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CASE REPORT

Nevoid-basal cell carcinoma syndrome: a case report and overview on diagnosis and management

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Abstract Nevoid Basal Cell Carcinoma Syndrome (NBCCS) is a rare condition characterized by varied clinical manifestations like multiple Basal Cell Carcinomas (BCC), multiple Keratocystic Odontogenic Tumours (KCOT), palmar and/or plantar pits and ectopic calcification of the falx cerebri, which are considered as the major criteria for diagnosis. The occurrence of jaw manifestations makes it an important diagnostic problem for oral and maxillofacial surgeons and often clinicians encounter this aspect which finally leads to the diagnosis of this syndrome. This paper reports a case of NBCCS and provides an overview on the diagnosis and management of this enigmatic entity.

Keywords Nevoid basal cell carcinoma syndrome · Gorlin–Goltz syndrome · Keratocystic odontogenic tumour

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Introduction

Nevoid Basal Cell Carcinoma Syndrome (NBCCS), also referred to as Gorlin-Goltz Syndrome, Basal cell nevomatosis, Nevoid Basal Cell Carcinoma Syndrome, is a hereditary condition transmitted as an autosomal dominant trait that exhibits high penetrance and variable expressivity [2,3]. It is characterized by several developmental defects and a predisposition to cancer [4]. Clinical manifestations are extremely varied and include Basal Cell Carcinoma (BCC), Keratocystic Odontogenic Tumour (KCOT), palmar and/or plantar pits and ectopic calcification of the falx cerebri, which are considered as major criteria for diagnosis [3,5].

Gorlin and Goltz defined the condition as a syndrome comprising the principal triad of multiple basal cell nevi, jaw keratocystic odontogenic tumours and skeletal anomalies. A spectrum of other neurological, ophthalmic, endocrine, and genital manifestations are now known to be variables associated with this triad [7].

It is a remarkable lesion for the oral and maxillofacial surgeons who are often the first clinicians involved in the diagnosis of this syndrome.

History

The NBCCS was probably first reported by Jarish in 1894, who published a case of multiple jaw cysts associated with skeletal abnormalities and basal cell naevi [7]. It has been a well recognized entity since Gorlin and Goltz published their paper in 1960 after analyzing 150 cases from the literature [7]. However, it was Howell and Caro (1959) who first associated basal cell nevus with other cutaneous disorders and anomalies [6]. Subsequently the paper by Gorlin et al. in 1963 provided an in-depth study of the syndrome as recognized today.

Tasanen et al. in 1975 could indicate the relative frequencies of the main signs in a limited series of seven cases with multiple keratocysts having 100% occurrence in most cases [7].

Epidemiology

The NBCCS prevalence has been variously estimated from 1 in 57000 [6] to 1 in 164000 [9], but there is now general agreement that the prevalence is about 1 per 60,000 live births [10]. The syndrome occurs with equal frequency in both sexes and arises in all ethnic groups, but most reports have been in whites [6,11]. It has both a sporadic and a familial incidence [12]. Although detected in very young patients, they are usually expressed between the ages of 17 and 35 years [4].

Genetics

This disorder has an autosomal dominant mode of inheritance, but can arise spontaneously or can have a variable phenotypic penetration. The causative gene of NBCCS is recognized on long arm of chromosome 9q (22.3–q31) and has no apparent heterogeneity [13].

The principal causative mutations occur in the human homologue of the drosophila 'patched' gene (PTCH), which is part of the Hedgehog (HH) – signaling pathway that is important in determining embryonic patterning and cell fate in the developing embryo [5]. This gene mainly function as a tumour suppressor gene as well as having other roles [14,15].

The mutations in this gene result in loss of control of several genes known to play a role in both organogenesis and carcinogenesis and also have an essential role in odontogenesis [16]. There is evidence that mutations in PTCH accounts

for the development of KCOT's as well as explain both congenital anomalies and cancer predisposition seen in NBCCS.

Clinical features

NBCCS is an ecto-mesodermal polydysplasia with numerous manifestations that affect multiple organs. The NBCCS is characterized by cutaneous anomalies, dentofacial anomalies, skeletal anomalies, ophthalmologic anomalies, neurological anomalies and sexual abnormalities that are summarized in Table 1.

