CHAPTER

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Basal cell nevoid carcinoma syndrome: A review

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ABSTRACT
Basal cell nevoid carcinoma syndrome (BCNCS) is a rare autosomal dominant genetic syndrome that is predisposed to cancer. It is characterized by the presence of multiple basal cell carcinomas (BCCs) on the skin, as well as numerous maxillary odontogenic keratocyst (QTOs), palmoplantar punctate depressions (pits), skeletal abnormalities, and other developmental defects. The genetic basis of this syndrome lies in causal mutations in the PTCH1 gene, a tumor suppressor gene located on chromosome 9. The present study aimed to review recent literature concerning SCNBC, addressing aspects such as clinical manifestations, diagnostic criteria, genetic etiology, and molecular tests used. A total of 88 articles were included, most of which were clinical cases. Among the clinical manifestations, QTOs were the most frequently mentioned major diagnostic criteria, followed by calcification of the cerebral sickle. Ocular anomalies, on the other hand, were the alterations belonging to the most prevalent minor criteria. A total of 18 clinical cases underwent molecular testing for mutations in the PTCH1 gene. The most used methods were genetic sequencing and the mutations frequently found were frameshift and nonsense mutation, which occurred in exons 2, 3, 6, 8, 11, 12, 18, and 21. Despite the existence of several mutations in the PTCH1 gene that are attributable to the etiology of SCNBC, the performance of diagnostic molecular tests were not performed in many of the studies analyzed, and even those that did not identify a correlation with the patient's phenotype or prognosis, and these are indicated only in some particular cases.

Keywords: Basal cell nevus syndrome, gorlin syndrome, odontogenic cysts, basal cell carcinoma.

1 INTRODUCTION

Basal cell nevoid carcinoma syndrome (BSCNC), also known as Gorlin syndrome, Gorlin-Goltz syndrome, or basal cell nevus syndrome (*Online Mendelian Inheritance in Men* - OMIM number 109400) is an autosomal dominant neurocutaneous disease characterized by developmental abnormalities such as palmoplantar punctate depressions (*pits*)), rib anomalies, odontogenic keratocyst (QTOs) in the maxilla or mandible, and predisposition to various tumors, including basal cell nevoid carcinoma (BCCs), medulloblastoma, ovarome, and cardiac fibroma (FUJII; Miyashita, 2014; SPIKER *et al*., 2023).

SCNBC is mainly caused by mutations in the human homologous gene of the drosophila, *Patched Tumor Suppressor (PTCH, OMIM 601309*), located on the long arm of chromosome 9 and responsible for encoding the receptor for the *sonic hedgehog protein* (KIMONIS *et al*., 1997; LO MUZIO, 2008; LO MUZIO *et al.*, 2013; PAZDERA *et al*., 2022). The *Hedgehog* signaling pathway (*HH),* in which this protein is inserted, plays a key role in the conformation of the human body, and

tumorigenesis and its dysregulation results in various developmental defects and tumors, such as those seen in SCNBC (FUJII; MIYASHITA, 2014).

The diagnosis of SCNBC only occurs when there is the appearance of the first signs and symptoms (GUO *et al*., 2013). Patients with the syndrome usually have macrocephaly or rib anomaly at birth and as they get older the palmoplantar pits are evident. At two years of age, 1% of patients may present with medulloblastoma, and by 10 years of age QTOs in the jaws are evidenced (FUJII; MIYASHITA, 2014). The presence of multiple QTOs in the jaws is the most common clinical manifestation and, although at a late age, is highly suggestive of the syndrome, even in the absence of cutaneous manifestations (POL *et al*., 2013; Hashmi *et al*., 2016; PACHOWICZ *et al*., 2017). Careful extra clinical and intraoral examinations and cranial and chest radiographs greatly assist in the diagnosis of SCNBC (KHALIQ *et al*., 2016).

Swellings in the face resulting from maxillary QTOs are often the first and only manifestations of the syndrome and therefore, generally, the first professional to come into contact with the patient is the dental surgeon (PEREIRA *et al*., 2015; KHALIQ *et al*., 2016). In addition, as patients have an increased risk of developing new cysts throughout life, the health professional is responsible for the preservation of these patients aiming at their early detection (HASHMI *et al*., 2016).

Because SCNBC is a condition that predisposes to cancer, it is of fundamental importance to early diagnosis of this syndrome. Long-term complications such as malignant neoplasms, orofacial deformations, and destruction can be reduced if diagnosis and treatment are carried out as soon as possible (CHANDRAN *et al*., 2015). Despite this, most patients with SCNBC have a good prognosis and normal life expectancy, although surgical interventions may be necessary to treat the conditions associated with the syndrome (GARCIA de MARCOS *et al*., 2009).

Thus, considering the need for regular observation of patients with SCNBC by a multidisciplinary health team, especially by dental surgeons, who are often responsible for the initial diagnosis of these patients, and taking into account the importance of knowledge of this syndrome for an early diagnosis of the morbidities underlying the syndrome, the present study aimed to perform a literature review on SCNBC, addressing aspects such as clinical manifestations, diagnostic criteria, and genetic etiology.

