

Nevoid basal cell carcinoma syndrome (Gorlin-Goltz syndrome)

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Abstract

The Gorlin-Goltz syndrome, also known as nevoid basal cell carcinoma syndrome (NBCCS), is an infrequent multisystemic disease inherited in a dominant autosomal way, which shows a high level of penetrance and variable expressiveness. It is characterized by odontogenic keratocysts in the jaw, multiple basal cell nevi carcinomas and skeletal abnormalities. This syndrome may be diagnosed early by a dentist by routine radiographic exams in the first decade of life, since the odontogenic keratocysts are usually one of the first manifestations of the syndrome. This case report presents a patient diagnosed as NBCCS by clinical, radiographic and histological findings in a 13-year-old boy. This paper highlights the importance of early diagnosis of NBCCS which can help in preventive multidisciplinary approach to provide a better prognosis for the patient.

Keywords: Bifid ribs, calcification of falx cerebri, nevoid basal cell carcinoma syndrome, odontogenic keratocysts, palmar and planter pits

Introduction

Nevoid basal cell carcinoma syndrome (NBCCS) also known as Gorlin-Goltz syndrome is an infrequent multisystemic disease that is inherited in a autosomal dominant way, which shows the high level of penetrance and variable expressiveness.^[1-3] NBCCS characterized mainly by the presence of multiple odontogenic keratocysts (75%), basal cell carcinoma (50-97%), bifid ribs (40%), palmar and planter pits (60-90%) and ectopic calcification of the falx cerebri (37-79%).^[4] This syndrome has received several names throughout the times such as, basal cell nevus syndrome, multiple NBCCS, multiple basal-cell carcinoma syndrome, multiple basalioma syndrome, jaw cysts-basal cell tumor-skeletal anomalies syndrome, odontogenic keratocysts-skeletal anomalies syndrome and fifth phacomatosis.^[5] Currently, this disorder is called as NBCCS, which was suggested by Professor Gorlin as this syndrome results from mutations in the PTCH1 gene.^[6] The estimated

prevalence varies from 1/57,000 to 1/256,000, with a male to female ratio of 1:1.^[7]

Jarisch and White in 1894 made a first descriptions by highlighting the presence of multiple basocellular carcinomas in patients with this syndrome.^[8,9] Later in 1939 a familiar case was described by Straith in which multiple basocellular carcinomas and cysts appeared.^[10] Gross in 1953 presented a case suggesting additional signs such as synostosis of the first left rib and bilateral bifurcation of the 6th ribs.^[11] Palmar and planter pits which is associated with the syndrome was first described by Bettley and Ward.^[12,13] In 1960 Gorlin-Goltz established a classical triad of basal cell carcinoma, odontogenic keratocyst and bifid ribs, that characterizes the diagnosis of this syndrome. Later this triad was modified by Rayner *et al.*, who established that for giving the diagnosis, at least cysts had to appear in combination with calcification of the falx cerebri or palmar and planter pits.^[14,15]

Case Report

A 13-year-old-boy reported to the Department of Pedodontics and Preventive Dentistry with the chief complaint of swelling and pain in the lower left back teeth region. On clinical examination, extra oral swelling which was tender and hard in consistency extending from the anterior border of the left ramus to the left parasymphysis region measuring approximately 4×3 cm [Figure 1a] was observed. On physical examination, presence of dysmorphic facial features like relative macrocephaly and ocular hypertelorism were observed. Sprangal scapular deformity [Figure 1b] and palmar and planter pits [Figure 1c] were also observed. On intraoral examination, grossly decayed mandibular left second primary molar and swelling in the vestibule region was observed.

Intraoral periapical radiograph revealed the presence of

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large radiolucent area with sclerotic border, suggestive of a cyst. Orthopantomograph revealed the presence of multiple cysts both in maxilla and mandible [Figure 2a]. Considering the possibility of the NBCCS with the above features, further investigations were carried out. Computed tomography showed ectopic calcification of the falx cerebrai [Figure 2b] and presence of multiple cysts in the maxilla [Figure 2c] and mandible [Figure 2d]. Antero-posterior view of the chest showed the presence of bifid rib in the posterior aspect of the right 3rd rib and rib expansion was noted in the anterior end of the left 3rd and 4th rib [Figure 2e]. Lateral cephalograph showed bridging of the sella turcica [Figure 2f].

