EGAS MONIZ SCHOOL of HEALTH & SCIENCE | INSTITUTO UNIVERSITÁRIO EGAS MONIZ

INSTITUTO UNIVERSITÁRIO EGAS MONIZ

MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

THE ORAL-FACIAL MANIFESTATIONS OF GORLIN SYNDROME

Trabalho submetido por
Kais Kammoun
para a obtenção do grau de Mestre em Medicina Dentária

julho de 2024

EGAS MONIZ SCHOOL of HEALTH & SCIENCE | INSTITUTO UNIVERSITÁRIO EGAS MONIZ

INSTITUTO UNIVERSITÁRIO EGAS MONIZ

MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

THE ORAL-FACIAL MANIFESTATIONS OF GORLIN SYNDROME

Trabalho submetido por
Kais Kammoun
para a obtenção do grau de Mestre em Medicina Dentária

Trabalho orientado por
Prof. Doutor José Furtado

julho de 2024

DEDICATÓRIA

Aos meus pais, Zouhaier e Nadia, por tudo que me ensinaram, pelos valores que me transmitiram e por estarem sempre presentes.

Ao meu irmão Dali, por todo apoio e força que sempre me deu durante essa longa jornada.

Dedico esta tese à minha esposa Ons, que me apoiou durante todas as provações e que se sacrificou para realizar este sonho.

Ao meu filho Skander, tenho estado longe de você, não tem sido fácil e espero que possamos recuperar o tempo perdido. Esta tese é para você.

AGRADECIMENTOS

Manifesto a minha gratidão ao meu orientador de tese o Prof. Doutor José Furtado pelo tempo, pela disponibilidade, pela crítica, pelos conselhos e sobretudo o meu muito obrigado pela perseverança e pela paciência.

Ao Prof. Doutor José João Mendes e todos os Professores da universidade de Egas Moniz que me acompanharam durante este percurso académico e ajudaram ao meu desenvolvimento pessoal e profissional, assim como a todos os meus colegas de curso especialmente o meu binómio Mourad que percorreu este caminho ao meu lado.

Em memória do Professor Doutor Martins dos Santos.

ABSTRACT

The Gorlin syndrome, also known as Nevoid Basal Cell Carcinoma Syndrome (NBCCS) or Gorlin-Goltz Syndrome (OMIM #109400), is an autosomal dominant genetic disorder primarily associated with mutations in the PTCH1 gene. Nevoid basal cell carcinoma syndrome is characterized by numerous basal cell tumors and epidermal cysts of the skin, calcified falx cerebri, keratocysts of the jaws, palmar and plantar pits, ovarian fibromas, medulloblastomas, mesenteric lymph node cysts, fetal rhabdomyoma, rib and vertebral malformations, cleft lip or palate, and cortical defects of the bones.

OBJECTIVE

The main objective of this thesis will be to conduct an updated and comprehensive literature review of the multiple clinical manifestations of Gorlin Syndrome, which extend far beyond basal cell carcinomas, including systemic, dermatological, skeletal, ophthalmological, and neurological features. Particular emphasis will be placed on oral and dental characteristics associated with Gorlin Syndrome, highlighting the importance of its diagnosis, particularly odontogenic keratocysts, dental and oral anomalies, and cleft palates.

Because specialized and differentiated dental care is necessary and crucial for individuals affected by this syndrome, research will be conducted on the latest studies considering different follow-up strategies for monitoring these patients. The importance of a specialized multidisciplinary approach will be emphasized, with the dentist playing a significant role in contributing to a better prognosis and well-being of these patients.

In our narrative review of Gorlin Syndrome, we conducted a comprehensive literature search using the terms "Gorlin syndrome etiology," "Oral-facial Gorlin syndrome malformations," and "Nevoid Basal Cell Carcinoma Syndrome."

We use authoritative databases such as "PubMed," "Mendeley," "Orphanet," and "OMIM," focusing on articles published from October 2020 to February 2024. We extracted relevant information from selected articles covering genetic markers, clinical features, oral manifestations, and treatment approaches and synthesized these findings to offer a comprehensive narrative overview.

Keywords: Nevoid Basal Cell Carcinoma Syndrome (NBCCS), Hedgehog signaling pathway, PTCH1 mutation, odontogenic keratocyst.

RESUMO

A Síndrome de Gorlin, também conhecida como Síndrome do Carcinoma Nevoide Basocelular (NBCCS) ou - Gorlin Goltz Síndrome (OMIM # 109400) é uma doença genética autossómica dominante, principalmente associada a mutações no gene PTCH1. A síndrome do nevo baso celular (SNBC) é caracterizada por numerosos tumores basocelulares e quistos epidérmicos da pele, pregas calcificadas, queratocistos dos maxilares, fossetas palmares e plantares, fibromas dos ovários, meduloblastomas, quistos linfo mesentéricos, rabdomiomas fetais, malformações das costelas e vertebrais, lábio leporino ou fenda palatina e defeitos corticais dos ossos.

OBJETIVO

Este trabalho teve como objetivo efetuar uma revisão bibliográfica atualizada e abrangente das múltiplas manifestações clínicas da Síndrome de Gorlin, que vão muito além dos carcinomas basocelulares, incluindo características sistémicas, dermatológicas, esqueléticas, oftalmológicas e neurológicas.

Foi dada particular enfase às características orais e dentárias que têm vindo a ser associadas à Síndrome de Gorlin, destacando a importância do seu diagnóstico, nomeadamente os queratócitos odontogénicos, anomalias dentárias e orais e fendas palatinas .

Porque é necessário e crucial um cuidado dentário especializado e diferenciado às pessoas afetadas com esta Síndrome, foi feita a pesquisa dos trabalhos mais recentes tendo em conta as diferentes estratégias de follow-up para o seguimento destes pacientes. É enfatizada a importância de uma abordagem multidisciplinar especializada, onde o médico dentista desempenha um papel relevante, contribuindo, também, para um melhor prognóstico e bem-estar desses pacientes.

Foi efetuada uma pesquisa abrangente da literatura utilizando os termos: "etiologia da síndrome de Gorlin", "malformações orofaciais da síndrome de Gorlin" e "Síndrome do Carcinoma Basocelular Nevoide", em bases de dados competentes como "PubMed", "Mendeley", "Orphanet", e "OMIM", com foco em artigos publicados de outubro de 2020 a fevereiro de 2024. Extraímos informações relevantes de artigos selecionados que abordam marcadores genéticos, características clínicas, manifestações orais e abordagens

de tratamento e sintetizamos esses achados para oferecer uma visão geral narrativa abrangente.

Palavras-Chave: Síndrome de Carcinoma Basocelular Nevoide (NBCCS), via de sinalização Hedgehog, mutação PTCH1, queratocisto odontogénico

INDEX

LIST OF FIGURES

LIST OF TABLES

LIST OF ACRONYMS

5-FU- 5-fluorouracil

BCNS- Basal cell nevus syndrome

BCC- Basal cell carcinoma

CLP- Cleft lip/palate

CT- Computerized tomography

CVS- Chorionic villus sampling

DHH- Desert hedgehog

DNA- Deoxyribonucleic acid

FDA- U.S. Food and Drug Administration (FDA)

GLI- Glioma-associated oncogene homolog

GS- Gorlin syndrome

HH- Hedgehog

IGFBP- The insulin-like growth factor-binding protein

IHC- Immunohistochemistry

IHH- Indian Hedgehog

IQs- Initial Quality Survey

Ki-67- Antigen Kiel 67

KCOT- Keratocystic Odontogenic Tumor

MLPA- Multiplex ligation-dependent probe amplification

MRI- Magnetic resonance imaging

NBCCS- nevoid basal cell carcinoma syndrome

NCBI- National Center for Biotechnology Information

NGS- Next-generation sequencing

OKC- Odontogenic keratocysts

OMIM- Online Mendelian Inheritance in Man

OPG- Orthopantomograms

P53- Tumor protein 53

P63- Tumor protein 63

PCNA- Proliferating cell nuclear antigen

PCR- Proliferating cell nuclear antigen

PTCH1- Patched one gene

SHH-Sonic hedgehog

SMO- Smoothened

SNBC- Síndrome do nevo baso celular

SUFU- Suppressor of fused homolog

TGF- Transforming growth factor

US- Ultrasound

UVB- Ultraviolet B

WHO- World Health Organization

WNT- Wingless-related integration

I. Introduction

Like many other syndromes, nevoid basal cell carcinoma syndrome (NBCCS); OMIM #109400) was initially identified in 1864 through clinical observation. It has been known by various names, such as multiple basal cell carcinoma syndrome, basal cell nevus syndrome (BCNS), jaw cyst-basal cell tumor-skeletal anomaly syndrome, and fifth phacomatosis.

During the 1960s, Dr. Goltz recognized and designated it as a separate condition, naming it nevoid basal cell carcinoma syndrome . Over time, many case reports have improved the diagnostic criteria for this disease. Furthermore, scientists have deepened our comprehension of the condition's basic pathophysiology and the genetic changes responsible for its occurrence. Initially, only odontogenic keratocysts (OKC), multiple basal cell nevi, and specific skeletal abnormalities were identified as clinical manifestations. Nevertheless, the range of symptoms associated with the syndrome has expanded to include presentations related to endocrine, neurological, genital, and ophthalmological manifestations.

For most patients, the burden of nevoid basal cell carcinoma on quality of life initially centers on treating recurrent odontogenic keratocysts and basal cell carcinomas(BCC). Our work aims to comprehend how this essentially molecular and genetic syndrome arises and present the clinical criteria in general, particularly on the bucco-facial level. We provide the findings of an updated and thorough bibliographic inquiry into the various clinical presentations of Gorlin Syndrome (GS).

