Nevoid Basal Cell Carcinoma Syndrome: A Long-Term Study in a Family

Thiago de Santana Santos, PhD¹ André Vajgel, PhD² Paulo Ricardo Saquete Martins-Filho, PhD³
 Almir Walter de Albuquerque Maranhao Filho, PhD² Ricardo José De Holanda Vasconcellos, PhD⁴
 Riedel Frota, PhD² José Rodrigues Laureano Filho, PhD²

¹Hospital Universitário, Universidade Federal de Sergipe, Rua Claudio Batista, Aracaju, Sergipe, Brazil

²Department of Oral and Maxillofacial Surgery, Pernambuco School of Dentistry, Camaragibe, Pernambuco, Brazil

³Department of Dentistry, Universidade Federal de Sergipe, Aracaju, Sergipe, Brazil

⁴Department of Oral and Maxillofacial Surgery, University of Pernambuco, Recife, Pernambuco, Brazil

Address for correspondence Thiago de Santana Santos, PhD, Investigative Pathology Laboratory, Universidade Federal de Sergipe, Rua Claudio Batista, S/n Bairro Sanatorio, Aracaju, Sergipe 49060-100, Brazil (e-mail: thiago.ctbmf@yahoo.com.br).

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Abstract

Keywords

- ▶ nevoid basal cell carcinoma syndrome
- ▶ Gorlin–Goltz syndrome
- ▶ basal cell carcinoma
- ▶ odontogenic keratocystic tumor

We present a family case series with 10 individuals having nevoid basal cell carcinoma syndrome (NBCCS) with a 10-year follow-up. All articles published in the literature between 1967 and 2011 on familial Gorlin–Goltz syndrome in any language were surveyed to determine the mapping of cases per country of occurrence of this disease. All patients in the present series were presented with calcification of the falx cerebri, mild hypertelorism, and frontal bossing. Odontogenic keratocystic tumors, palmar and plantar pits, and multiple basal cell carcinomas occurred in 90, 40, and 20%, respectively, of the patients. One of the patients died of skin cancer. Diagnosis of odontogenic keratocyst tumors was confirmed by histopathological examination. NBCCS is a rare autosomal dominant cancer predisposition syndrome; it is important to recognize it when a patient has multiple odontogenic keratocyst tumors because life-long monitoring is essential for patient management.

Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin–Goltz syndrome, is a rare autosomal dominant disorder with two distinct phenotypic features: predisposition to develop malignant tumors and developmental defects.^{1–4} The disease was described in the 1960s by Gorlin and Goltz,⁵ who established the classic triad of multiple basal cell carcinomas (BCCs), keratocystic odontogenic tumors (KCOTs), and bifid ribs. The disease has a high penetrance, but variable expressivity, including the possible presence of other abnormalities, such as palmar and plantar pits, bilamellar calcification of the falx cerebri, macrocephaly, fusion of vertebrae, spina bifida, polydactyly, cleft lip or palate, hypertelorism, ovarian fibroma, and medulloblastoma (MB).⁶

In recent decades, it has been demonstrated that NBCCS is a chromosome instability syndrome, characterized by spontaneous chromosomal rearrangements, increased frequency of sister chromatid exchanges, and slowing of the cell cycle.⁷ The human homolog of *Drosophila* patched (PTCH) is a tumor suppressor gene localized at chromosome 9q22.3–q31 (GenBank accession numbers: U43148 and U59464),^{8,9} member of the Hedgehog/Patched (or *sonic hedgehog* [SHH]/*smoothed* [SMO]/PTCH) signaling pathway, which seems to have a fundamental role during embryogenic development and appears to underlie many disease states when dysregulated.¹⁰ Increased PTCH expression has been detected immunohistochemically in sporadic and Gorlin syndrome–related KCOTs.¹¹

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Few studies in the English language literature include all members of the same family. Thus to better understand this syndrome, we present a familial case series of 10 family members with a 10-year follow-up, with the development of clinical signals years from the first observations. In addition, we also discuss the recurrence potential of KCOT and the efficacy of photodynamic therapy (PDT) as a treatment for multiple BCCs.