Histopathological Findings

Histopathological findings of the incisional biopsy showed cystic lining overlying the connective tissue capsule. The lining epithelium was of 6-10 layers thick. The basal layer showed hyperchromatism and pallasading appearance [Figure 3]. The surface was corrugated and showed pyknotic nuclei, the epithelium was folded and showed separation from the

capsule in many areas. With all these histological findings the biopsy was confirmed as parakeratinized odontogenic keratocyst.

With the above clinical, radiographic and histopathological findings the present case was diagnosed as the NBCCS.

Discussion

NBCCS was first described by Jarisch and White in 1894^[9] and later established as a unique syndrome by Gorlin and Goltz in 1960.^[14] The pathogenesis of NBCCS is attributed to abnormalities linked to the long arm of chromosome 9 (q22.3-q31) PTCH1 gene with no apparent heterogeneity. The malformative pattern of NBCCS suggests that the gene has a fundamental function in controlling growth and development of normal tissue and data suggests that the product of this gene acts as a tumor suppressor. This gene was first isolated in 1996 as the human homolog of the *Drosophila* PTCH1 gene, simultaneously in Australia and in the USA. NBCCS includes abnormalities in the skin, stomatologic system, ectopic calcification of the CNS and other brain signs, skeletal system, ocular system, genitor-urinary system, mesenteric cysts and cardiovascular system. The syndrome initially consisted of the



Figure 1a: Profile picture



Figure 1b: Sprangal scapular deformity



Figure 1c: Planter pits

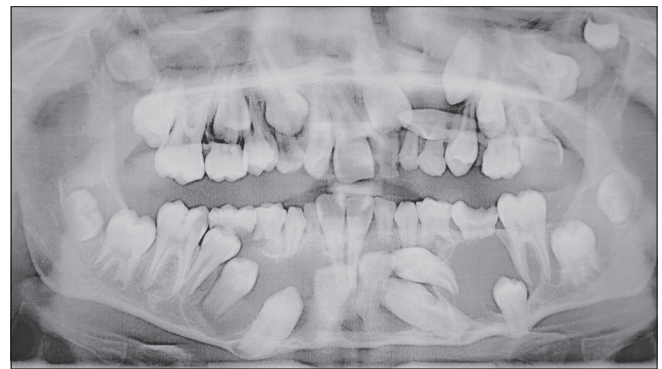


Figure 2a: Orthopantomograph showing multiple cysts and impacted teeth

triad of basal cell carcinoma, jaw cysts and skeletal anomalies. Basal cell carcinoma usually appears between puberty and 35 years of age, but cases have been reported in 3-4-year-old

patients also.^[5] The incidence varies widely among ethnic groups, studies have shown that only about 40% of black patients affected by NBCCS manifest basal cell carcinoma, while in whites they are reported in up to 90% of cases. Odontogenic