II. Development

1. Historical

Robert James Gorlin was a geneticist and oral surgeon born on January 11, 1923, in Hudson, New York. He died in the Minnesota city of Minneapolis on August 29, 2006, at the age of 83, from cancer. (Figure 1) Gorlin joined the military during the Second World War and subsequently pursued a dental education at the University of Washington. He completed his studies in 1947 and obtained a master's degree in chemistry from the State University in Iowa. Following his tenure in several academic roles, he assumed the position of professor and director of the Division of Oral Pathology at the University of Minnesota in 1956, where he remained until his final days.

Gorlin's career significantly changed in 1940 when he discovered work on *acanthosis nigricans* by dermatologist Helen Curth. This dermatosis primarily causes thickened and pigmented skin in the armpits, neck, and genital-crural regions. Gorlin was fascinated by the potential for systemic disorders to exhibit oral signs. He gained renown for his research on the oral symptoms of various syndromes. He named about 100 syndromes with his colleagues and characterized the genes responsible for nearly half. Gorlin's name became synonymous with genetics and medicine, and many doctors considered him a pioneer in dermatology, genetics, and pathology.

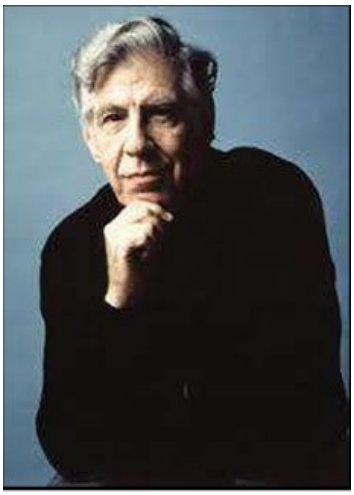


Figure 1: Robert James Gorlin

Robert J. Gorlin was an exceptionally prolific writer. He wrote around 600 articles and about 60 book chapters and co-authored or edited 20 volumes. His works have been published in several languages, including Japanese, Spanish, and Russian.

Gorlin is primarily known for his contributions to understanding NBCCS, also known as GS. In 1960, he was the first to describe the relationship between multiple BCC manifesting on the body, encompassing eye defects and tumors, non-exposed regions, bone lesions, and rib deformities. These abnormalities are now known as Gorlin syndrome, and Gorlin helped to identify the responsible gene, the PTCH gene (NCBI Reference Sequence NM_000264.3). OMIM # 601309

Thanks to his extensive knowledge, Gorlin taught various classes at Minnesota University, such as dermatology, pathology, otolaryngology, pediatrics, gynecology, and obstetrics.

He also presided over several prestigious organizations, including the American Academy of Oral Pathology, the International Society of Craniofacial Biology, and the International Association for Dental Research.

Gorlin received several prestigious awards for his remarkable contributions to science, medicine, and society.Currently, the standards for diagnosing Gorlin syndrome are purely clinical, but genetic testing remains the only definitive diagnosis (Akbari et al., 2018; Robert J. Gorlin and Robert W. Goltz, 1960). If one parent is affected by the condition, it is advisable to do genetic testing on siblings for early identification.

2. Gorlin syndrome: The diagnostic challenge

2.1. Diagnostic criteria

NBCCS, or Gorlin syndrome, is an autosomal dominant disorder inherited and characterized by numerous maxillary keratocysts, cerebral calcifications, and BCCs. (John & Schwartz, 2016) The estimated prevalence of NBCCS is roughly one in 50,000 to 256,000 persons (Lo Muzio, 2008).

Aside from BCCs, other major criteria consist of jaw keratocysts, the calcification of the cerebral falx, affected first-degree relatives, and palmar or plantar skin pits, or the two (Verkouteren et al., 2022). Minor diagnostic criteria include Lympho-mesenteric or pleural cysts, childhood medulloblastoma, cleft lip/palate (CLP), macrocephaly, preaxial or postaxial polydactyly, vertebral/rib anomalies, ocular abnormalities, and ovarian/cardiac fibromas (Evans et al., 1993; Kimonis et al., 1997). The diagnostic criteria for NBCCS were initially established by Evans et al (Evans et al., 1993) and later amended by Kimonis et al (Kimonis et al., 1997). Moreover, Bree et al. revised the information above in 2011 (Bree & Shah, 2011).

NBCCS results from a heterozygous germline mutation in the Patched one gene (PTCH1) located on chromosome 9q22 (Hahn et al., 1996; Johnson et al., 1996). PTCH1 codes for the transmembrane receptor, patched homolog 1, responsible for binding to the hedgehog (Hh) pathway (Fuse et al., 1999).

PTCH1 functions as a gene that suppresses tumor growth. It has been shown that the second allele of PTCH1 is inactivated in jaw keratocysts, medulloblastoma, and BCCs (Aszterbaum et al., 1998; Johnson et al., 1996). Furthermore, there is limited documentation of hereditary mutations in other individuals involved in the Hedgehog pathway, such as SUFU (Suppressor of fused homolog) and PTCH2 (Fan et al., 2008; Smith et al., 2014).

Individuals with a hereditary alteration in the SUFU gene have a marginally elevated possibility of developing medulloblastoma during childhood (Betancourt et al., 2022; Evans et al., 2017).

GS is a potential diagnosis if a patient presents with one major criterion and genetic confirmation, two major criteria, or one major and two minor criteria (Tables 1 and 2).

Table 1: The diagnostic criteria for NBCCS published by Kimonis et al. A diagnosis requires the presence of either one major criterion and two minor or two major criteria. Adapted from (Kimonis et al., 1997).

Major Criteria:
1. More than two BCCs or one under the age of 20 years.
2. OkC of the jaw, confirmed by histology.
3. Three or more plantar or palmar pits.
4. Bilamellar calcification of the falx cerebri.
5. Bifid, splayed, or fused ribs.
6. First-degree relative with GS syndrome.

Minor Criteria (Any One of the Following Features):
1. Macrocephaly determined after adjustment for height.
2. Congenital malformations: CLP, frontal bossing, “coarse face,” moderate or severe hypertelorism.
3. Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits.
4. Radiological abnormalities: bridging of the sella turcica, 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.
5. Ovarian fibroma.
6. Medulloblastoma

Table 2: Diagnostic criteria for Nevoid Basal Cell Carcinoma Syndrome. Diagnosis necessitates the satisfaction of two major criteria, two minor criteria, and one major criterion, or one major criterion, along with genetic validation. Adapted from (Bree & Shah, 2011).

Major Criteria :
1. One BCC or multiple BCCs in a person younger than 20 years
2. Odontogenic keratocysts
3. Plantar or palmar pits
4. Lamellar calcification of the falx cerebri
5. Medulloblastoma in early childhood
6. First-degree relative with NBCCS
Minor Criteria (Any One of the Following Features) :
1. Bifid, splayed or fused ribs
2. Other specific radiologic and skeletal abnormalities (pectus excavatum, i.e., hemivertebrae, scoliosis, syndactyly of digits, Sprengel deformity, flame-shaped lucencies of phalanges bony bridging of the Sella turcica)
3. Macrocephaly
4. CLP
5. Cardiac, ovarian or fibroma

If the clinical symptoms are unclear, genetic testing can be employed to detect a heterozygous mutation in PTCH1 or SUFU in the germline (Evans et al., 2002).

Some studies suggest that NBCCS is underdiagnosed. In response, the Department of Maxillofacial and Oral Surgery at the University of Rio Grande do Sul located in Brazil implemented an updated procedure: all patients diagnosed with odontogenic keratocysts (OKC) are now required to undergo a skull radiograph, posteroanterior and lateral cranial tomography, chest radiograph, and hand radiograph (Visioli et al., 2010).

Radiographic imaging is essential in confirming a diagnosis, continuing illness care, and surveillance. The recommended initial radiographic imaging consists of brain magnetic resonance imaging, panoramic jaw X-ray, pelvic ultrasound for female patients, echocardiography, and X-rays of the spine, chest, skull, hands, and long bones (John & Schwartz, 2016).

The same university has also studied the appropriate age for genetic testing in children. According to them, specific clinical manifestations would lead us to the right time for the test (Akbari et al., 2018).However, since this syndrome has a familial origin, it is possible to detect it much earlier. Let us cite in this sense:

2.2. Prenatal diagnosis

Prenatal diagnosis offers significant benefits in preventing and managing potential complications associated with genetic disorders. It enables the detection of genetic mutations responsible for the fetus's disease. Prenatal diagnosis is an invaluable tool for the early detection of Gorlin syndrome, enabling optimal patient care from birth and offering appropriate genetic counseling for afflicted families (Evans et al., 2024). Here are the key points to consider:

- A significant majority, approximately 70% to 80%, of NBCCS cases stem from an affected parent, while around 20% to 30% result from a spontaneous pathogenic mutation. Offspring of those affected carry a 50% chance of inheriting NBCCS. Detection of a deleterious mutation in the genes PTCH1 or SUFU within an affected family member allows for prenatal testing in high-risk pregnancies (Evans et al., 2024).
- Ultrasound scans (US) during pregnancy can objectify early developmental anomalies such as an enlarged cranial diameter, a palatine cleft, or even a cardiac fibroma, although rare. Fetuses affected by NBCCS may have a cranial diameter above average and thus need assistance during childbirth, namely forceps or possibly a cesarean section (Mak & Leung, 2019).

Amniocentesis and chorionic villus sampling (CVS) are suggestive means for early in-utero detection of NBCCS. Any patient with a confirmed genetic alteration in the PTCH1 gene should be informed of the need for prenatal diagnosis and possible preimplantation genetic diagnosis (Lo Muzio, 2008), a confirmed technique that practically eliminates the transmission of many genetic diseases from parents to children. This technique is utilized during an in vitro fertilization procedure to identify any abnormalities in the embryo prior to its transfer into the woman's uterus (Zimmerman et al., 2016).

Prenatal diagnosis requires detailed phenotyping, which relies on fetal imaging techniques like magnetic resonance imaging (MRI) and ultrasound (US) as illustrated in figure. 2.