Methods

A retrospective study of a family with NBCCS was performed (►Fig. 1). The sample was obtained after the first individual attended the hospital for treatment in the period between January 2004 and January 2014. The clinical, radiographic, and histological data of a 10-year study of 10 cases in a Brazilian population with NBCCS were recorded and analyzed. NBCCS was diagnosed with two major or one major and two minor criteria; the diagnostic criteria for NBCCS proposed by Evans et al,¹² as modified by Kimonis et al,⁶ were used (►Table 1).

This study was approved by the ethics committee (CEP/UPE: 135717/07). All participants provided written informed consent.

After treatment of each case, data on gender, age, site, the presence of associated systemic disorders, time elapsed since onset of the disease, and treatment were gathered. In all cases, the specimens were sent for histopathological analyses to confirm the diagnosis.

All of the patients with KCOT underwent operations soon after admission to the emergency ward. Under general anesthesia, peripheral osteotomy (PO) with curettage was employed.

Literature Review

All articles published between 1967 and 2014 on familial NBCCS were surveyed to determine the mapping of cases per country of the occurrence of the disease. The Medline (PubMed) database was used for this search, using the

following descriptors (basal cell nevus syndrome or Gorlin syndrome or Gorlin–Goltz syndrome) and (familial or family). Articles that did not have familial reports (cyto)genetic studies of families that had not provided complete clinical information on affected members, suspected cases (that were not confirmed), articles without abstracts, and those performed in countries that no longer exist were excluded. After defining the sample, the familial cases were counted and separated by country. Among a total of 232 articles found in the search, 175 were excluded because they did not represent familial reports, as were 11 due to the absence of an abstract, 9 genetic studies, and 2 suspected cases. Two were excluded because the origin of the article could not be identified. Thus, in total, 199 articles were excluded and 33 articles satisfied the inclusion criteria. The familial cases per country^{1,12–43} included in this study are distributed on the map in ►Fig. 2.

Results

Since 2002, we have reviewed the findings in 10 affected individuals with NBCCS in a Brazilian population (mean age $\pm$ standard deviation: 23.5 ± 11.39 years, range: 11–45 years). The patients consisted of four (40%) males and six (60%) females. All patients (100%) presented calcification of the falx cerebri (►Fig. 3), mild hypertelorism, and macrocephaly (►Fig. 4). KCOTs (►Fig. 5) had occurred in 90% of the patients. The number of total jaw lesions ranged from 0 to 3. Palmar and plantar pits were seen in 40% of the patients (►Fig. 6). Multiple BCCs (►Fig. 7) occurred in 20% of the patients; one was treated with topical PDT with satisfactory cosmetic outcome and no recurrence, and another was later diagnosed with a large facial tumor and died within a few months. Only one patient, a 41-year-old, had been affected by ovarian calcified fibroma (►Fig. 8). The same patient also had a bifid rib in a chest X-ray (►Fig. 9; ►Table 2).

Discussion

In this study, we reviewed the clinical and radiological manifestations in 10 Brazilian individuals with NBCCS from

Fig. 1 Pedigree of the patient family. Filled symbols indicate affected individuals.

Table 1 Diagnostic criteria for NBCCS

Major criteria	Minor criteria
Multiple BCCs (> 2) or one under age 20	Macrocephaly
KCOTs of the jaws proven by histology	Congenital malformation
Palmar or plantar pits (≥ 3)	Other skeletal abnormalities
Bilamellar calcification of the falx cerebri	Radiological abnormalities
Bifid, fused, or markedly splayed ribs	Ovarian fibroma
First-degree relative with NBCCS	Medulloblastoma

Abbreviations: BCC, basal cell carcinoma; KCOT, keratocystic odontogenic tumor; NBCCS, nevoid basal cell carcinoma syndrome.