1.1 EPIDEMIOLOGY

The prevalence of SCNBC is 1 case for every 50 thousand - 150 thousand individuals and men and women seem to be equally affected (PASTORINO *et al*., 2012; KHALIQ et al., 2016).

1.2 DIAGNOSTIC CRITERIA

The first description of a patient affected by SCNBC was published in 1894 when Jarisch described a 22-year-old patient presenting with short stature, milia (small cysts filled with keratin, seen on the face, below the eyes, or on the forehead), mental disability, marked scoliosis, and multiple BCCs since the age of 14. But it wasn't until 1960 that SCNBC was described in detail by Robert Gorlin and Robert Goltz, who established the classic triad of multiple BCCs, multiple QTOs, and bifid ribs (GORLIN; GOLTZ, 1960).

In 1993, Evans et al. established the diagnostic criteria, which were later modified by Kimonis et al. (1997). According to the researchers, the presence of two major criteria or one major criterion plus two minor criteria is required for the diagnosis of this syndrome. (EVANS *et al.*, 1993; KIMONIS *et al*., 1997). These criteria are detailed in Table 1.

Table 1 - Diagnostic criteria of the SCNBC.

EVANS *et al.* (1993)	**KIMONIS *et al.* (1997)**
MAJOR CRITERIA	
Multiple BCC (>2) or 1 BCC under 30 years or > 10 basal cell nevi	Multiple BCC (>2) or 1 BCC in a patient < 20 years of age
QTO in jaws (histologically proven) or polyostotic bone cysts	QTO in jaws (histologically proven)
Palm or *plantar depressions (pits) (3 or more)*	Palm or *plantar depressions (pits) (3 or more)*
Early ectopic calcification (< 20 years) bilaminar of the cerebral sickle	Bilaminar calcification of the cerebral sickle
Family history of SCNBC	Bifid, fused, or markedly enlarged rib
	First-degree relative with SCNBC
MINOR CRITERIA	
Macrocephaly	Macrocephaly
Congenital malformations such as cleft lip or palate, frontal bossing, polydactyly, or ocular anomalies (cataracts, coloboma, microphthalmia)	Congenital malformations such as cleft lip or palate, frontal bossing, face coarse, and moderate or severe hypertelorism
Congenital skeletal anomalies: such as bifida, fused, absent, or enlarged rib; fused, absent, bifid, wedge-shaped vertebrae; *Sprengel*'s deformity, or marked pectoral deformity (*Pectus excavatum)*	Other skeletal anomalies (*Sprengel*'s deformity, marked breast deformity, and marked digital syndactyly
Medulloblastoma	Radiological abnormalities (covering of the sella turcica, vertebral anomalies, patterned defects of the hands, flame-shaped feet of the hands and feet
Ovarian or cardiac fibroma	Ovarian fibroma or medulloblastoma (not applicable in male patients)
Lymphasenteric cyst	

BCC: Basal cell carcinoma; QTO: Odontogenic keratocyst; SCNBC: Basal Cell Nevoid Carcinoma Syndrome

In 2011, an international multidisciplinary colloquium was organized to better define the findings of the syndrome. According to the colloquium, a suspicious diagnosis should be considered if there is a greater criterion and molecular confirmation; two major criteria; or a major and a minor criterion. However, there was no consensus among participants for a formal recommendation regarding

the syndrome (BREE *et al*., 2011). The criteria established by the colloquium are presented in Chart 2.

Table 2 - Diagnostic criteria of the SCNBC, according to the multidisciplinary colloquium of 2011.

MAJOR CRITERIA	**MINOR CRITERIA**
BCC before 20 years of age or an excessive number of BCCs, disproportionate to previous sun exposure and skin type	Rib anomalies
QTO of jaws before 20 years	Macrocephaly
Palm or plantar depressions	Other specific skeletal malformations and radiological changes (vertebral anomalies, chyphoscoliosis, small fourth metacarpal bone, postaxial polydactyly)
Lamellar calcification of the cerebral sickle	Cleft palate or lip
Medulloblastoma typically desmoplastic	Ovarian/cardiac fibroma
First-degree kinship with SCNBC bearer	Lymphosenteric cysts
	Eye abnormalities (strabismus, hypertelorism, congenital cataracts, glaucoma, coloboma)

BCC: Basal cell carcinoma; QTO: Odontogenic keratocyst; SCNBC: Basal Cell Nevoid Carcinoma Syndrome

The diagnosis should be made as early as possible, and in addition to the importance of clinical findings, radiographic examinations are crucial for the same (THOMAS *et al*., 2016; PACHOWICZ *et al*., 2017).

According to Lo Muzio (2008), the protocol for diagnosing the syndrome should take into account the following aspects:

- Family history: previous dental and medical histories.
- Clinical examination: skin, oral, central nervous system, head circumference; interpupillary distance, eyes, genitourinary, cardiovascular, respiratory, and skeletal systems.
- Imaging tests:
    - Radiographs of the chest (posteroanterior and anteroposterior), lateral of the skull, cervical and thoracic vertebrae; pan; hands (for pseudocysts); pelvis (women).
    - Ultrasound: ovary (women) to check for ovarian fibroma.
    - Echocardiogram: (child) to check for cardiac fibroma.
- Genetic testing.