Diagnostic criteria

Diagnosis of NBCCS may be difficult because of variability of expressivity and because of different ages of onset for the different traits of this disorder [4]. The diagnosis is however made clinically by using the major criteria suggested by Evans et al. [17] and Kimonis et al. [18] NBCCS can be considered, if the clinician finds any 2 major and 1 minor criteria or 1 major and 3 minor criteria in the suspected patients (Table 2 and 3). Additionally, recently laboratory testing for PTCH gene in the diagnosis of this syndrome is gaining ground. Other laboratory findings include high levels of cyclic adenosine monophosphate and alkaline phosphatase and impaired phosphate diuresis upon parathormone challenge [5,12].

Average age of diagnosis of NBCCS is 13 years while average age for detection of basal cell carcinoma is 20 years [4,17]. The clinical expression of the syndrome varies among individuals within the same family and even more among different families. Multiple KCOT's should alert the dentist to the possibility of this syndrome and trigger a thorough investigation [12,18–20].

Case report

A 21-year-old male with no significant past medical history was referred to the Department of Oral Surgery with a chief complaint of pain and swelling on the right side of maxilla. The pain was dull and intermittent and extra-orally a mild swelling was evident in the right middle third of the face. Clinical examination revealed a mild frontal bossing and hypertelorism.

Intra-oral examination showed firm, non-tender and diffuse swellings in the right maxillary premolar region and mandibular anterior region. Multiple malaligned teeth were also evident.

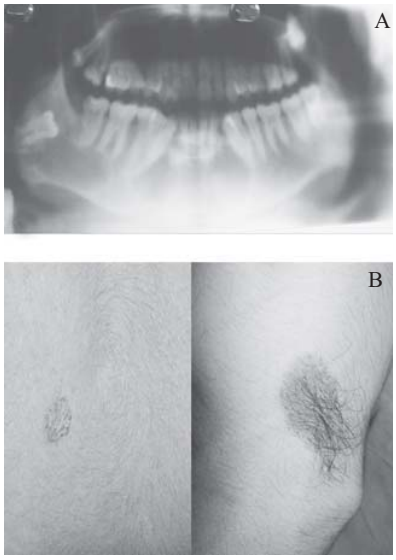

Fig. 1 A) Orthopantomograph depicting multiple radiolucencies in the mandible B) Basal Cell nevi on the back and thigh

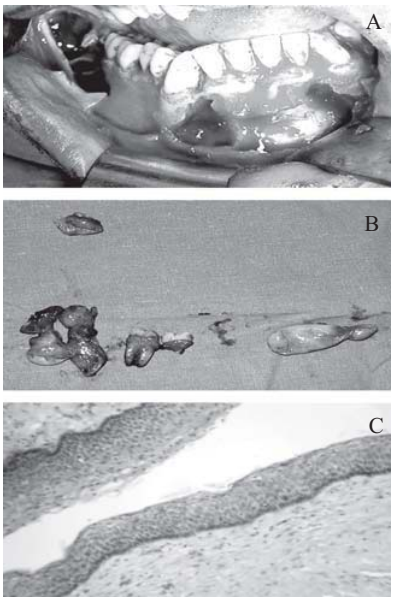

Fig. 2 A) Intraoperative photograph following cyst enucleation B) Gross photograph of the cystic specimens C) Photomicrograph demonstrating a typical keratocystic odontogenic tumour.

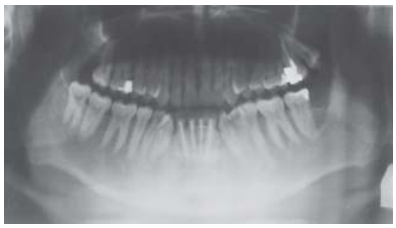

Fig. 3 Orthopantomograph showing adequate healing and no evidence of recurrence after two years

A radiographic examination revealed 4–5 well defined cystic lesions with sclerotic borders (Fig. 1A). The largest lesion was located in the right mandibular angle region measuring around 3 x 2cm in diameter, extending into the ramus and associated with an impacted right mandibular third molar. The second cyst was in the mandibular anterior region in the apical region of the incisors and extending laterally to involve the canines on either side. The third cyst was noted in the same mandibular anterior region, restricted only to four incisors. The fourth radiolucency was seen at the apices of left mandibular premolars and molars while the fifth cyst was seen between the two maxillary right premolars causing displacement of their roots. A provisional diagnosis of multiple KCOT's was considered.

Under local anesthesia, an incisional biopsy was planned and carried out in the mandibular right anterior region and the cystic lining was sent for histopathological investigation. The histological analysis confirmed the diagnosis of keratocystic odontogenic tumour.