However, prenatal diagnostics and fetal pathology have been effectively addressed using next-generation sequencing (NGS) (Rinaldi et al., 2022).

Since its inception, NGS has markedly enhanced the effectiveness of diagnosing rare disorders within healthcare. Widely adopted as a standard procedure for analyzing monogenic conditions across numerous countries, NGS provides a favorable equilibrium between affordability, procedural demands, and diagnostic effectiveness. In the realm of diagnosis, NGS attains a molecular diagnosis through meticulous scrutiny of possible harmful variants, familial medical history, and correlation of clinical manifestations with observed phenotypes. Irrespective of the methodology employed, a comprehensive clinical phenotype remains indispensable for precise diagnostic outcomes (Tatsi et al., 2020).

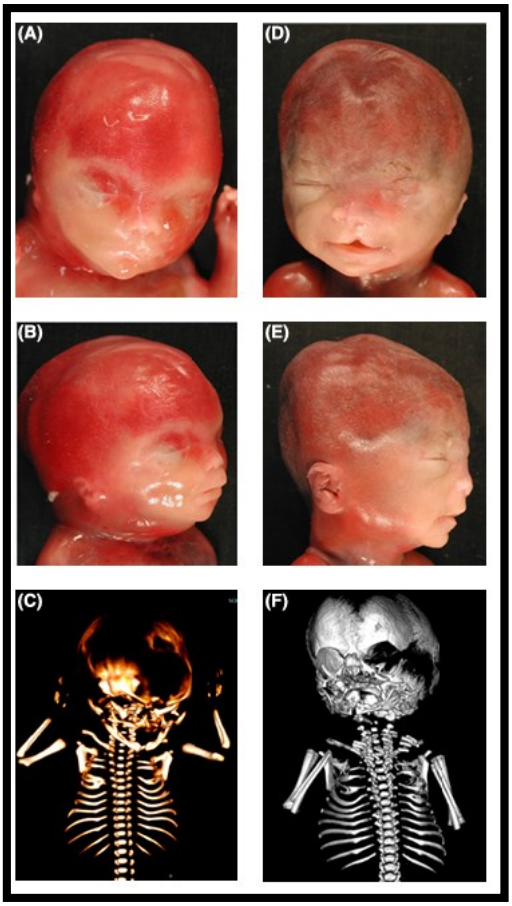


Figure 2: The CT scan reveals the facial appearance of 1st fetus in C, A, and B, as well as the facial appearance of the 2nd fetus in F, E, and D. There are noticeable anomalies in the ribs on both sides in (C) and (F). Adapted from (Rinaldi et al., 2022).

2.3. Genetic counseling

Gorlin syndrome is a genetic disorder inherited in an autosomal dominant manner. It is highly likely expressed in individuals who carry the gene, but the severity of the symptoms might vary.

Genetic counseling is crucial for families that are impacted, as it allows for the differentiation between hereditary abnormalities and newly occurring mutations, as well as the evaluation of the heightened risk of cancer. Preferably, conversations on genetic risk and prenatal testing should occur before conception. It is essential for young adults

who are impacted or in danger to also undergo counseling in order to make well-informed choices (Evans et al., 2024).

Given the significant occurrence of PTCH1 mutations in NBCCS, prenatal diagnostics, and genetic counseling are especially advantageous. Hence, it is imperative to provide comprehensive genetic counseling to all individuals diagnosed with NBCCS, utilizing established criteria. This information will help individuals effectively manage their disease and make well-informed health and family planning decisions (Pan et al., 2010).

2.4. Postnatal diagnosis

When considering familial backgrounds, examination at birth or shortly after that should entail scrutiny for an enlarged cranial circumference, frontal or temporal bossing, cleft palate, ocular abnormalities, bifid ribs, or vertebral anomalies (Peris et al., 2023). From birth, it is advisable to undergo neurological testing every six months for the early detection of medulloblastoma. Assessments can be conducted annually from three until the child reaches seven years old. At this point, the likelihood of developing medulloblastoma is improbable. An electrocardiogram can also be performed to detect cardiac fibroma (Bouyssi-Kobar et al., 2019).

Furthermore, it is advised to conduct orthopantomograms (OPGs) of the maxillae between the ages of 4 and 8, continuing until age 40, to facilitate early detection of OKCs. Specifically, individuals with a heterozygous PTCH1 mutation should undergo OPG screening every two years (Wilke et al., 2023).

Following the initial diagnosis of an OKC, annual OPG follow-ups are recommended. Even after age 22, dental monitoring should persist, with additional OPGs performed as needed in unexplained tooth displacement or pain (Verkouteren et al., 2022). One may detect manifestations of maxillary underdevelopment, and varying degrees of mandibular prognathism with hyperplasia may be observed. Additionally, infrequent skeletal abnormalities such as dental crowding and malocclusion may arise due to the presence of keratocysts, leading to eruption failure, root resorption, and dental displacement (Spadari et al., 2022).

A complete dermatological examination should also be performed at least once a year from puberty, but this should be requested more quickly if nevi begins to appear

(Verkouteren, 2023). Ultrasound can detect Ovarian fibroma in the first or second decade (Lee et al., 2024).

Thus, the diagnosis of Gorlin syndrome proves to be a real challenge revealed before or after birth based on clinical criteria or genetic tests. All means would be suitable for an early and, above all, correct diagnosis (Yamada et al., 2020).

2.5. Differential diagnosis

NBCCS has a limited number of oral manifestations. Nonetheless, because OKCs are very common and arise early in this condition, the finding of a histologically proven OKC should prompt further investigation to exclude NBCCS (Fazel, 2019).

The list of potential differential diagnoses encompasses rare dermatologic conditions characterized by an increased susceptibility to early-onset skin cancer development. These conditions include, but are not limited to, xeroderma pigmentosum, Bazex–Dupré–Christol syndrome, and Rombo syndrome (Bresler et al., 2016).

When there is macrocephaly and different problems in newborns, it is essential to investigate the possibility of Beckwith-Wiedemann syndrome, Sotos syndrome, and megalencephaly or isolated hydrocephalus (Spadari et al., 2022). Arsenic exposure can also serve as a distinguishing factor (Srinivas et al., 2019).

3. Genetic basis of the syndrome

3.1. Role of the Hedgehog signaling pathway

The sonic hedgehog signaling (SHH) pathway, which controls a variety of processes in both vertebrates and invertebrates, including cellular proliferation, the epithelial-mesenchymal transition, embryogenesis, and numerous pathological variants, is the primary cause of the development of NBCCS (Gonzalez & Medici, 2014; Ingham, 2022; M. G. Reinders et al., 2018).

This pathway is crucial in maintaining homeostasis in numerous tissues, including stem cells in the digestive system and musculoskeletal tissue (Briscoe & Thérond, 2013). Scientific research has demonstrated that aberrant HH (Hedgehog) signaling plays a vital role in promoting the development of tumors and the growth of cancerous cells.

The Hedgehog signaling pathway begins with Hedgehog ligand processing in secretory cells, which involves forming a polypeptide from the cleaved precursor protein that is dual-lipid modified at the amino terminus (Chen et al., 2011).

The signal-receiving process occurs through preserved receptors on the cell's membrane, consisting of two essential transmembrane proteins, PTCH1 and Smoothened (SMO). PTCH1 is a transmembrane protein with 12 membrane-spanning segments, whereas SMO is a transmembrane protein with seven membrane-spanning segments. The binding of the hedgehog ligand to PTCH1 lifts the inhibition of SMO as illustrated in Fig. 3.

The activation of the hedgehog signaling pathway in mammals stimulates a transcriptional response in the nucleus of the receiving cell, which is facilitated by glioma-associated oncogene homolog (GlI) (Nguyen & Cho, 2022). The GlI proteins consist of different parts, including an amino-terminal domain that represses transcription, a DNA binding domain made of zinc finger, and a transcriptional activation domain located at the carboxy-terminus.

When the GLI is inactive, it undergoes protein hydrolysis, producing a shortened carboxy-terminal activation domain. The GlI variant in question functions as a repressor, impeding the transcription of the target genes (Spadari et al., 2022). SUFU, a negative regulator of the GlI protein, is essential for activating the pathway in mammals (Svärd et al., 2006).

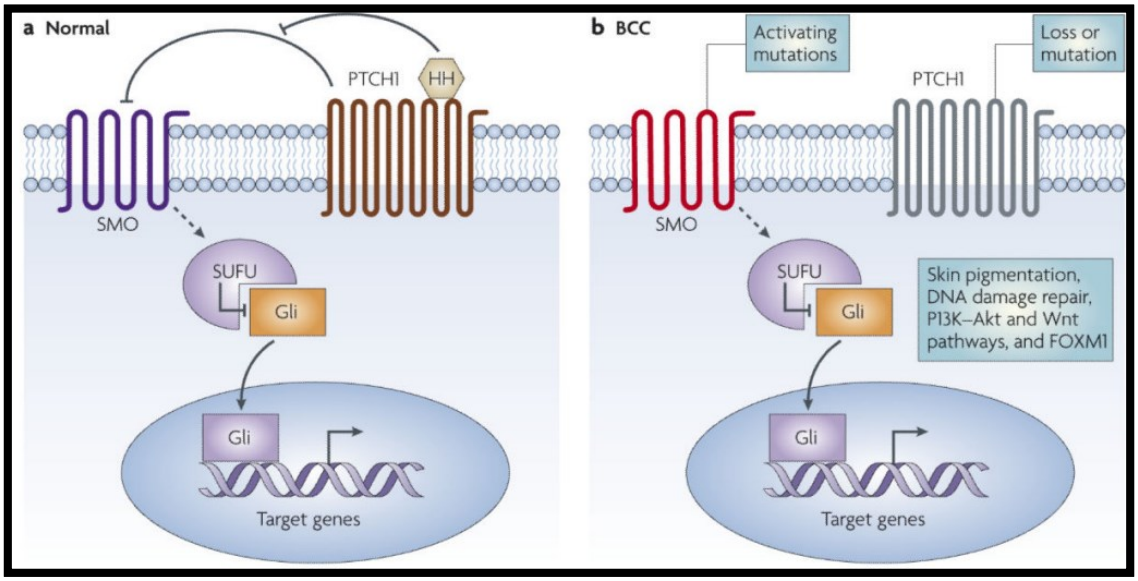


Figure 3: An elementary diagram illustrating the Hedgehog (HH) signaling pathway. Adapted from (Epstein, 2008).