Fig. 2 Number of families per country affected by NBCCS. NBCCS, nevoid basal cell carcinoma syndrome.

the same family. Characteristics seen in more than 90% of the patients were frontal bossing, mild hypertelorism, calcification of the falx cerebri, and the presence of multiple KCOTs. On the contrary, BCCs were diagnosed in 20% of the patients (→Table 3). These frequencies were similar to some previous reports,^{13,15–17,26} but quite different from others,^{1,12,14,18–21,24,25,27,28} including another Brazilian series^{22,23} indicating the wide phenotypic heterogeneity of this syndrome even in the same ethnic background. The exact incidence of this syndrome and its different manifestations are unrecorded and it is typically difficult to identify the condition clinically until jaw cysts or skin cancers become apparent. Nevertheless, this syndrome probably occurs in all ethnic groups, although few cases have been published in certain races.³⁵ The relative lack, for example, of BCCs in African Americans may partially reflect ultraviolet radiation protection, resulting from increased skin pigmentation.³⁵ The presence of melanin reduces the absorption of ultraviolet radiation in the skin and, consequently, DNA damage. This may explain the lack of familial reports in Africa (→Fig. 1) because BCCs are the most evident clinical sign of the

syndrome. Also, we believe that the wide variation in NBCCS phenotypes may be associated with genetic mutations, especially in the *PTCH* gene,^{13,44,45} in addition to environmental variation.⁴⁶

As in the present series, literature reports show that skeletal anomalies in the craniofacial complex are the most common features in patients with NBCCS. However, although characteristic facies are part of the syndrome, not every patient has the typical skull and facial features (→Table 2), which consist basically of macrocephaly (due to frontal and temporoparietal bossing) combined with prominent supra-orbital ridges as well as a broad nasal root, resulting in an appearance of hypertelorism. Increased dural calcification, especially in the falx region, is a quite common radiological manifestation in patients with NBCCS. According to Pritchard et al,⁴⁷ the radiographic appearance is that of one or more flat sheets extending more widely (> 2.0 mm) than in the normal person. Although Kimonis et al⁶ reported that calcification of the falx cerebri is more common in patients older than 20 years, our series showed that at least 60% of patients < 20 years already had signs of dural calcification at first

Fig. 3 Calcification of the falx cerebri (patient II-2).

attendance. These data suggest that children with a familial history of NBCCS should undergo cranial imaginological exams in searching for the first signs of the syndrome.

Other craniofacial skeletal anomalies, such as bridge sella turcica, high-arched palate, and cleft palate, are less frequent^{39,48} but should not be overlooked. In contrast to the present series, the occurrence of mental retardation, short

Fig. 4 Macrocephaly, hypertelorism, and the presence of multiple basal cell nevi in the face (patient III-3).

Fig. 5 (a) KCOT in the body of the mandible associated with unerupted tooth (patient III-1). (b) Radiolucent lesion, diagnosed as KCOT, associated with impacted permanent maxillary canine (patient III-2). KCOT, keratocystic odontogenic tumor.

metacarpals, and low phosphorus excretion have been described in adult and child patients with NBCCS, suggesting the presence of pseudohypoparathyroidism, but this endocrine aberration seems not be linked to deformity of the pituitary fossa. However, the skeletal anomalies and the mandibular prognathism are suggestive of a growth disturbance.⁴⁹ Thus, the clinical importance of these findings remains open to discussion. In addition, earlier studies have described skeletal

Fig. 6 Palmar pits (patient II-2).

Fig. 7 (a) Multiple basal cell carcinomas on the face. (b) Post-PDT treatment. PDT, photodynamic therapy.

anomalies in the thoracic cage, including bifid ribs and fusion of the thoracic vertebrae.⁵⁰ Although bifid ribs are of little consequence to the patient, as in case 1, vertebral deformities may cause scoliosis or compression of the spinal dorsal roots, leading to peripheral pain and disability. In this series, no patient was diagnosed with vertebral anomalies.