A possibility of nevoid basal cell carcinoma syndrome was considered. Further, dermatological examination of the patient showed multiple basal cell naevi (Fig. 1B) on the right forearm as well as on the back and multiple palmar and plantar pits. Additionally, radiological examination of the chest revealed fused ribs. A thorough general physical examination did not reveal any other abnormality.

Based on the diagnostic criteria of Evans et al. (Table 2) and Kimonis et al. (Table 3), the patient was diagnosed as NBCCS.

Under general anesthesia, enucleation of all the cysts and disimpaction of 48 was planned and carried out uneventfully (Fig. 2A). The cystic cavity was then packed with gauze and carnoy's solution applied over it for 5min. The cavity was then irrigated thoroughly and closure done with an antibiotic soaked gauze in it. The non-vital mandibular anterior teeth were treated with root canal treatment. The enucleated cystic linings were sent for histopathological examination which revealed typical corrugated, uniform thickness parakeratinised epithelial lining with evidence of basal cell palisading covering a mildly inflamed cyst capsule. Few daughter cysts were also evident. The

Table 1 Anomalies in nevoid basal cell carcinoma syndrome. Taken from Manfredi et al. [6]

1. Skeletal anomalies
   - ❖ Bifid ribs
   - ❖ Splayed/fused ribs
   - ❖ Cervical ribs
   - ❖ Absent/rudimentary ribs (26%)
   - ❖ Scoliosis (15%)
   - ❖ Hemivertebrae
   - ❖ Flame-shaped lucencies hand/feet
   - ❖ Polydactyly (3%)
   - ❖ Syndactyly
   - ❖ Shortened 4th metacarpal (12%)
   - ❖ Spina bifida (3%)
   - ❖ Osteoporosis (3%)
2. Craniofacial anomalies
   - ❖ Frontal bossing (25%)
   - ❖ Parietal and temporal bossing
   - ❖ Brachycephaly
   - ❖ Macrocephaly (40%)
   - ❖ Coarse Face (50%)
   - ❖ Calcification of Falx (37–79%)
   - ❖ Tentorsirum cerebellum calcification (3%)
   - ❖ Bridged sella turcica (21%)
3. Neurological anomalies
   - ❖ Agenesis/disgenesis of corpus callosum
   - ❖ Congenital hydrocephalus (3%)
   - ❖ Mental retardation (6%)
   - ❖ Medulloblastoma (3–5%)
   - ❖ Meningioma (1% or less)
   - ❖ Schizoid personality
4. Oropharyngeal anomalies
   - ❖ Cleft lip and/or palate (4%)
   - ❖ High arched palate or prominent palatine ridges (40%)
   - ❖ Odontogenic keratocysts (75–100%)
   - ❖ Malocclusion(s) maxillary hypoplasia and mandibular hyperplasia, cleft palate (9%)
   - ❖ Dental ectopic position
   - ❖ Impacted teeth and/or agenesis (3%)
5. Skin anomalies
   - ❖ Basal cell carcinoma (50–97%)
   - ❖ Palmar and/or plantar pits (90%)
   - ❖ Benign dermal cysts (21%)
6. Sexual anomalies
   - ❖ Uterine and ovarian fibromas (15%)
   - ❖ Calcified ovarian cysts (3%)
   - ❖ Supernumerary nipple
   - ❖ Hypogonadism (3%)
7. Ophthalmic anomalies
   - ❖ Congenital amaurosis
   - ❖ Exotropia
   - ❖ Hypertelorism (40%)
   - ❖ Ptosis
   - ❖ Internal strabismus (15%)
   - ❖ Glaucoma (3%)
   - ❖ Coloboma (3%)
   - ❖ Blindness (15%)
8. Cardiac anomalies
   - ❖ Cardiac fibroma (3%)
9. Laboratory findings
   - ❖ Increased serum uric acid levels (3%)
   - ❖ High levels of cyclic adenosine monophosphate
   - ❖ High levels of alkaline phosphate

Table 2 Diagnostic criteria for NBCCS taken from Evans et al. [17]

Major criteria:

- ❖ More than 2 basal cell carcinomas (BCCs), one BCC in patients younger than 30 years of age or more than 10 basal cell nevi
- ❖ Any odontogenic keratocyst (proven by histology) or polyostotic bone cyst
- ❖ Three or more palmar or plantar pits
- ❖ Ectopic calcification in patients younger than 20 years of age (lamellar or early falx cerebri calcification)
- ❖ A positive family history of NBCCS

Minor criteria:

- ❖ Congenital skeletal anomaly (e.g. bifid, splayed, fused or missing rib, or bifid wedged or fused vertebra)
- ❖ Occipital–Frontal circumference greater than the ninety-seventh percentile, with frontal bossing
- ❖ Cardiac or ovarian fibromas
- ❖ Medulloblastoma
- ❖ Lymphomesenteric cysts
- ❖ Congenital malformations such as cleft lip/palate, polydactylism or eye anomaly (e.g. cataract, coloboma or microphthalmos)

findings were suggestive of keratocystic odontogenic tumours (Fig. 2B, 2C).