1.3 COMMON MANIFESTATIONS

The clinical presentation of SCNBC differs between individuals, even within the same family or in different families. The presence of multiple QTOs is the most common and representative manifestation of the syndrome and is usually detected in the first and second decades of life (POL *et al*., 2013; MANJIMA *et al*., 2015; SUBRAMANYAM *et al*., 2015; KAMIL; TARAKJI, 2016; THOMAS *et al*., 2016). The QTOS may present an average of five per patient (ranging from 1 to 30), presenting a high recurrence rate after removal, justified by the presence of satellite cysts (daughter

cysts). These, in turn, are located on the periphery of the lesion and have a friable coating. In syndromic patients, the recurrence rate is higher. Preservation is recommended for a long period, being annual for five years and then, every two years, for the entire life of the patient (KAMIL; TARAKJI, 2016; KHALIQ *et al*., 2016; THOMAS *et al*., 2016).

BCCs associated with the syndrome are often reported in young patients in unexposed areas of the body. In general, the diagnosis occurs, on average, at 25 years of age (LO MUZIO, 2008; THOMAS *et al*., 2016). BCCs range clinically from pigmented papules to ulcerated plaques, with diameters of 1 to 10 mm, most commonly located on the face, back, and chest. The number ranges from 2 to 1000 BCCs (LO MUZIO, 2008; CHEN *et al*., 2015).

Evans et al. (1993), when studying 84 members of 29 families, found a prevalence of 71% of cases of palmoplantar depressions (which did not turn into carcinomas); 66% presence of QTOs in the jaws; 47% of BCC cases; 26% of ocular anomalies, the most common being strabismus; 24% of ovarian fibromas in women and no cases of cardiac fibroma. Only 5% of cases of medulloblastoma were diagnosed. The authors stated that the screening of cases should be initiated in the prenatal care of mothers or fathers with the syndrome, and cardiac tumors and cleft palates can be detected early. These children should be treated with periodic examinations, including DNA tests, for early diagnosis, before puberty, of any change related to the syndrome, avoiding complications.

Santos *et al*. (2016), when studying 10 Brazilian individuals from the same family with the syndrome, found that all had calcification of the cerebral sickle, hypertelorism, and prominent frontal bossing. Multiple QTOs occurred in 90% of patients, palmoplantar depressions in 40%, and multiple BCCs in 20% of patients.

Other alterations, such as skeletal anomalies, are quite frequent in syndromic patients. Above 60% of patients have rib anomalies (PACHOWICZ *et al*., 2017). The most frequently found radiographic alteration is calcification of the cerebral sickle (LO MUZIO, 2008; CHEN et al., 2015*), and in addition to this, the presence of multiple QTOs can be considered pathognomonic radiographic findings of the syndrome, observed using computed tomography (HAJALIOGHLI et al., 2015)*

1.4 *PTCH1* AND GENETICS

SCNBC exhibits an inherited autosomal dominant characteristic of complete penetrance and variable expressivity (GARCIA de MARCOS *et al*., 2009). Mutations in *PTCH1* are known to be associated with the etiology of SCNBC (HOOPER *et al*., 2013; THOMAS *et al*., 2016). However, causal mutations in other genes of the signaling pathway *HH*how *SUFU* and *PTCH2* have already been identified in patients with the syndrome (EVANS *et al*., 2017).

O gene *PTCH1,* whose chromosomal location is 9q22, consists of 23 exons encoding a transmembrane glycoprotein composed of 1447 amino acids, with 12 domains and two large turns (*loops*) hydrophilic extracellular, which function as receptors for the sonic hedgehog protein (SHH).

The SHH protein is inserted in the family *HH* of regulatory factors responsible for repressing the transcription of certain genes encoding signaling proteins belonging to the transforming growth factor (TGF-β) and Wnt families. During embryogenesis, the SHH pathway plays an important role in the ongoing development of the stem cell population, also adjusting the development of hair follicles and sebaceous glands. In adults, the SHH pathway is deactivated and aberrant activation of this pathway is associated with several neoplasms including BCCs.

Under normal conditions, the *PTCH1* constitutively inhibits SMO (a signal-transducing protein of the SHH pathway), however, the binding of *PTCH1* the SHH protein drives the release of SMO which activates transcription factors (Gli1, Gli2, and Gli3) that are transported to the nucleus and there activate target genes involved in cell growth and proliferation including *PDGFRA*, FOX gene family, MYCN, cyclins, *CTNNB1*, beta-cateninas e *RUNX3* (LO MUZIO, 2008; SÁ'S BELT; SILVA; Lopes, 2015).

O gene *PTCH1* acts both as a developmental gene and as a tumor suppression gene. Mutations in *PTCH1* They result in the non-formation of the second hydrophilic extracellular turn of the transmembrane receptor to which the SHH protein would bind, resulting in a non-inhibition of several genes that control the cell cycle and genes responsible for the fate, patterning, and growth of cells. Genetic analysis of patients with SCNBC identified more than 230 mutations in the *PTCH1*, including deletions, insertions, *Splicing,* and mutations *nonsense* and *missense*, and more than 80% of the mutations are related to the error during the reading phase of the codons (*frameshift*), or related to the insertion of a premature stop codon, which implies a non-functional protein (LO MUZIO, 2008).