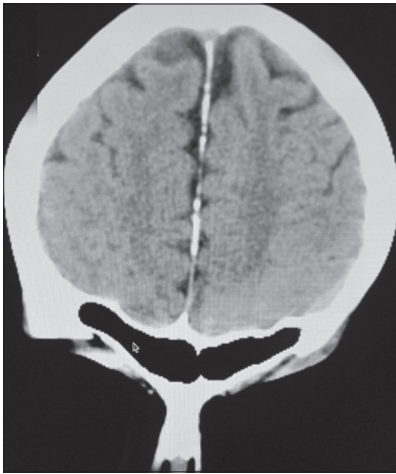


Figure 2b: CT scan showing calcification of falx cerebri



Figure 2c: CT scan showing multiple cysts in maxilla

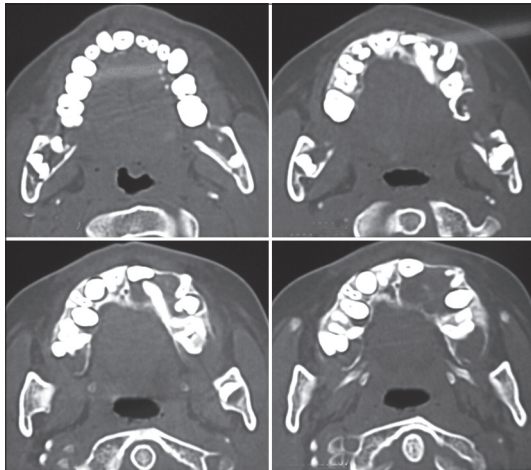


Figure 2d: CT scan showing multiple cysts in mandible



Figure 2e: A-P view of chest showing Bifid rib in the posterior aspect of the right 3rd rib

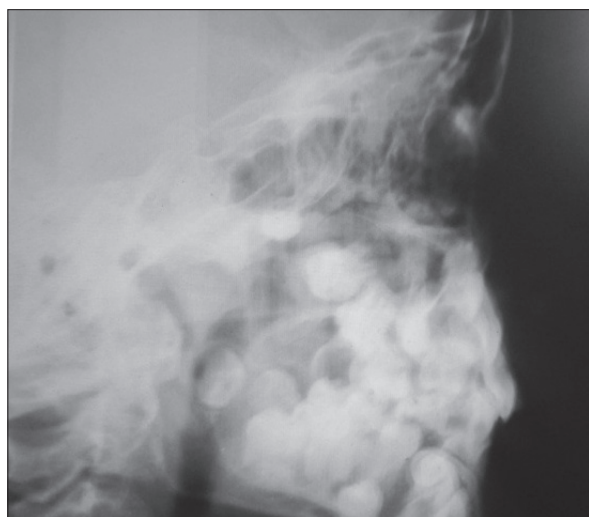


Figure 2f: Lateral cephalograph showing bridging of the sella turcica

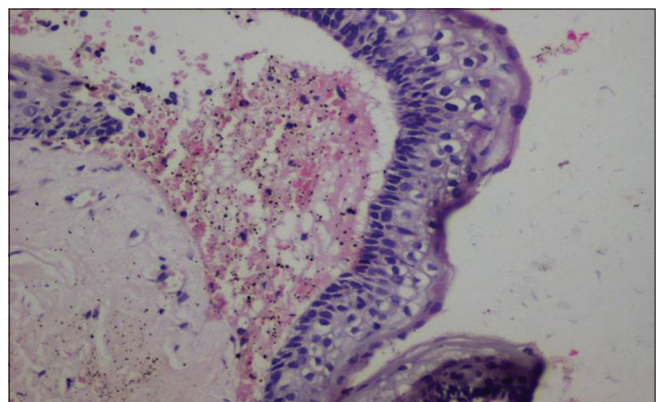


Figure 3: Photomicrograph of odontogenic keratocyst showing hyperchromatism and palisading appearance (H and E, original magnification $\times 40$)

keratocysts develop in more than 50% of NBCCS patients, often in the first decade of life. NBCCS is essentially a clinical and radiological diagnosis, and diagnosis of NBCCS can be made when two of the five major manifestations or one major and two minor manifestations are present.^[15] The diagnostic criteria based on the most frequent and/or specific features of the syndrome are given by Evans *et al.* Later these criteria were modified by Kimonis *et al.* in 1997.^[16] The major criteria and minor criteria for the diagnostic purpose are listed in Table 1^[16] and the clinical examination protocol for patients with NBCCS as suggested by Lo Muzio are listed in Table 2.^[5]

In our case four major manifestations such as odontogenic keratocysts, bifid rib, ectopic calcifications of the falx cerebri, palmar and planter pits were identified. Basal cell carcinoma was not found in our case as the patient was only 13-years-old, but cases have been reported in 3-4-year-old patients also.^[5] And four minor manifestations such as ocular hypertelorism, macrocephaly, frontal bossing, bridging of sella tursica were identified and diagnosed as NBCCS.

