the cases described here. They generally are asymptomatic and discovered as incidental radiographic findings, although rarely they may become infected, causing expansion of the jaws and/or fistulization[16].

Other oral alterations include impacted teeth, tooth agenesis, cleft lip and palate, mandibular prognathism, and malocclusion, as observed in our patients. Coronoid process hyperplasia and high-arched palate have also been reported[1,17-19]. Although OKs are considered the main oral hallmark of the NBCCS, dentists should be aware of the other possible alterations, which can help to recognize the syndrome promptly.

BCC, the most important skin feature of the NBCCS, was also common in our patients. It usually occurs at an early age, between puberty and 35 years of age; Caucasians are more affected than are blacks. BCC may vary from few to hundreds, and the sites more commonly involved are the face, neck and thorax[1,5,16]. As sunlight is an important risk factor for BCC, patients with the NBCCS should be advised protection against sun exposure[1,16]. Moreover, dentists can play an important role in recognizing these lesions, particularly on the face, and refer syndromic and nonsyndromic patients to a dermatologist.

CONCLUSION

The management of patients with the NBCCS depends on the anomalies present; consequently, conservative treatments are possible only after early diagnosis. Besides the clinical characteristics, complete genetic evaluation, particularly to detect *PTCH* mutations in children, are important for early diagnosis. In addition, genetic counseling should be considered for patients with a family history of the NBCCS.

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