Being a tumor suppressor gene, *PTCH1* follows the model of the two activations of tumor suppressor genes to occur disordered tumor growth. According to this model, there is a need for two distinct episodes of DNA damage, with the inactivation of both alleles of the tumor suppressor gene, for tumor development (KNUDSON, 1971).

The occurrence of two mutations in both alleles or a mutation in one allele of the tumor suppressor gene accompanied by allelic loss of the wild remnant is required for the development of neoplasm. In patients with SCNBC, the first activation is a germline mutation of the *PTCH1 gene,* and the second activation involves somatic mutation that inactivates it, or deletion, resulting in constitutive activation of signals from the HH signaling pathway (AGARWAL *et al*., 2014; TATE *et al*., 2014). All *PTCH1* mutations cause changes in this signaling pathway during development. There are more than 100 germline mutations of *PTCH1* associated with the syndrome (RODRIGUES *et al*., 2014).

According to Tate *et al.* (2014), the two inactivations *of PTCH1 were highly prevalent in BCC specimens from patients with the syndrome, although cases of absence of any activation of* PTCH1 may also exist. In the cases evaluated by the authors, there was interruption⁄ biallelic rupture in all 16 BCC specimens examined from two sisters with the syndrome.

The first was the germline mutation of c.2313delC and the second was the somatic loss of the wild allele of the PTCH1 gene, resulting in the lack of expression of the PTCH1 protein and then leading to activation *of the HH* pathway and finally, the formation of BCC. All BCC specimens showed loss of the wild allele of exon 16 of PTCH1*, indicating that the loss of heterozygosity resulted in biallelic disruption* of PTCH1 in multiple *BCCs* of the same patient.

These results indicated that the single-base germline deletion of *PTCH1* (c.2613 delC) is the first activation and the loss of heterozygosity of the wild allele is the second activation, implying that all 16 BCCs of the two sisters fit the two-activation carcinogenesis model.

Although genetic testing is considered the gold standard for the diagnosis of SCNBC, it has a high cost and demands time because it is laborious, due to the PTCH1 gene presenting 23 exons (LO MUZIO, 2008; HOOPER *et al*., 2013; THOMAS *et al*., 2016).

It was determined by the multidisciplinary colloquium that the genetic testing of the *PTCH1* gene is indicated only in prenatal testing if there is any mutation of this gene in the family; for confirmation of the diagnosis in patients with some clinical signs, but who do not meet all the criteria, allowing greater vigilance; and as a predictive test for patients with an affected family member, that is at risk but does not meet clinical criteria (BREE *et al*., 2011).

Guo *et al*. (2013), when analyzing 14 patients with the syndrome, carriers of QTOs, identified 34 mutations in 11 (78.6%) of the syndromic patients (11 germinative and four somatic), and in 13 (44.8%) of the 29 patients without the syndrome (all of them somatic), presenting sporadic QTOs. The predominant germline mutation was the mutation that causes protein truncation *PTCH* (mutation *nonsense*). In addition, 29 new mutations were identified, including 20 truncations, five non-truncations, and four *splices.*

The mutations were widely distributed across the entire gene sequence: 12 in the two large extracellular turns (*Large extracellular loops*), eight in the sterol-sensitive domain (*sterol-sensing domain - SSD*), four in the N-terminal region, three in the eighth to tenth transmembrane regions (TM8-10), and two in intracellular turns 4 and 5 (ICL4 and ICL5).

The presence of germline mutations in individuals with the syndrome justifies the appearance of QTOs at early, multifocal ages in both jaws, while sporadic QTOs are unique and appear in older patients, and preferably located in the mandible. The authors suggested that the syndrome may also be caused by genes other than the *PTCH1*, with interference from environmental factors.

Ponti *et al.* (2013) found that the protein profiles of fibroblasts obtained from BCCs had statistically significant differences when they came from *missense* and *nonsense* mutations of the *PTCH1 gene*.

These fibroblasts could play a role in the development of BCC, even without sun exposure, with the production of different proteins (cytokines and growth factors), promoting the proliferation of basal cells.

There was no evidence of a transcriptome-associated *PTCH*1 *nonsense mutation, but the authors hypothesized that the mutations were coding for degradation mRNA bound to cytosolic variants of the PTCH* protein, rather than transmembrane proteins.

The absence of the transmembrane protein receptor may be related to the constitutional activation of the HH signaling pathway, which increases protein synthesis and secretion. Conversely, *missense mutation of the* gene should lead to the production of defective receptors, which should explain the poor ability of fibroblasts to synthesize.

Morita *et al.* (2015) screened 15 individuals (10 affected and 5 non-syndromic relatives) with a history of SCNBC (six families) looking for genetic changes using hybridization and PCR by next-generation sequencing (*next-generation sequencing-NGS*).

Through the re-sequencing of all coding exons in the junction regions between exon and intron, as well as evaluation of the status of changes in the number of copies (*copy number alterations-CNA*), using alignment map files obtained via *NGS*, the authors found that several mutations in the *PTCH1*, including large deletions, could explain the different phenotypes of the syndrome.