3.2. PTCH1 gene mutations

The molecular underpinnings of GS have been understood since 1996 when the condition was linked to specific genetic mutations in the PTCH1 gene (Shimkets et al., 1996).

Two separate heterozygous mutations affecting the PTCH1 gene were found in two individuals diagnosed with NBCCS (Evans et al., 1993).

It has been determined that a germline mutation in the PTCH1 gene is present in as many as 85% of patients with NBCCS (John & Schwartz, 2016). Segmental or unilateral NBCCS, induced by postzygotic mosaicism, was either documented (Torrelo et al., 2013; Verkouteren et al., 2022).

PTCH1, a human version of the Drosophila patched gene, is a gene that suppresses tumor growth and is associated with both sporadic OKC and NBCCS, which are in q22.3–q31 region (M. G. Reinders et al., 2018).

The gene comprises 24 exons, initiating transcription from exon one and concluding at exon 23. PTCH1 codes for a transmembrane glycoprotein consisting of 1447 amino acids shown in figure 4. This protein is a component of the Hh pathway (Evans et al., 2024).

Typically, PTCH1 combines with SMO to create a receptor complex that interacts with the SHH ligand. The binding of SHH to PTCH1 hinders the transmission of growth signals, similar to how PTCH1 binds to SMO.

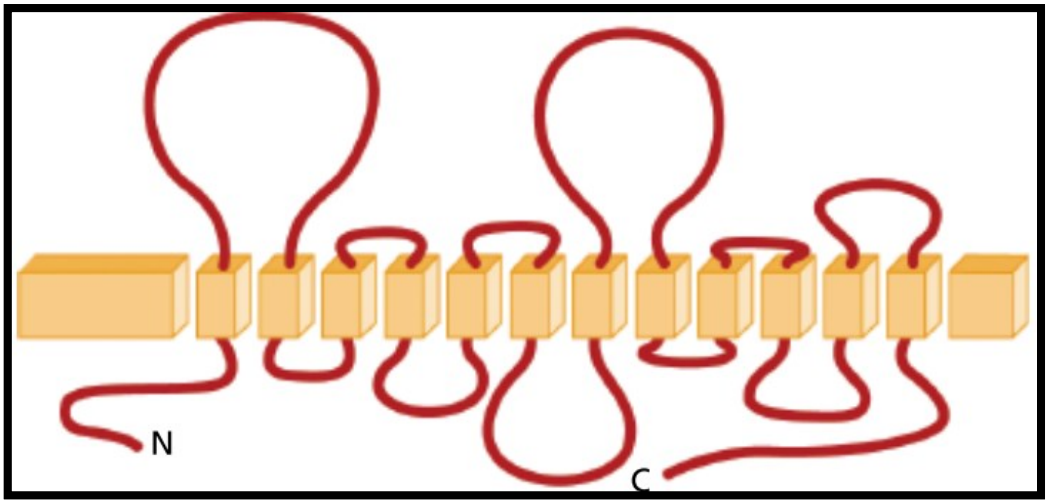


Figure 4: PTCH protein's projected structure in humans. Adapted from (Ong, K. R., & Farndon, 2019).

3.3. Molecular basis of the syndrome

3.3.1. Drosophila studies

PTCH encodes the receptor for the diffusible morphogenic protein SHH, which is a protein possessing 12 transmembrane domains, two loops located outside the cell membrane, and an intracellular domain, the human ortholog of Hedgehog (HH) identified in Drosophila, and is essential for segment polarization during embryonic development (Mizuochi et al., 2015).

In the absence of its ligand, PATCH represses signaling activation by inhibiting a transmembrane protein called SMO. On the other hand, in target cells, binding of SHH to its receptor activates the SMO-dependent pathway, which in turn activates the SHH-dependent pathway and leads to the transcription of genes whose products are involved in controlling the balance between differentiation and proliferation as seen in figure 5.

The numerous Drosophila mutants and rare human pathologies due to the loss of integrity of the SHH pathway underline its essential involvement in the control of tissue interactions, notably in Gorlin syndrome, holoprosencephaly 1 (mutations in SHH), Greig and Pallister-Hall syndromes 2 (mutations in the GLI3 transcription factor), constitute a family of genetic, developmental diseases called "hedgehogopathies." (Hahn et al., 1996).

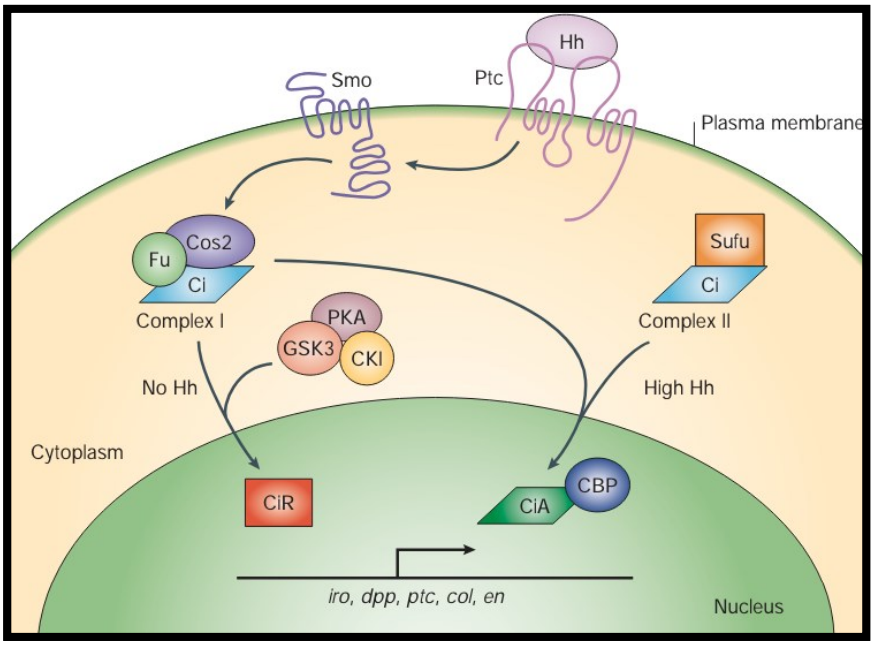


Figure 5: Hedgehog signaling in Drosophila. Adapted from (Hooper & Scott, 2005).

3.3.2. PTC/SHH signaling pathway in vertebrates

In the absence of its ligand, PATCH represses activation of the Homologs of several members of this pathway that have been identified in vertebrates, where it appears to function similarly to that in Drosophila, albeit with a higher level of complexity (Martinez et al., 2019; Ponti et al., 2013). two PTC homologs, PTCH1 and PTCH2, have been described as both able to interact with HH and SMO (Nguyen & Cho, 2022).

However, although PTCH1, whose locus gene is located on chromosome 9, is well characterized, little is known about the role of PTCH2. Additionally, three homologs of HH have been discovered: Desert (DHH), Indian (IHH), and Sonic (SHH) Hedgehog. Only one SMO homolog has been identified, and three zinc-finger transcription factors named GLI3, GLI1, and GLI2 (Martinez et al., 2019).

GLI1 acts primarily as an activator and is the central transcriptional effector of this pathway. At the same time, GLI2 and GLI3 possess transcriptional activator and repressor domains (Niewiadomski et al., 2019).

There is still much debate about how GLI proteins transduce the SHH signal, and most studies suggest a complex balance between divergent functions. Only one cytoplasmic protein acting upstream of GLI, the negative regulator of hedgehog signaling (SUFU) homolog, has been identified in humans (Ruel & Thérond, 2009).

3.3.3. PTC/SHH signaling pathway and cell proliferation

Although the mechanisms underlying the functioning of the PTC/SHH remain poorly understood, its activation appears primarily in increased proliferation.

The high degree of conservation of this pathway in Drosophila and vertebrates suggests that activation of proliferation involves members of the transforming growth factor beta (TGFβ) and Wingless-related integration site (WNT) families, the latter possessing a broad spectrum of functions (Gonzalez & Medici, 2014).

Moreover, studies have established a direct link between activation by HH and increased transcription of cyclins D and E, proteins directly involved in cell cycle activation (Kenney & Rowitch, 2000).

Finally, transfection of rat kidney cells with the Gli1 gene leads to changes in the gene profile compatible with increased proliferation via various pathways such as increased cell division, reduced cell adhesion, and apoptosis.

Recognition sites for the Gli1 protein in the promoter of at least four modulated genes (cyclin D2, IGFBP- 6, osteopontin, and plakoglobin) have been recognized (Javelaud et al., 2012; Longhitano et al., 2021).

3.4. Cancer development in Gorlin syndrome

3.4.1. PTC/SHH signaling pathway and cancer

The contribution of the PTCH gene to cancer development was first observed in basal cell carcinoma (BCC) (Bale & Yu, 2001), with mutations in both sporadic and familial forms of the disease.

PTCH markers located in the 9q area exhibit loss of heterozygosity. Overexpression of GLI1 and mutations in the SHH or SMO genes have also been linked to basal cell carcinoma, indicating that any anomaly leading to GLI1 overexpression in basal layer skin cells can result in carcinoma (Bale & Yu, 2001).