An immediate postoperative orthopantomograph was taken and the patient was discharged with strict postoperative instructions of not involving in any contact sports in view of reduced mandibular osseous substance.

The patient is being followed up for the past two years on regular basis without evidence of any recurrence (Fig. 3).

Discussion

The patient in this report presented with multiple cystic lesions leading to a suspicion of nevoid basal cell carcinoma syndrome, even though there was no apparent family history of the same. This was confirmed on further medical and radiological investigations which revealed multiple keratocystic odontogenic tumours, multiple basal cell nevi and bifid ribs. The dental findings were therefore significant in leading to the diagnosis of NBCCS. KCOT's are usually the first sign and most constant finding of this syndrome. The presence of even one KCOT in a patient younger than 20 years should alert the dentist to the possibility of NBCCS, particularly in case of multiple KCOTs occurring simultaneously or one after the other [3,21,22].

In our case, the patient presented with five KCOT's simultaneously at the age of 21 yrs with few other manifestations of the syndrome but did not give any family history.

The treatment of KCOT in patients affected by NBCCS is not much different from that of KCOT in patients without the syndrome. An additional problem is that syndromic KCOT's are suggested to have a higher recurrence rate than non-syndromic cysts [12,18,24–26]. As the lining is thin and presence of multiple satellite cysts are common in NBCCS; only surgical treatment may not be very effective. Adjunctive therapies like cryotherapy or carnoy's solution are usually indicated. Carnoy's solution is particularly effective and generally safe. It has been found that the application of carnoy's solution into the cyst cavity for 3 minutes after enucleation results in a lower rate of recurrence (0–2.5%) without damage of inferior alveolar nerve in KCOT [27,28]. Furthermore, early diagnosis and treatment followed by close clinical and radiological follow-up is as important as the actual surgical treatment [12,18,2]. An annual dental panoramic radiograph is usually suggested between the ages of 8 to 40 years which can aid in monitoring the recurrence or development of new KCOT's [12,29].

It can be valuable for patients and their families when dentists assist in the early diagnosis of NBCCS. This is of supreme importance for general health, since affected patients are prone to develop

Table 3 Diagnostic criteria for NBCCS taken from Kimonis et al. [18]

Major criteria:
- More than 2 basal cell carcinomas (BCCs) or one BCC in patients younger than 20 years of age.
- Odontogenic keratocysts of the jaw (proven by histologic analysis)
- Three or more palmar or plantar pits
- Bilamellar calcification of the falx cerebri
- Bifid, fused or markedly splayed ribs
- A first degree relative with NBCCS

Minor criteria:
- Macrocephaly
- Congenital malformations (e.g., cleft lip or palate, frontal bossing, coarse faces and moderate or sever hypertelorism)
- Other skeletal abnormalities (e.g., sprengel deformity, marked pectus deformity and marked syndactyly of the digits)
- Radiological abnormalities (e.g. bridging of the sella turcica, vertebral anomalies, modeling defects of the hands and feet, or flame-shaped lucencies of the hands and the feet).
- Ovarian fibroma or medulloblastoma

cancer early in life. Other recommendations include; patients with NBCCS should have dermatological examination every 3–6 months with removal of basal cell nevi exhibiting evidence of growth, ulceration or hemorrhage. Patients should be advised to reduce exposure to UV Light. In addition, neurological examination every six months is recommended in children with NBCCS as they have increased risk of developing medulloblastoma [30,31].

Genetic counseling for the patient as well as family members particularly to explain its familial nature has to be advocated [31]. As this syndrome is inherited as an autosomal dominant trait, every family member should be investigated to allow early detection of any syndromic features.

Due to the multi-system involvement and variable expressivity, a multidisciplinary approach to management, together with periodic follow-up are advocated for the general well-being of all NBCCS patients and their families.

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