According to the authors, as it is advisable to examine the *CNAs*, in cases of absence of mutations, the methodology *NGS*, which simultaneously screens all exons of the signaling pathway genes *HH*, is useful because it simultaneously detects single nucleotide variations (*single nucleotide variations-SNVs*) and *CNAs* in the regions of the target genes.

The authors found that *SNVs* of *PTCH1* caused amino acid changes in four families (seven individuals), while the *CNAs* in or flanking *PTCH1* were found in two families, in which *SNVs* were not detected. Numerous germline mutations of *PTCH1*, including errors in reading *frameshift* mutations *Nonsense, Missense and Splicing*, as well as large insertions and gross deletions, were observed.

1.5 PATIENT MANAGEMENT AND AVAILABLE TREATMENTS

The management of patients with the syndrome should be multidisciplinary, involving dental surgeons; pediatricians, radiologists, otolaryngologists, urologists, cardiologists, gynecologists, ophthalmologists, surgeons, plastic surgeons, neurologists, oncologists and geneticists (ACHARYA *et*

al., 2013; GUPTA *et al*., 2013; CHANG *et al*., 2014; CHEN *et al*., 2015; RAMESH *et al*., 2015; SKODRIC-TRIFUNOVIK *et al*., 2015; KAMIL, TARAKJI, 2016; KHALIQ *et al*., 2016). Dermatologists should also be involved in the early detection of BCCs (HASHMI *et al*., 2016; TANDON *et al*., 2016).

Genetic counseling with or without genetic testing should be considered for family members of the patient with the syndrome (LO MUZIO, 2008; KIRAN *et al*., 2012; ACHARYA *et al*., 2013; DONG-UK *et al*., 2016; HASHMI *et al*., 2016; SANTOS *et al*., 2016). The family should be carefully informed about the changes responsible for the disease, prognosis and risks of more individuals affected by the syndrome since each child of a syndromic has a 50% chance of inheriting the defective gene (LO MUZIO, 2008; SANTOS *et al*., 2016).

The treatment of QTOs has been performed by several modalities, one of them being the Carnoy solution (absolute alcohol, chloroform, glacial acetic acid, ferric chloride), which can be used as an adjunct to surgical enucleation, its most common treatment.

A systematic review by Diáz-Belenguer *et al*. (2016) revealed that only enucleation presented a recurrence rate from 0 to 58.8% and using Carnoy's solution as the only adjuvant, recurrences ranged from 0 to 100%. With the use of more than two adjuvant treatments, the recurrence rate was from 0 to 7.9%.

However, studies using more than two adjuvants involved fewer patients and their proservation time was different, which may induce bias. Another type of treatment is the surgical removal of the QTOs in which it requires exposure of the lesion utilizing an osteotomy in the jaw under local or general anesthesia, for the meeting of the cyst wall and its total removal. Only in extreme cases is it necessary to remove the entire region of the affected jaw.

The treatment of BCCs with radiation is contraindicated for patients with syndromes that predispose to cancer (FECHER; SHARFMAN, 2015). Another important factor is that due to the strong positive correlation of BCCs with sun exposure, it is indicated that patients avoid excessive sun exposure, also using sunscreen and glasses during sun exposure.

As a treatment of superficial BCCs without follicular involvement, there is an indication for the topical use of Tretinoin 0.1% cream. Surgical excision is only indicated when the number of lesions is limited and other treatments may be more efficient than surgical removal of multiple lesions such as ablation, photodynamic therapy, and topical chemotherapy.

Another form of treatment for BCCs is photodynamic therapy (PDT), which involves the use of a photosensitive pigment given intravenously or topically that preferentially accumulates inside malignant cells and is then activated by a red light that kills the cells. Interferon therapy has also been proposed in experimental studies (LO MUZIO, 2008).

Vismodegib is an orally administered drug approved by the U.S. *Food and Drug Administration* (FDA), used to treat metastatic, locally advanced, and unresectable BCCs, and is effective and safe (CHANG *et al*., 2016). It is an inhibitor of the *HH* signaling pathway, acting through its interaction with the*mothened* s protein (smo), inhibiting the *SMO gene pathway*. Ally *et al*. (2014) found that Vismodegib also could decrease the size (by 50%) of QTOs of patients with the syndrome. However, four patients had decreased QTOs and in two there was no change in lesion size (ALLY *et al*., 2014).

The approximate monthly cost of treatment with Vismodegib is $7,500.00, and considering that it lasts for many months, it becomes unfeasible for patients (MOHAN; CHANG, 2014). Added to this is the presence of the many adverse effects of the drug, such as cramps and muscle spasms; loss of weight, taste and hair; fatigue and dysgeusia (TANG *et al*., 2012; CHANG *et al.,* 2014; BOOMS *et al*., 2015), which lead to discontinuity of treatment. More than half of the patients studied by Tang *et al*. (2012) discontinued the use of Vismodegib due to its adverse effects.