GLI1 oncogenic nature has been validated by its ability to transform cells when working with the adenovirus E1A gene. Mutations in the PTCH1 and SMO genes have also been discovered in primary neuroectodermal tumors and medulloblastomas. Finally, mice with an inactivated PTCH gene allele frequently develop rhabdomyosarcomas (Kimonis et al., 1997; Tostar et al., 2006).

3.4.2. Double event theory

The typical features of NBCCS arise from haploinsufficiency (Wicking et al., 1997), and the development of NBCCS tumors follows the two-hit hypothesis proposed by Pan and Knudson (2001) Sun, Li, & Dong (2010). In the second scenario, there are two possibilities: either both gene alleles have a mutation, or the deletion of the wild allele accompanies one mutated allele.

Knudson's Two-Hit Model of Tumor Suppressor Genes: Tumor suppressor genes play a critical role in preventing cancer by regulating cell growth, division, and apoptosis. One

well-known model explaining their function is the two-hit hypothesis, first proposed by geneticist Alfred Knudson in 1971.

Background:

Tumor suppressor genes act as “brakes” to prevent cells from becoming cancerous. When these genes are inactivated, cells can bypass normal growth control mechanisms.

Unlike oncogenes (which promote cell growth), tumor suppressor genes are recessive in nature. This means that both alleles (copies) of a tumor suppressor gene must be mutated for cancer to develop.

The Two-Hit Hypothesis:

According to Knudson’s model, a cell needs two hits (mutations) in its tumor suppressor genes to become cancerous:

First Hit: A germline mutation (present in all cells) occurs in one allele of the tumor suppressor gene. This, alone, is not sufficient for cancer development.

Second Hit: A somatic mutation (specific to the affected tissue) or deletion inactivates the remaining wild-type allele. Both alleles are mutated, leading to uncontrolled cell growth and tumor formation.

Knudson initially studied retinoblastoma, a childhood eye cancer. In retinoblastoma, retinoblasts (cells in the developing eye) fail to differentiate, leading to tumor formation if both RB1 tumor suppressor gene alleles are mutated1.

Application to Nevoid Basal Cell Carcinoma Syndrome (NBCCS):

NBCCS, also known as Gorlin-Goltz syndrome, is an inherited disorder characterized by multiple basal cell carcinomas (BCCs), jaw cysts (such as keratocystic odontogenic tumors or KCOTs), and other tumors.

In NBCCS, the first hit is a germline mutation in the PTCH1 gene (a key player in the Hedgehog signaling pathway).

The second hit occurs somatically, leading to KCOT development. KCOTs are aggressive jaw cystic tumors with a high recurrence rate.

Interestingly, isolated defects similar to KCOTs can occasionally occur in the general population due to homozygous PTCH1 gene inactivation in early progenitor cells2.

Distinct Non-Clock-Like Signatures:

Recent research has shown that BCCs (including KCOTs) in NBCCS exhibit distinct genomic alterations, mainly clustered into non-clock-like mutational signatures related to ultraviolet exposure and certain alkylating agents 3.

These findings highlight the complexity of tumor development and the interplay between genetic factors and environmental influences.

In summary, Knudson's two-hit model provides valuable insights into the genetic basis of cancer, including conditions like NBCCS, where KCOTs play a significant role. Understanding these mechanisms, helps guide diagnosis and treatment strategies for affected individuals.

Studies on mouse models suggest that rhabdomyosarcoma and medulloblastoma may occur due to haploinsufficiency of PTCH1, which may be linked to a condition called haploinsufficiency of PTCH1 (Pan et al., 2010).

That suggests that these types of cancer may not necessarily follow the traditional two-hit concept (Calzada Wack et al., 2002; Zurawel, Allen, Wechsler-Reya, Scott, & Raffel, 2000). Individuals with typical NBCCS findings have a 50-85% mutation detection frequency of the PTCH1 gene through DNA sequencing analysis (Lam, Ou, & Billingsley, 2013). Mosaic manifestations of NBCCS can occur (M. G. Reinders et al., 2018; Torrelo et al., 2013).

3.5. The different genetic tests

The GS genetic test is highly accurate, with 100% sensitivity and specificity. It requires clinicians to provide blood samples for analysis by an external laboratory.

Identifying genetic alterations requires skilled professionals and a significant amount of time. Molecular genetic testing for GS is crucial for disease prognosis, clinical diagnosis, genetic counseling, and treatment family counseling.

The test should encompass a comprehensive sequencing of the PTCH1 all exons gene and their adjacent introns and several Polymerase chain reaction (PCR) techniques, like quantitative multiplex fluorescence PCR or MLPA (multiplex ligation-dependent probe amplification).

3.6. Importance of genetic testing

Most Gorlin syndrome diagnoses rely on clinical presentations and established criteria, such as the Kimonis diagnostic criteria, which typically do not mandate genetic testing.

Genetic testing can be necessary when there is suspicion of Gorlin syndrome.

Genetic testing is recommended for specific people who are believed to have Gorlin syndrome. Prenatal testing is conducted when there is a reported hereditary mutation:

Diagnosis verification should be performed on patients who exhibit specific clinical indications but do not fit the criteria. This approach would enable enhanced monitoring and lead to better patient treatment results.

Predictive tests are when individuals have family members who present a risk but do not match the condition's clinical criteria (Huq et al., 2018).

Methods for molecular testing involve sequential testing of a solitary gene (PTCH1, SUFU), utilizing a multigene panel, or more extensive genomic testing.

molecular testing for Gorlin Syndrome, there are several approaches available. Let’s explore them:

1. **Sequential Testing of Solitary Genes:**
    - This method involves testing individual genes one by one. For instance, if there’s a suspicion of a specific gene mutation (such as PTCH1 or SUFU), it can be directly assessed.
    - While straightforward, this approach can be time-consuming and costly if multiple genes need evaluation.
2. **Multigene Panel Testing:**
    - Multigene panels simultaneously analyze several genes associated with Gorlin Syndrome.
    - These panels are efficient because they cover a broader range of genes, allowing for comprehensive testing.
    - However, they may still miss rare mutations not included in the panel.

3. **Comprehensive Genomic Testing:**
    - This approach involves whole-genome or whole-exome sequencing, providing a comprehensive view of an individual's genetic makeup.
    - It identifies mutations across the entire genome, including known and novel variants.
    - While powerful, it can be expensive and yield incidental findings unrelated to the initial clinical question.

In summary, the choice of method depends on clinical context, available resources, and the specific genetic aberrations being investigated. Researchers continue to refine these methods to enhance accuracy and cost-effectiveness (Spadari et al., 2022).

The current advancements in NGS technology are pretty impressive. By employing Next-Generation Sequencing (NGS), there is the potential to develop a genetic diagnosis panel, and the process could become more streamlined, rapid, and cost-effective. Undoubtedly, such advancements would be indispensable for diagnosing GS (Tatsi et al., 2020).

An in-depth analysis of the relationship between clinical symptoms and GS mutant characteristics may progressively uncover a connection between clinical symptoms and the specific location of missense mutations. Studies have shown that biallelic mutation in PTCH1 is responsible for 80% of sporadic KCOT cases (Stojanov et al., 2020).

Genetic testing is a crucial diagnostic tool for families affected by certain conditions, especially when clinical criteria are inconclusive. Despite its relatively high cost, in some cases, it becomes essential to assist clinicians in providing genetic advice to the affected families, such as avoiding ultraviolet or X-rays from the moment of diagnosis (Martinez et al., 2019).

3.7. The SUFU gene mutation

A radiological and clinical investigation was conducted on individuals from the same family with desmoplastic medulloblastoma to evaluate the potential genetic susceptibility to GS. The study identified a SUFU germline mutation, which suggested genetic heterogeneity in the syndrome. It is noteworthy that members of this family suffering from the syndrome did not manifest basal cell carcinomas.

There might be two potential reasons for this absence. Firstly, it is possible that neither the parent nor the child showed signs of BCC by chance, as Gorlin syndrome is known to have a wide range of clinical presentations.

Furthermore, it is plausible that GS caused by SUFU mutations has unique clinical characteristics and does not present with basal cell carcinomas (Ng et al., 2005).

Other studies on individuals with a SUFU mutation and suffering from Gorlin syndrome have shown that Odontogenic keratocysts are absent in these patients.

That implies that a mutation in this gene mainly leads to medulloblastoma in most cases (Pennisi et al., 2017). Patients with SUFU germline mutation have a marginally elevated likelihood of developing medulloblastoma throughout childhood (Evans et al., 2017).

4. General manifestations of the syndrome

In the case of Gorlin syndrome, two types of diagnosis are indicated: clinical diagnosis, the criteria for which are numerous in the literature and which we will discuss in the following two chapters, and molecular diagnosis, which is mainly indicated for confirmation or when the clinical criteria are inconclusive.

4.1. General diagnosis criteria

In general, Gorlin-Goltz syndrome is diagnosed when two major criteria occur: one major criterion and two minor criteria (Table 3).

Table 3: General diagnosis criteria of NBCCS

Major criteria: (35)	**Minor criteria**:
• Multiple basal cell carcinoma • Familial basal cell carcinoma • Odontogenic keratocysts • Palmar or plantar pits • Cerebral calcification • Familial nature of the disease	• **CUTANEOUS:** ➢ Dermoid cysts; Epidermal cysts Lipoma • **HEAD AND NECK** ➢ Macrocephaly ➢ Frontal and biparietal humps; Mandibular prognathism ➢ Lateral displacement of medial canthus; Hypertelorism ➢ Ogival Palace; Cleft lip or palate ➢ Cysts of the ocular conjunctiva; Congenital cataract ➢ Coloboma of the iris Glaucoma ➢ Strabismus ➢ Ameloblastoma • **CARDIOVASCULAR** ➢ Cardiac fibroma • **PULMONARY** ➢ Congenital lung cyst • **GASTROINTESTINAL** ➢ Mesenteric cysts, often calcified ➢ Hamarthomatous polyps of the stomach • **GENITOURINARY** ➢ Ovarian fibroma; Carcinoma of ovary ➢ Cryptorchidism; Hypospadias; Gynecomastia • **SQUELETTIQUES** ➢ Skeletal deformities; Cyphoscoliosis; Abnormal cervical vertebra; Hypoplastic ribs; Bifid ribs Polydactyly; Syndactyly; Brachydactyly ➢ 4th metacarpal short ➢ Gigantism • Pectus excavatum; Marfanoid appearance **NEUROLOGICAL** ➢ Mental retardation; Epilepsy; Spina bifida ➢ Medulloblastoma, Meningioma

These same diagnostic criteria were initially defined by Evans et al. in 1993, then changed by Kimonis et al. in 1997 and Bree et al. in 2011 (Bree & Shah, 2011; Kimonis et al., 1997).