KCOTs are the second most common features associated with NBCCS, with a peak occurrence in the second and third decades and with a predilection for the third molar region,⁵¹ as in the present cases. In children and adolescents, the lesions may cause displacement of developing teeth and delay dental development.²² Although most KCOTs present as solitary lesions, multiple lesions are a well-recognized feature of NBCCS. In fact, there are authors who state that the presence of multiple keratocysts—even *just* keratocysts if there is a family association—is sufficient for its establishment.²⁵ However, most authors make the diagnosis if two major criteria (KCOTs of the jaws, nevoid BCCs, palmar and plantar pits, cerebral falx calcifications, family history, and skeletal anomalies) or one major and two minor criteria (macrocephalus,

hypertelorism, MB, ovarian calcification) are presented.² Early diagnosis and treatment is essential, as is family detection and genetic counseling. It is important to recognize when a patient has multiple KCOTs because life-long monitoring is essential for patient management.

Recently, the WHO Working Group defined this lesion as “a benign uni- or multicystic, intraosseous tumor of odontogenic origin, with a characteristic lining of parakeratinized stratified squamous epithelium and potential for aggressive, infiltrative behavior.” When the syndrome is present, the tumor can be larger and may be associated with painful symptoms, swelling, or drainage. KCOTs in patients with this syndrome tend to have more satellite cysts, solid islands of epithelial proliferation, and odontogenic epithelial rests within the fibrous capsule than do isolated tumors.⁵² These characteristics lead to a great rate of recurrence.^{53,54} In addition, it has been suggested that recurrence is higher in multilocular large lesions with high SMO⁵⁵ and podoplanin expression.⁵⁶

Fig. 8 Calcified ovarian masses are noted in pelvic Rx (patient II-2).

Fig. 9 Posteroanterior chest radiograph showing a bifid rib (patient II-3).

Table 2 Characteristics of study patients

	II-2	II-3	II-4	III-1	III-2	III-3	III-4	III-5	III-6	III-7
Age (currently)	41	27	-	18	17	12	11	24	21	19
Age at first attendance	31	24	45	10	13	8	7	21	19	16
Gender	F	F	M	F	F	M	F	M	M	F
Skin										
BCC	+	-	+	-	-	-	-	-	-	-
Epidermal cysts	-	-	-	-	-	-	-	-	-	-
Palmar or plantar pits	+	+	-	-	-	-	-	-	+	+
Facial milia	-	-	-	-	-	-	-	-	-	-
Skeletal										
Macrocephaly	+	+	+	+	+	+	+	+	+	+
Prominent supraorbital ridges	+	+	+	+	+	+	+	+	+	+
Broad nasal root	+	+	+	+	+	+	+	+	+	+
Calcification of falx cerebri	+	+	+	+	+	+	+	+	+	+
Rib abnormalities	-	+	-	-	-	-	-	-	-	-
Vertebral abnormalities	-	-	-	-	-	-	-	-	-	-
Polydactyly/syndactyly	-	-	-	-	-	-	-	-	-	-
Shortening of metacarpal bones	-	-	-	-	-	-	-	-	-	-
Oral										
KCOT	+	+	+	+	+	+	+	+	+	+
Cleft lip and/or palate	-	-	-	-	-	-	-	-	-	-
Others										
Hypertelorism	+	+	+	+	+	+	+	+	+	+
Ocular anomalies	-	-	-	-	-	-	-	-	-	-
Renal anomalies	-	-	-	-	-	-	-	-	-	-
Cardiac fibromas	-	-	-	-	-	-	-	-	-	-
Ovarian fibromas	+	-	-	-	-	-	-	-	-	-
Medulloblastomas	-	-	-	-	-	-	-	-	-	-
KCOT										
Location	Mandible	Mandible/maxilla	Mandible	Mandible	Maxilla	Mandible/maxilla	-	Mandible/maxilla	Mandible	Mandible
Region	Symphysis	Body (bilat)	Body (bilat)	Body and angle	Canine. region	Body/post. region	-	Body right, angle left/post. region	Body	Body
Surgical procedure	PO + C	PO + C	No surgery	PO + C	PO + C	PO + C	-	PO + C	No surgery	PO + C
Recurrence	-	-	-	+	-	-	-	+	-	-
Time after surgery	-	-	-	6 y	-	-	-	2 y	-	-
Death	-	-	+	-	-	-	-	-	-	-
Follow-up	10 y	3 y	-	8 y	4 y	4 y	4 y	3 y	-	3 y

Abbreviations: BCC, basal cell carcinoma; KCOT, keratocystic odontogenic tumor; PO, peripheral osteotomy.