Early diagnosis of NBCCS is crucial to the affected children and their families, considering the risk of developing malignancies such as medulloblastoma and aggressive skin cancers,^[17] it is very important to screen for medulloblastoma in the early years of life in patients with NBCCS as it may be a potential cause of early death and early diagnosis is important to give adequate genetic advice.^[4,5] A negative family history could hamper the early clinical recognition of patients with NBCCS: Nonetheless, patient can be diagnosed during early childhood if the clinician is also aware of the minor clinical signs of the disease.^[18]

Table 1: Diagnostic criteria for Gorlin syndrome

Major criteria
Macrocephaly determined after adjustment for height
Odontogenic keratocysts of the jaws proven by histopathology
Palmar or plantar pits (3 or more)
Bilamellar calcification of the falx cerebri
Bifid, fused or markedly splayed ribs
First degree relatives with NBCCS
Minor criteria
Macrocephaly determined after adjustment for height
Congenital malformation: Cleft lip or palate, frontal bossing, "coarse face", moderate or severe hypertelorism
Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits
Radiological abnormalities: Bridging of the sella tursica, vertebral anomalies such as hemivertebrae, fusion or elongation of the vertebral bodies, modeling defects of the hands and feet, or flame-shaped lucencies of the hands or feet
Ovarian fibroma
Medulloblastoma

Kimonis *et al.*: Am J Med Genet 1997;69:299-308

The treatment of NBCCS is the specific therapeutics of its clinical manifestations. There are two methods for the treatment of odontogenic keratocysts, a conservative and an aggressive. In the conservative method, simple enucleation with or without curettage and marsupialization are suggested. Aggressive methods include peripheral ostectomy, chemical curettage with Carnoy's solution and resection.^[19] Radicular interventions such as enucleation with shaving of surrounding bone or sometimes resection, might contribute to prevention of recurrences and improve the prognosis.^[19,20] However, serious consideration should be given to *en bloc* resection in the following cases (1) When odontogenic keratocysts recur despite previous enucleation with an adjunctive procedure. (2) When odontogenic keratocysts recur despite previous marsupialization followed by enucleation with an adjunctive procedure. (3) In cases of multilocular (multilobular) aggressive intraosseous odontogenic keratocysts. (4) In cases of multiple nonsyndromic and syndromic odontogenic keratocysts of NBCCS. (5) In a diagnosed odontogenic keratocysts exhibiting particularly aggressive clinical behavior that should require resection as the initial surgical treatment.^[21]

If the patient is in the first decade and has still unerupted permanent teeth involving odontogenic keratocysts, it would be difficult to make a decision of aggressive surgery

Table 2: Diagnostic protocols in NBCCS

Family history
Past medical and dental history
Clinical examinations
Oralw
Skin
Central nervous system
Head circumference
Interpupillar distance
Eyes
Genitourinary system
Cardiovascular system
Respiratory system
Skeletal system
Genetic testing
X-ray
Chest
A. P. and lateral skull
Panoramic radiograph
Cervical and thoracic spine-A. P. and lateral
Hands (for pseudocysts)
Pelvic (female)
Ovarian ultrasound (female) for ovarian fibroma
Echocardiogram (children) for cardiac fibroma
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over conservative management. In children with unerupted teeth, conservative management should be considered first because an aggressive operation can have an adverse effect on the eruption process and the development of the involved jaw.^[22] Thus, younger patients should usually receive conservative rather than aggressive treatment.

Conclusions

The present case highlights the importance of awareness of this rare syndrome especially in young patients without skin lesions and its importance to make early diagnosis and its proper management, which has cancer predisposition. In order to arrive at an early diagnosis of the syndrome, specialists should carry out a clinical, radiographic testing in early ages of life. In this way, different health specialists like pediatricians, specialists in genetics, dentists, maxillofacial surgeons, dermatologists, etc., must have good basic knowledge of the main features of the syndrome to work accordingly in their different health specialities.^[4] Guidelines for follow-up have been established and include the following: Neurological examination twice yearly, cerebral MRI once in a year for 1-7 years of age, orthopantomogram every 12-18 months starting at the age of eight years, yearly skin examination and cardiologic examination according to the signs and symptoms.^[17] The families of the patients with NBCCS should be examined and genetic counseling should be offered, as it is inherited as an autosomal dominant disorder.

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