4.2. Cutaneous and mucosal signs

The two main cutaneous and mucosal signs considered major criteria are nevi and BCCs. Due to their preferential location on the face, we will discuss them further in the chapter on oral-facial manifestations.

4.2.1. Palmoplantar pits

The specific pits observed on the soles and palms of the feet are highly characteristic and serve as a significant diagnostic criterion for the condition as seen in figure 6. (Smith et al., 2014).

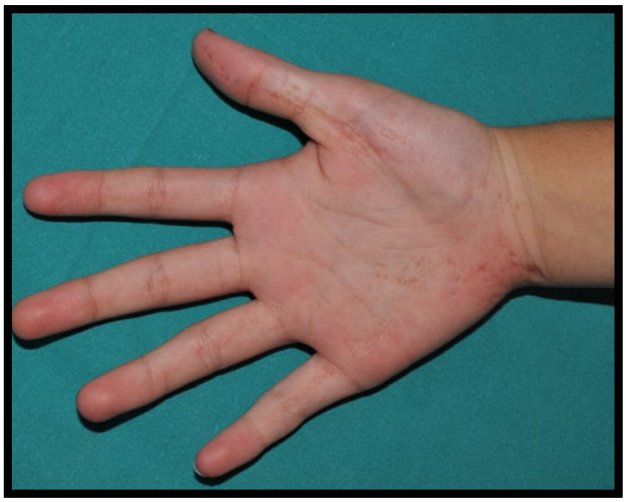


Figure 6: Palmoplantar pits in Gorlin Syndrome. Adapted from (Torrelo et al., 2013).

4.2.2. Epidermoid cysts

Epidermoid cysts are non-cancerous growths that typically measure between one and two centimeters in size. In more than 50% of cases, several epidermoid cysts resembling OKC are found on the trunk, limbs, and surrounding the knee as shown in figure 7.

If they cause discomfort or inconvenience, they are usually removed through surgical excision (Ong, K. R., & Farndon, 2019).

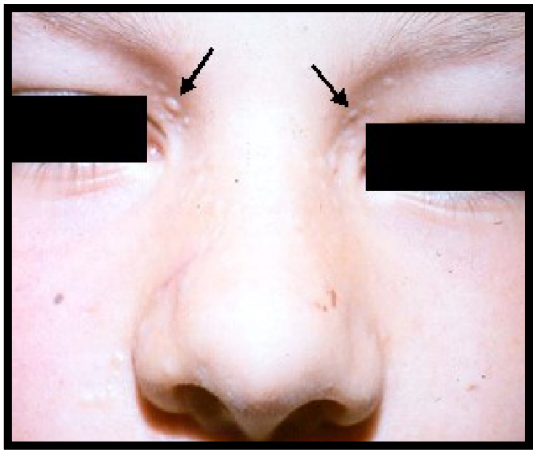


Figure 7: Several epidermal cysts in GS. Adapted from (John & Schwartz, 2016).

4.3. Neurological manifestation

Neurological examination of Gorlin syndrome can reveal many destabilizing features, some of which are inconsistent, such as intellectual disability with below-normal Initial Quality Survey (IQs), motor dysfunctions such as the inability to swim or clap, and sphincter incontinence (Lo Muzio, 2008).

Calcification of the cerebral falx, observed inside a brain, is a significant diagnostic indicator. It can manifest at an early age, become more noticeable during the latter years of childhood, and increase in severity with time as seen in figure 8 (Spadari et al., 2022).

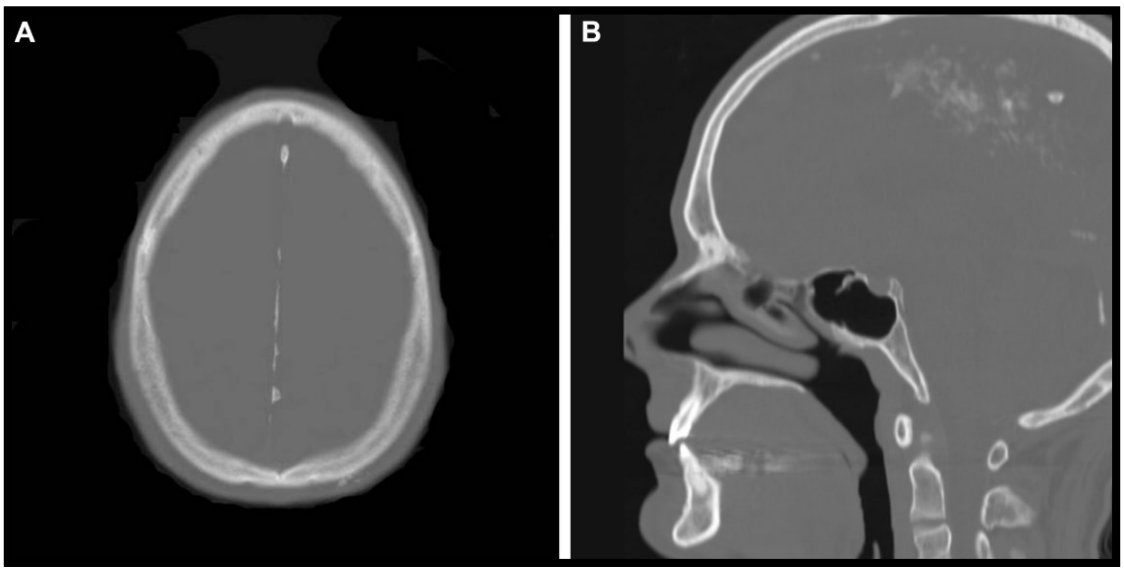


Figure 8: Computed tomograms of patient Illustrating calcified falx cerebri. Adapted from (Carlson et al., 2015).

Brain tumors have been associated with Gorlin syndrome, including astrocytoma, which is another type of infiltrating brain tumor related to astrocytic cells. A study published in the Danish Medical Journal reported a GS patient whose ancestor died from this tumor at the age of 47 (Kristine Larsen et al., 2014).

Patients treated with radiotherapy may subsequently develop infiltrating tumors such as BCC and secondarily infiltrating tumors such as intracranial and sinus tumors (Kristine Larsen et al., 2014).

4.3.1. Medulloblastoma

According to certain experts, a small percentage 3 to 5 % of patients with GS are diagnosed with medulloblastoma, typically occurring at an average age of 2 years. In contrast to the general population, the average age of medulloblastoma onset is 6.5 years.

The predominant histological subtype of medulloblastoma linked to GS is desmoplastic. Some authors believe that desmoplastic medulloblastoma diagnosed before age two is indicative of GS, and all children under five with this type of tumor should undergo PTCH gene testing (Massimino et al., 2016).

Late development of medulloblastoma is possible, emphasizing the importance of early Gorlin syndrome diagnosis.

- **Circumstances of Diagnosis**

A biannual neurological survey can identify a deficiency that suggests the presence of a medulloblastoma. Regular computerized tomography (CT) scanning or exaggerated X-ray exposure should be avoided due to the potential risk of causing skin cancers. (Conclusion from research in a specific study has revealed that scanning should be targeted on children who have a SUFU mutation) (Smith et al., 2014).

Clinical tests can be conducted annually from three until the child reaches seven years old. Beyond that age, the occurrence of medulloblastoma is quite improbable.

Despite the limited accuracy of these tests, a parent should seek medical attention from a specialized department if any concerning symptoms arise.

It has been recommended that magnetic resonance imaging be performed yearly until the child reaches eight (Evans & Farndon, 2018). However, due to the potential need for general anesthesia, it is not advisable to do this procedure in young patients having PTCH1-related GS, as the associated risk is approximately 2% (Evans et al., 2024).

It is advisable to undergo a basic ophthalmological exploration and participate in regular programs that monitor developmental progress, hearing, and vision.

4.4. Skeletal abnormalities

4.4.1. Ribs anomalies

Although considered a minor diagnostic criterion, including bifid, fused, or spaced ribs, Kimnosis et al. highlighted them as a major criterion due to their high prevalence (42% of patients) and early detection, especially in the pediatric population, which generally does not present major criteria as shown in figure 9. (Singh Dhull et al., 2013).

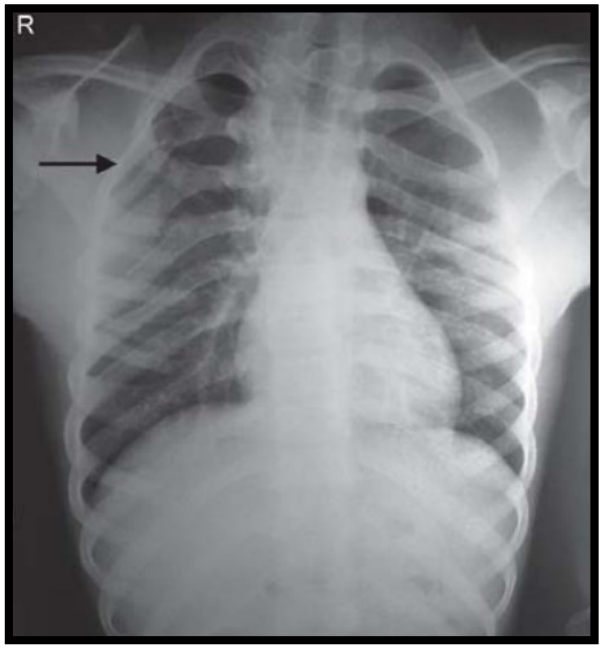


Figure 9: A posteroanterior (PA) view of a chest X-ray reveals a distortion in the vertebral rib in the cervicodorsal area. Adapted from (Singh Dhull et al., 2013).