Kis *et al.* (2012) performed treatment with electrochemotherapy (use of electric current and administration of antineoplastic drugs) as intravenous bleomycin, in three patients who had 99 BCCs located on the face and trunk and obtained a positive response in 99% of the lesions, with 87% of these with complete response. Numerous tumors can be treated in the same session and the sessions can be repeated if necessary.

Chaudhary *et al*. (2015) in a study with murine mice, reported that the administration of inhibitors (vismodegib/**itraconazole/cyclopamine) of** the SMO *pathway* or nonsteroidal anti-inflammatory drugs (sulindac/**sulfasalazine**) separately resulted in partial resolution of Ultraviolet (UVB)-induced BCCs. The combined administration of these inhibited the growth of BCCs by 90%. For the authors, SKH-1 mice are relevant and viable animal models for the study of SCNBC, accelerating the development of therapeutic modalities to be used in affected patients.

2 MATERIAL AND METHODS

This is a review of the recent literature on SCNBC. The bibliographic survey was performed through the NCBI online database (PubMed) (https://www.ncbi.nlm.nih.gov/pubmed/), the term " being used*Gorlin Goltz Syndrome*" as a search engine. Articles published on the subject in the last five years were included in the review and, from these, only those freely available in their full version were selected (*Free Full Text).* After the initial screening, the downloaded articles were sequentially numbered and read to verify the adequacy of the theme, and those that did not refer strictly to the theme were excluded. The remaining articles were then classified according to the type of article: research articles, literature reviews, clinical case, and clinical case associated with the review. Subsequently,

the articles were also evaluated for the number of clinical cases per article, the most frequently cited clinical criteria among the clinical cases, as well as the performance of molecular tests and corresponding methodology.

In addition to the articles mentioned, we sought to include ref-classical rerences necessary for discussion of the topic, such as Gorlin; Goltz (1960), Knudson (1971), Lo Muzio (2008), Bree *et al.* (2011) and Evans et al. (2013, 2017).

3 FINDINGS

Out of a total of 115 full-text articles available, located by the database *PubMed*, 27 articles (23.5%) were excluded because they did not refer strictly to the theme, resulting in a final number of 88 articles included in the study.

Of the 88 articles used, 21 (23.9%) were classified as research articles; 14 (15.9%) as literature review articles, 45 (51.1%) as clinical cases, and eight (9.1%) as concomitant clinical case articles and literature reviews.

The articles containing clinical cases alone (n=45) added to those associated with the review (n=8) resulted in a total of 53 (60.2%) articles, of which the majority were from a single case report (n=49, 92.4%), four articles reported more than one clinical case (7.6%). Most cases were reports of the syndrome affecting males (n=33, 55%) and 27 (45%) were reported in females. Two (3.8%) articles did not report gender.

The clinical manifestations of the syndrome reported in the 53 articles of clinical cases surveyed are presented in chart 4. Regarding the phenotypic manifestations of the syndrome, of the major criteria, the most prevalent cited was the QTO (n=45, 84.9%), followed by calcification of the cerebral sickle (n=31, 58.4%), palmoplantar depressions (*pits*) (n=28, 52.3%). BCCs had a prevalence of 41.5% (n=22). Regarding the minor criteria, the most prevalent manifestations were ocular anomalies (n=30, 56.6%), followed by skeletal and radiological alterations (n=27, 50.9%) and rib anomalies (n=26, 49%). Of the ocular anomalies, hypertelorism was the most prevalent (n=25, 83.3%). Other phenotypic clinical alterations were mentioned by 36 articles (67.9%), which may or may not be related to the syndrome.

Table 3. Criteria for the diagnosis of SCNBC (BREE et al., 2011), observed in the case report articles.

	MAJOR CRITERIA						MINOR CRITERIA					
Case *	1 CBC	2 QTO	3 Depression foot, hand	4 Calc. Brain sickle	5 Medulo blastoma	6 Family history SCNBC	*1 Anomal. Rib*	*2 Macro cefalia*	*3 Other skeletal and radiological malformations (AV, ST, F, BF, P, S, Si, P, E)*	*4 Cleft lip or P*	*5 Fibroid (O, C)*	*6 Annon. Oculars (AO) Hypertelorism(H)*
2	X	X					X		X (AV, E)			
3		X		X			X					X (H)
4		X		X			X					
8	X	X	X				X		X (E)			X(H)
9		X		X			X	X	X (ST, BF)			X (H)
12		X	X	X		X		X	X (BF, E)			X (AO H)
13		X	X		X		X					
14		X		X								
18		X		X			X					X (H)
19		X	X	X								X (H)
24	X	X	X	X								X (H)
26		X	X	X			X	X	X (BF, Sp, E)			X (H)
27		X					X					X (H)
30	X	X						X				X (H)
33		X		X			X		X (AV)			
35	X	X	X	X		X	X		X (E)			X (H)
37					X	X	X	X	X(BF)			
38		X	X			X	X		X (BF, Si)			
39		X	X				X	X	X (BF, E)			X (H)
40		X					X		X (AV)			X (AO, H)
41	X		X									
42	X	X		X								
44	X	X	X	X		X	X	X	X (P, E)			X (H,)
46		X		X			X					
48	X	X		X			X		X(BF)			
50		X	X	X			X					
52		X		X			X		X (P)			X (AO)
53		X										X (AO)
57	X	X	X	X				X	X (BF, E)			X (AO, H)
60	X		X	X			X		X (E)			
65	X		X			X		X				X (H)
66	X		X	X								
68		X	X	X					X (BF)			
74		X			X							X (H)
77			X			X		X				
80	X		X	X		X			X (Si)			
82		X	X	X				X	X (BF)			X (H, AO)
84		X	X									X (AO)
86		X	X	X					X (AV, E)			
89	X	X	X	X		X						
92	X	X										
97	X	X		X		X						X (AO, H)
98		X							X (P, Si)			X (H)
99	X	X	X									
100	X	X	X	X			X	X	X (ST, BF, Sp)			X (H)
101		X	X	X			X	X	X (Sp, E)			X (AO)
102	X										X (C)	
106		X				X					X (O)	
107		X		X		X	X	X	X(BF)			X (TO H)
108		X					X		X (BF)			X (H)
109	X	X	X	X			X		X (ST P, E, Si)	X (FL)		X (AO, H)
112		X		X					X (ST, F, E, Sp, P)		X (O)	X (AO)
115	X	X	X									X (H)
T	22 41,5%	45 84,9%	28 52,8%	31 58,4%	3 5,6%	12 22,6%	26 49%	14 26,4%	27 50,9%	1 1,9%	3 5,6%	30 56,6%