Table 3 Frequencies of clinical findings

Clinical manifestation	n	Percentage
50% or greater		
Calcification of the falx cerebri	10	100
Mild hypertelorism	10	100
Macrocephaly	10	100
Odontogenic keratocystic tumors	9	90
30–50%		
Palmoplantar pits	4	40
29% or less		
Basal cell carcinoma	2	20
Ovarian fibromas	1	10
Rib abnormalities	1	10

A range of surgical treatment approaches have been described in the literature for KCOTs, including simples enucleation (with or without curettage), enucleation with adjunctive liquid nitrogen therapy, or the application of Carnoy solution, marsupialization, cryotherapy, electrocautery, removal with peripheral osteotomy, and localized or segmental resection. According to Borgonovo et al,⁵⁷ the goals of treatment should involve eliminating the potential for recurrence, while also minimizing the morbidity and a two-stage treatment protocol was suggested for young patients with NBCCS, involving conservative surgical treatment, based on marsupialization and later enucleation with peripheral osteotomy. In our series, all cases were treated with PO and curettage, with a recurrence rate of 28.5% (two cases). The two cases of recurrence occurred 6 and 2 years after the surgery, indicating the need for long-term follow-up. Unfortunately, in a recent systematic review,⁵⁸ it was observed a lack of evidence regarding the optimal surgical treatment for KCOTs in NBCCS patients, although enucleation and marsupialization appeared to be the most common treatments in the literature.

Recent advances have linked *Shh* pathway signaling activation to a variety of human cancers, including BCCs of the skin and MBs, common malignancies diagnosed in patients with Gorlin syndrome. It has been hypothesized that loss-of-function mutations of PTCH-1, a critical membrane protein for embryonic development and a human tumor suppressor gene, at human chromosome 9q22 repress constitutive signaling activity of a second membrane protein, known as SMO, leading to activation of the Shh pathway.⁵⁹ It has been demonstrated experimentally that conditional ablation of PTCH-1 with UV irradiation⁶⁰ and consequently the overexpression of Shh⁶¹ are needed for the occurrence of BCCs in mice, similar to that found in NBCCS patients, suggesting that exposure to solar radiation is important in the development of these tumors, even in patients with NBCCS.

An oncogenic two-hit model has been proposed that states that normal cells require two mutagenic hits to produce a cancer. Patients with the syndrome have a germline defect in

the DNA sequence in one of the two copies of the *PTCH-1* gene; this is insufficient to cause malignant transformation. However, if loss of the normal allele occurs at the same locus, a second hit, as a consequence of mitotic nondisjunction, deletion, or mitotic recombination, the cell may become malignant.^{62,63} According to Gorlin,⁶⁴ in cases of BCCs, both hits come from the somatic type of mutation, needing only one additional hit, due to solar radiation, for tumor development. In addition, it was noted that 70% of KCOTs exhibit loss of heterozygosity of one or more of the common tumor suppressor genes, indicating that the behavior of these lesions could resemble low-grade tumors more than congenital malformations.⁶⁵

In clinical practice, the incidence of BCCs related to Gorlin syndrome is higher in fair-skinned patients, probably due to the lack of melanin, a complex polymeric pigment that absorbs all wavelengths of damaging ultraviolet radiation, reducing or preventing its penetration further into the body. Dark-skinned patients with NBCCS only rarely have more than a few BCCs over a life time. Thus, because skin tumors in NBCCS tend to appear earlier in life than their nonsyndromal counterparts, the introduction of a specific disease prevention program should be instituted for these patients and should include information about risks related to sun exposure, regular dermatological examinations, and use of sunscreens and long-brimmed hats. These measures are important especially in tropical countries, such as Brazil, most of the territory of which is subject to strong solar radiation, and activities in the primary sector of the economy, such as agriculture, livestock, and fisheries, are common.

In the present series, educational measures and preventive strategies against solar radiation have been effective because, so far, no family member younger than 30 years has developed skin cancer. In contrast, two patients older than 30 years were diagnosed with BCCs, located on the face. One patient (case 3) was diagnosed too late and died 1 year after the diagnosis. Case 1 was treated with PDT, with satisfactory outcome (► Fig. 7).