Gorlin syndrome is associated with the presence of pectus excavatum, a deformity of the chest wall. In pediatric instances of Gorlin syndrome, this characteristic occurs with an approximate frequency of 20% as shown in figure 10.

This contributes to the variety of physical symptoms linked to the syndrome, which encompasses a range of skin, bone, and other bodily abnormalities (Ong, K. R., & Farndon, 2019).

The prevalence of pectus excavatum as a relatively frequent characteristic highlights the significance of thorough clinical assessment in affected children to guarantee prompt detection and suitable treatment of the different symptoms of Gorlin syndrome.

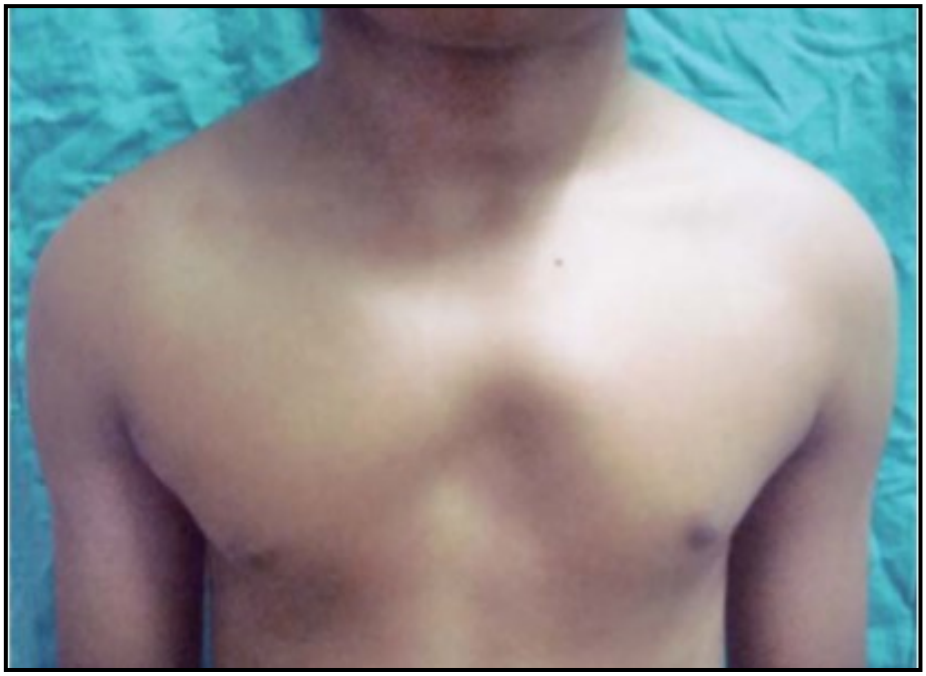


Figure 10: Pectus excavatum. Adapted from (Singh Dhull et al., 2013).

4.4.2. Spinal abnormalities

Approximately 49% of individuals with this condition exhibit diagnostic indicators such as abnormalities in the cervical or thoracic spine as seen in figure 11. The spinous processes of the C7, C6, T2, and T1 vertebrae are commonly affected (Ong, K. R., & Farndon, 2019).

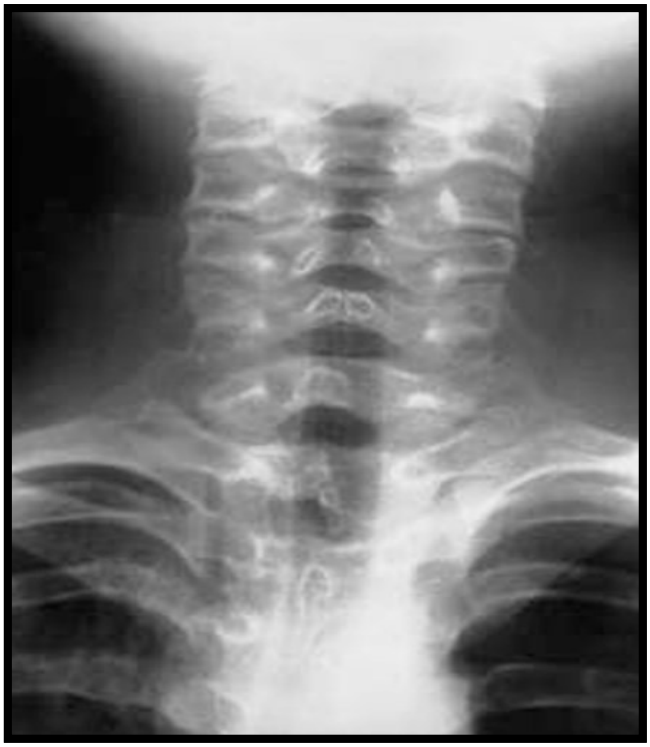


Figure 11: Thoracic radiograph displaying abnormalities in the upper vertebrae. Adapted from (Ong, K. R., & Farndon, 2019).

- **Scoliosis**

Individuals with Gorlin syndrome tend to have scoliosis more frequently than the average population, although the difference is insignificant. However, many affected individuals have more severe scoliosis due to developmental anomalies such as hemivertebrae or fused vertebral bodies. On the other hand, spina bifida is not frequently observed in the Gorlin syndrome population compared to unaffected individuals (Figueira et al., 2018).

4.4.3. Polydactyly

These manifestations are rare in patients with Gorlin 3% syndrome and may be localized to a single hand or foot in most cases or to both as shown in figure 12 (Singh Dhull et al., 2013).

GS exhibits a greater prevalence of polydactyly in the postaxial form than in the preaxial form, occurring in approximately 0.08% to 1.4% of every 1000 live births (Bubshait, 2022).

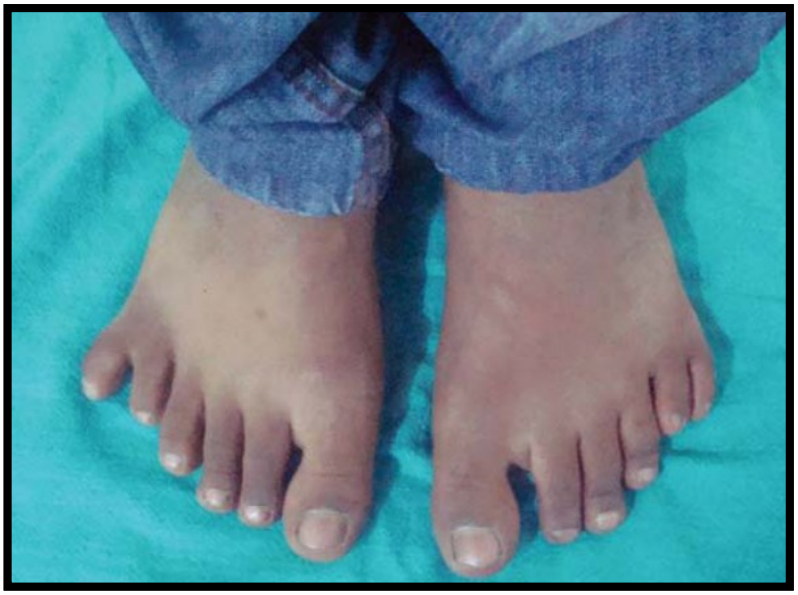


Figure 12: Polydactyly in both feet. Adapted from (Singh Dhull et al., 2013).

4.4.4. Sprengel's deformity

Approximately 11% of those diagnosed with NBCCS exhibit a Sprengel deformity or congenital elevation of the scapula. This anomaly is characterized by the upward and medial displacement of one or both scapulae, resulting in distortion and, occasionally, the immobilization of the misplaced bone to the spine as shown in figure 13. The elevation results from the bone's incapacity to descend into its usual position during fetal development (Kimonis et al., 2004).

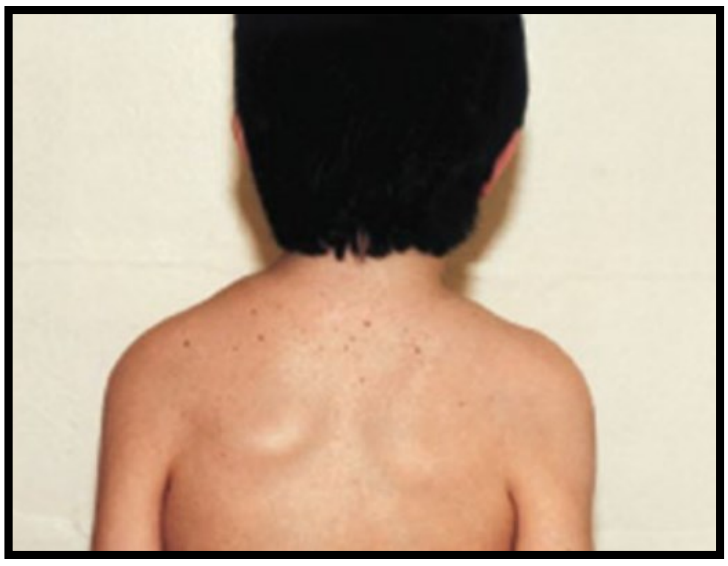


Figure 13: Sprengel's deformity. Adapted from (Ong, K. R., & Farndon, 2019).

4.4.5 Craniofacial anomalies

- **Frontal bossing**

Patients with NBCCS have skull-shape anomalies. While these defects may be considered minor criteria for the condition, they are of significant diagnostic importance due to their visibility from birth.