BCC: Basal cell carcinoma; QTO: Odontogenic keratocyst; SCNBC: Basal Cell Nevoid Carcinoma Syndrome *See references

It can also be verified that a total of 18 (34%) articles of clinical cases performed molecular tests in search of mutations in the *PTCH1* gene. Of these, 8 (44.4%) did not detail them, and only one of them mentioned the presence of a new insertion mutation. The mutations frequently found are described in chart 4 and were mostly reading errors (*frameshift*) and premature stop codons (*nonsense mutation),* affecting different exons, such as *2, 3, 6, 8, 11, 12, 18, 21.*

Os métodos moleculares utilizados citados nos artigos foram sequenciamento genético, sequenciamento de nova geração, hibridização genômica (*Array-based comparative genomic*

hybridization-a-CGH), *Multiplex ligation-dependent probe amplification (MLPA*), *Polymerase Chain Reaction* em tempo real (*PCR-Real Time),* Método *Nanostring, Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR), quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR), Fluorescent in situ Hybridization* (*FISH*), *Whole Exome Sequencing (WES),* imunofluorescência e imunohistoquímica.

Table 4: Mutations found in clinical case articles (n=18).

Author and year	Type of mutation	Strain reached	Mutation specification	Location of the mutation	Result
Ishitsuka et al. (2012)	Nonsense mutation		c.584G>A	Exon 3	*Aberrant* splicing
Chang et al. (2013)					Increase in gli1, ptch1, pik3c proteins
Hooper et al. (2013)	Heterozygous deletion				
Gentzsch et al. (2014)	Heterozygous deletion *Frameshift*			Exon 11 e 12	*Frameshift,* Premature stop codon
Rodrigues et al. (2014)	*Frameshift*	Germinative	c290dupA	Éxon 2	Protein truncation, with loss of function
Diociaiuti et al. (2015)	*Inappropriate splicing*		c585-1G>A	Íntron 3	Transcribed without exon 4
Gururangan et al. (2015)	Mutations espontânean onsense *missense*	Germinative	C>T G>A c.1670 C>G	Éxon 18 Exon 12 in the *splice* of the donor site Éxon 12	
Hettmer et al. (2015)		Germinative	IVS15-1G>A; c2560+1G>A	Splice do Íntron 15	Destruction of the canonical splicing acceptor site, *with* abnormal *splicing*
Rajan et al. (2015)	Deletions	Germinative	c.456_460del	Éxon 3	Premature stop codon
Skodric-Trifunovik et al. (2015)	Mutation *Frameshift, nonsense*	Somatic Germination	c.903delT c.3524delT c.1148C>A	Éxon 6 Exon 21 Exon 8	Premature stop codon, truncated protein, mRNA degradation
Ozcan al. (2016)	New insertion mutation	No details			
Fini et al. (2013), Nakamura et al. (2013), Saulite et al. (2013), Chen et al. (2015), Hajalioghli et al. (2015) Hashmi et al. (2016), Jiang et al. (2016)	Genetic testing	No details			

4 DISCUSSIONS

SCNBC is a rare syndrome with wide phenotypic heterogeneity, which makes it difficult to identify until the presence of QTOs or BCCs becomes apparent. The diagnostic challenge lies in identifying some of the more than 100 clinical manifestations that affect many organs and systems. These are characterized by the presence of skeletal, craniofacial anomalies, neurological, oropharyngeal, dermal, sexual, ophthalmic, and cardiac (ACHARYA *et al*., 2013; CHEN *et al.,* 2015; SAINTS *et al*., 2016). The clinical presentation of SCNBC differs between individuals, even within the same family or in different families.