The treatment of BCCs in patients with Gorlin syndrome is complex. Currently, inhibitors and modulators of the Shh pathway are being tested with promising results. In a randomized, double-blind, placebo-controlled trial, it was demonstrated that vismodegib, a new orally administered hedgehog pathway inhibitor, reduced the basal cell carcinoma tumor burden and blocked growth of new basal cell carcinomas in patients with NBCCS.⁶⁶ However, while a curative breakthrough for BCCs may occur in the foreseeable future, most cases have been treated with surgical excision and cryotherapy. However, these methods can result in significant disfigurement due to scarring. Topical PDT has been used as an alternative to surgery for patients with NBCCS, especially for facial lesions which are < 2 mm thick on ultrasound assessment.⁶⁷ Photodynamic inactivation involves the photoactivation of a photosensitizer agent, such as cationic phenothiazinium dyes (methylene blue and toluidine blue), porphyrins, crystal violet, indocyanine green, and erythrosine, by visible light, generating singlet oxygen ($^1\text{O}_2$).⁶⁷ $^1\text{O}_2$ is an excited form of molecular oxygen characterized by the opposite spin of a pair of electrons, and is less stable and more reactive than the normal triplet oxygen (O_2). This reactive oxygen molecule causes irreparable damage to cellular components, leading to cell death.^{68–70} Although in most cases photosensitizers are activated by red light, from low-power lasers, the choice of light source should be based on photosensitizer absorption (fluorescence excitation and action spectra), disease features, cost, and size. On the contrary, the clinical efficacy of PDT is dependent on complex dosimetry that includes total light dose, light exposure time, and light delivery mode.⁷⁰

In addition to cosmetic appearance, topical PDT appears to have a series of advantages versus surgery, as follows: the possibility of treating several BCCs at the same time, the need for only one visit for each treatment, minimally invasive treatment, the possibility of retreating a previously treated area, minimal discomfort, and temporary epilation following treatment.^{67,71} In a study by Lancaster et al,⁷¹ the local control rate at 12 months after PDT was 56.3%, and the overall average percentage reduction in lesion thickness was 68% at 12 months and 65% at 24 months. Itkin and Gilchrest⁷² used topical PDT for the treatment of multiple lesions on two patients with NBCCS, resulting in an 89% complete clinical response of superficial tumors in contrast to 31% of nodular BCCs. Thus, although there are no existing guidelines about the use of topical PDT in NBCCS patients, this method seems to be adequate for superficial BCCs. For lesions > 3 mm thick, a debulking curettage can be performed 6 weeks before PDT. Extensive lesions that preclude the application of a topical sensitizer should be treated with an intravenous photosensitizer, such as porfimer sodium.⁷¹

A wide range of reproductive anomalies has been reported in patients with NBCCS, including uterine and ovarian fibromas, calcified ovarian cysts, supernumerary nipples, hypogonadism, and cryptorchidism. In this familial series, only one case of reproductive anomaly was observed; a bilateral ovarian fibroma was diagnosed in a 31-year-old woman (case 1).

Ovarian fibromas are uncommon benign neoplasms of gonadal cell stroma origin, composed of spindly fibroblastic cells that produce collagen. The tumors appear as unilateral masses in 90% of cases, generally in older, menopausal patients, but a peak frequency between 20 and 40 years has been described.⁷³ Although most ovarian fibromas appear sporadically, some tumors may be associated with Meigs syndrome (ovarian fibroma, hydrothorax, ascites), familial polyposis (such as Gardner and Richard syndrome and Peutz-Jeghers syndrome), and NBCCS.