Consistent with the literature, QTOs were the most prevalent manifestations in the articles of clinical cases consulted in this study. When in the presence of multiple QTOs, SCNBC should initially be suspected considering the protocol proposed by Lo Muzio *et al.* (2008) and the classifications of Bree *et al*. (2011) (MANJIMA *et al*., 2015; SUBRAMANYAM *et al*., 2015). Khaliq *et al.* (2016), in a clinical-pathological study of seven syndromic patients, found that all had multiple QTOs as the first manifestation of the syndrome, most of them being located in the mandible (77%), with unilocular pattern (71%) and associated with teeth (88%). All patients also had calcification of the cerebral sickle.

As the treatment is multidisciplinary, the referral of the patient is of fundamental importance, for the diagnosis of other alterations and possible interventions, as early as possible. The patient should be proservated by different specialists, especially the dermatologist, due to the high predisposition to BCC and other neoplasms (KIRAN *et al*., 2012). Despite naming the syndrome, the presence of BCCs reported in the articles of clinical cases surveyed was not very frequent, being cited in less than half of the articles.

Generally, the clinical diagnosis of the syndrome is already sufficient, without the need for genetic confirmation (PIRSCHNER *et al*., 2012). This was verified in the case-reporting articles surveyed, where a minority reported the use of genetic tests as a diagnostic tool, and only clinical criteria were used for the diagnosis of cases. *PTCH1* is the only gene in which mutations are known to cause SCNBC, but because it has many exons, its sequencing becomes costly (HOOPER *et al*., 2013; THOMAS *et al*., 2016). Although sequenced, there is no genotype correlation of the *PTCH1 gene* with the patient's phenotype, and the detection of mutations does not provide information about the prognosis or clinical manifestations of the disease (RODRIGUES *et al*., 2014).

Because it is a hereditary condition, counseling and genetic testing are important for clarification of the patient and search for relatives at risk, especially children. As the syndrome is of autosomal dominant inheritance, the offspring have a 50% risk of being affected by the syndrome (LO MUZIO, 2008; ACHARYA *et al*., 2013; SUBRAMANYAM *et al*., 2015). The high mutation detection rate of the *PTCH1* gene enables a molecular diagnosis to become a tool of great value in establishing

an early diagnosis, especially in atypical phenotypes or even in unaffected family members (ACHARYA *et al*., 2013; SKODRIC-TRIFUNOVIC *et al*., 2015). However, the high cost of molecular tests makes it impossible to perform them as a routine.

Among the mutations most commonly reported in clinical cases are *frameshift*, *nonsense* and *splicing site mutations*. While the *frameshift* mutation is usually caused by the insertion or deletion of nucleotides, modifying the mRNA reading sequence and as a consequence, altering the synthesized protein, the *nonsense* mutation entails a premature stop codon and can predict a truncated protein, usually of smaller size than desired. Mutations in the *splicing sites* (exon/intron junctions*)* result in the alteration of exon and intron excision and different transcripted mRNA and generation of different proteins, which may or may not be functional. Such mutations have been found in germ cells and also in somatic cells. Germline mutations are the most common in the syndrome, and there are more than 100 related to the syndrome (RODRIGUES *et al.*, 2014), and are inherited by the next generation. The somatic ones will not be passed to the progeny (LO MUZIO, 2008; RODRIGUES *et al*., 2014). Above 80% of mutations occur in the reading phase, causing error (*frameshift*), or leading to premature truncation of the encoded protein. The remaining mutations lead to the production of an abnormal receptor (LO MUZIO, 2008).

The most used techniques for detecting *PTCH1* mutations identified in the articles were PCR amplification followed by genetic sequencing. Sequencing is important since most patients have a new spontaneous mutation, with no history of an affected family member (CHEN *et al*., 2015). The sequencing recommended by Sanger *et al.* (1977) is based on the controlled interruption of DNA enzyme replication and is considered first-generation. There is new generation sequencing, and the more sophisticated the technique, the more expensive the method (PILLAI *et al*., 2017).

The limitations of the study were the use of only freely available articles in the database, which may represent a bias of the present study since more relevant and current research articles might not have been included. This fact is made more concrete by the observation that the vast majority of the articles surveyed are clinical cases, considered to have low scientific impact, and the presence of few available research articles.

5 FINAL CONSIDERATIONS

From the results found in this literature review it can be concluded that SCNBC is a syndrome still little studied given its rarity in the population and its description in the literature, mostly in the form of clinical cases. The most prevalent sex reported in clinical cases was male. Although quite numerous, clinical manifestations still constitute the main means of diagnosing the syndrome. It was found that, among the major criteria for diagnosis, QTOs were the most cited clinical manifestations,

followed by calcification of the cerebral sickle. Ocular anomalies were the most prevalent minor criteria. For many of these criteria, imaging tests function as a complementary diagnostic tool of great value.

The molecular tests most commonly verified in the articles were the sequencing of the *PTCH1* gene, and germline and somatic mutations can be detected in it. Despite the existence of several mutations in the *PTCH1 gene* that are attributable to the etiology of SCNBC, the performance of diagnostic molecular tests was not performed in many of the studies analyzed, and even in those in which the mutations were identified, there was no correlation with the patient's phenotype or with the prognosis, which makes the performance of molecular tests is indicated only in some particular cases.

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