According to Gorlin,⁷⁴ approximately 2 to 25% of females with NBCCS will develop ovarian fibromas, leading to challenges in gynecological care and counseling. In patients with NBCCS, the tumors are often bilateral and calcified,⁷⁵ as in case 1 here. In rare cases, the ovarian fibromas may be related to endocrine manifestations, with the presence of pelvic pain, metrorrhagia, and abdominal distension.⁷³

In most cases, the treatment of these lesions is based on surgery because there is some risk of malignancy.⁷⁶ Tumorectomy is indicated for young and bilateral salpingo-oophorectomy for menopausal patients.⁷⁴ When counseling patients, the clinician should consider the patient's desire for future fertility and attempt to conserve normal ovarian tissue if fertility is desired. In addition, factors such as age, ovarian reserve, presence of comorbidities, partner availability, and financial resources or insurance coverage for fertility preservation should be considered.⁷⁶ Although no data exist about the fertility potential of females with NBCCS, a patient diagnosed with ovarian fibromas in this series had four children with the syndrome and did not undergo surgery for personal reasons. In pediatric patients, the development of ovarian fibromas is rare,⁷⁷ but regular gynecological follow-up is required.

Also, as part of the interdisciplinary investigation in patients with NBCCS, other anomalies should not be overlooked, such as the presence of hand alterations, intracranial tumors, eye alterations, and cardiac fibromas. Hand alterations include the presence of palmar pits, polydactyly, syndactyly, and shortening of the metacarpal bones. Of these, palmar pits are the most common alterations, affecting 85% of patients with NBCCS over the age of 20 years.⁴⁶ Clinically, the lesions appear as punctiform depressions in the skin of the palms, but in some cases, the soles of the feet, the back, the face, and the chest may also be affected.⁷⁸ In the present series, some cases of palmar pits were observed in patients younger than 20 years. Although difficult to detect, the presence of three or more palmar/plantar pits constitutes a major diagnostic criterion in NBCCS. Thus, when lesions are discovered, a careful physical and radiological examination is mandatory, especially in children with a positive familial history of NBCCS.

Tumors of the central nervous system are not uncommon in patients with NBCCS. MB is the brain tumor most frequently associated with the syndrome and is one of the features included in the minor criteria for its diagnosis. It is estimated that 5% of all NBCCS patients will develop cranial tumors, with a high incidence in those younger than 5 years.⁷⁵ Desmoplastic MB is the most common histological type associated

with NBCCS, and seems to have a better prognosis than other histological variants, with a decreased propensity for metastasis and higher sensitivity to chemotherapy.^{79,80} In addition, some authors^{80–82} have shown that patients with syndromic MBs treated with craniospinal irradiation often develop late-onset neoplasms, increasing morbidity and mortality in this population. Thus, it has been suggested that syndromic children < 5 years old with desmoplastic MB should be treated with surgical excision, followed by chemotherapy, to prevent sequelae secondary to radiation.⁸⁰ In the present series, although no case of MB had been diagnosed, all patients continue to be closely monitored by neurologists because the development of MB is not restricted to the first years of life.

Ophthalmic lesions and cardiac fibromas are minor diagnostic criteria for NBCCS and affect 26 and 3% of these patients, respectively.⁷⁵ Ophthalmic lesions include the presence of hypertelorism (as in the present cases), strabismus, nystagmus, cataract, coloboma, and microphthalmos.⁵ Recently, four cases of BCC of the eyelid associated with the syndrome were reported⁸³ and, thus, ophthalmic evaluation should be mandatory in patients with NBCCS. In contrast, no case of cardiac fibromas was found in the present series. Most cases of these tumors arise in the left ventricle, are asymptomatic,⁸⁴ and are discovered after an echocardiography or magnetic resonance examination. In some circumstances, patients may present episodes of syncope,⁸⁵ fatigue, chest pain, and dyspnea,⁸⁶ as well as ventricular tachycardia.⁸⁷ The presence of dysrhythmia, conduction defects, or congestive heart failure is rare but may lead to death.⁸⁸ For this reason, any cardiac symptom in a patient with NBCCS should be evaluated promptly by a cardiologist to rule out a cardiac tumor.

In summary, it is important that families with NBCCS are carefully informed about the genetic alterations responsible for the disease, prognosis, risks of having other children with the problem, and what can be done to improve the quality of life for everyone living with this condition.

Note

This article has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: <http://www.textcheck.com/certificate/18GWy3>.

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