Around 66% of individuals diagnosed with NBCCS have distinct facial characteristics like coarse facial features, hypertelorism, frontal bossing as seen in figure 14, and macrocephaly (Jones et al., 2011).

According to the study conducted by Kimonis (Kimonis et al., 1997). In 105 patients diagnosed with Gorlin syndrome, it has been found that macrocephaly occurs more frequently (in 50% of cases) compared to the general population. Hypertelorism exhibits the same characteristic.

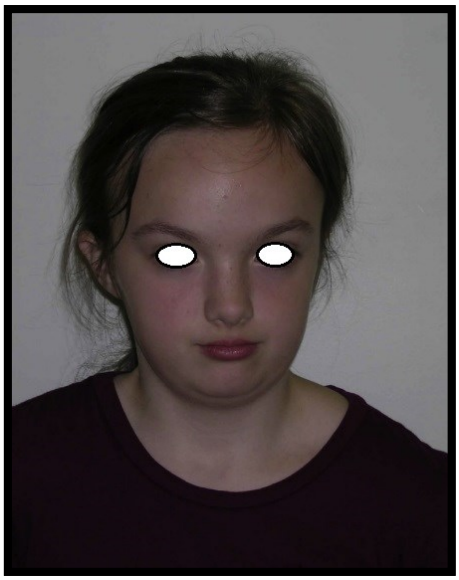


Figure 14: Frontal bossing. Adapted from (Carlson et al., 2015).

4.5. Sexual anomalies

4.5.1 Ovarian Fibroma

Ovarian fibromas are present in approximately 13 to 60% of female individuals diagnosed with NBCCS, typically occurring between the ages of 16 to 45 (Lo Muzio, 2008). Ovarian

fibromas in individuals with NBCCS commonly exhibit calcification, bilateral occurrence, and a development pattern characterized by several foci or nodules as seen in figure 15 (DeLair & Soslow, 2016). Typically, they do not show any symptoms and do not have an impact on fertility.

Ovarian torsion is an infrequent event that can happen in the presence of ovarian fibromas (Scalia et al., 2018). If there are no gynecologic symptoms present, it is not advisable to undergo surgery since it could potentially lead to decreased fertility, which involves an earlier onset of menopause due to the reduction of ovarian tissue (Khodaverdi et al., 2018; Morse et al., 2011).

Patients who require surgery and wish to protect their fertility should be advised about the least invasive alternatives to safeguard their reproductive options (Khodaverdi et al., 2018; Morse et al., 2011).

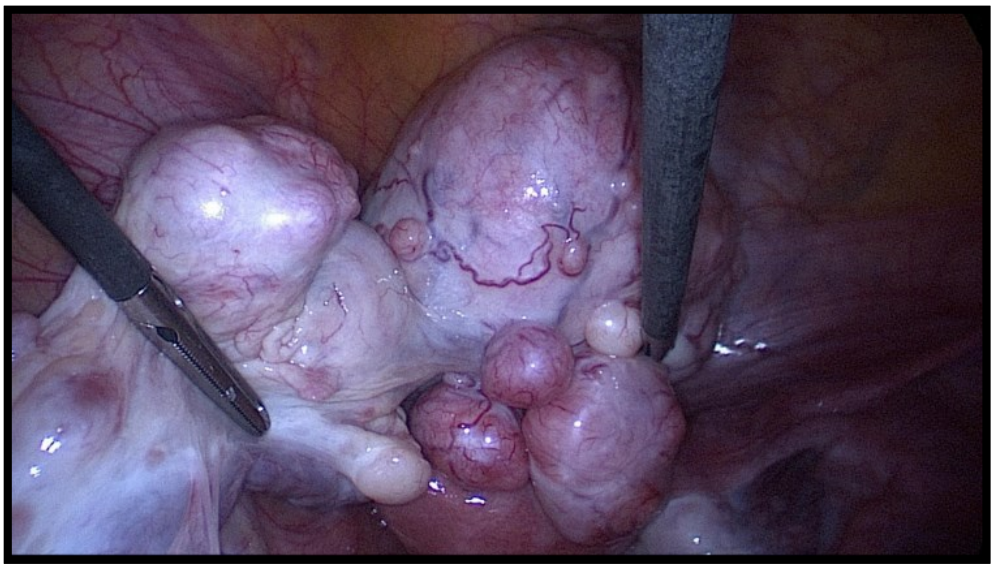


Figure 15: Multiple uterine and ovarian fibromas in a patient with NBCCS. Adapted from (Scalia et al., 2018).

4.5.2. Hypogonadism

Approximately 5-10% of males may exhibit symptoms of hypogonadism, including cryptorchidism, limited body or facial hair, female pubic hair, gynecomastia, and anosmia. Gorlin provided a multitude of examples. According to Shanley et al.'s survey, 10% of cases were found to have anosmia (Ossama et al., 2017).

4.6. Gastroenteric system anomalies

Lymphomesenteric cysts are a diagnostic criterion of minimal importance, and their particular frequency is currently unknown. Single or multiple lymphomesenteric cysts have been documented.

The cyst has a diameter ranging from two to 14 cm, is asymptomatic, and is frequently detected incidentally. The contents are chylous but may also be hemorrhagic (Lo Muzio, 2008). CT scans, MRI, and Ultrasound can detect the cysts; however, a histological analysis is required to establish a definitive diagnosis (Verkouteren, 2023).

4.7. Cardiovascular anomalies

Cardiac fibroma has been described in 3 to 5% of people with the syndrome. It is well-circumscribed, non-encapsulated, 3 to 4 cm in diameter, and may contain calcifications (MacDonald, 2015). The anomaly is primarily in the left anterior ventricle wall; extending into the cardiac cavities could cause hemodynamic balance problems.

Conduction problems (e.g., arrhythmia) could also occur if it spreads to the interventricular septum (Lo Muzio, 2008).

5. Oral and facial manifestations

5.1. Ocular manifestation

Patients with NBCCS may experience a range of ocular issues at a higher rate than the total population (Lo Muzio, 2008). The following conditions are associated with NBCCS: strabismus, Hypertelorism as seen in figure 16, congenital cataract, cysts on the eyelids, coloboma of the iris, choroid and/or optic nerve, nystagmus, congenital glaucoma, subconjunctival epidermoid cysts, iris transillumination defects, microphthalmia, epiretinal membranes, myelinated nerve fibers, retinal hamartomas and macular hole (Jen & Nallasamy, 2016; Moramarco et al., 2019).

Prompt identification and intervention are crucial to prevent impaired visual system development and visual impairment resulting from frequently occurring ocular symptoms (Verkouteren, 2023).

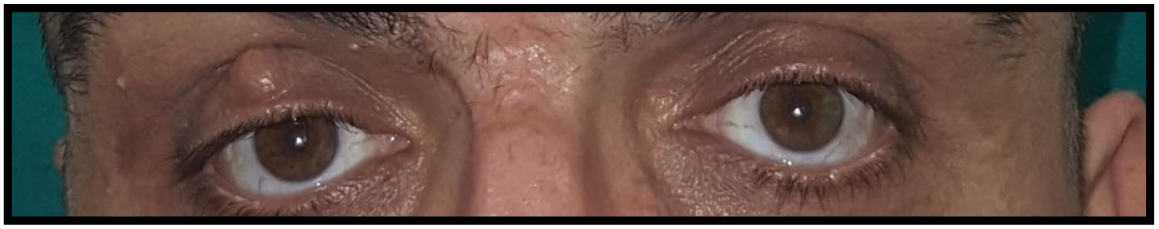


Figure 16: Hypertelorism. Adapted from (Moramarco et al., 2019).

5.2. Cutaneous and mucosal signs

5.2.1. Nevus cell nevi

Nevi impacts 53% of individuals aged below 20, and this percentage increases to 74% for those aged 20 and above. Common nevus cell nevi are congenital and are found in approximately 4% of individuals unaffected by the condition. Nevertheless, impacted family members state that the nevi tend to emerge in clusters, progressively multiplying in quantity as time progresses as shown in figure 17. Individual nevi can also manifest as lesions; a patient may exhibit no nevi, a small number, or a large number of hundreds.

The nevi can have a complexion that ranges from flesh-colored to reddish-brown, or they may have a pearly appearance. Some nevi undergo rapid growth for a period ranging from a couple of days to a few weeks, but the majority stay unchanged (Ong, K. R., & Farndon, 2019).

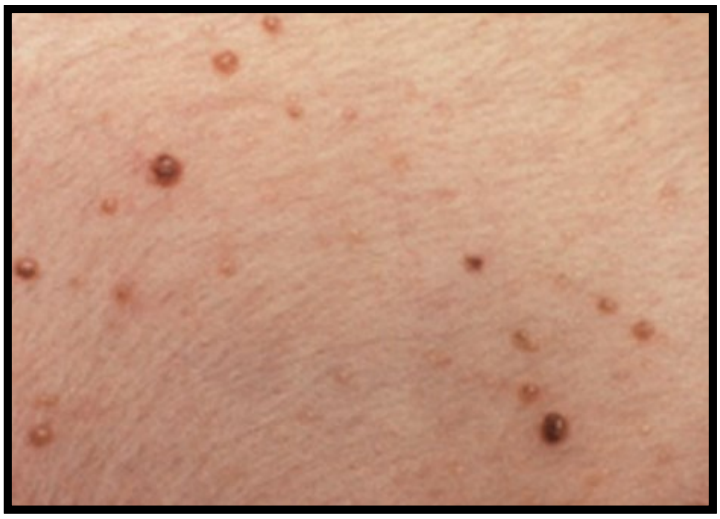


Figure 17: Naevi. Some individuals have a skin-colored, reddish-brown, or translucent appearance. Adapted from (Ong, K. R., & Farndon, 2019).

5.2.2. Basal cell carcinoma (BCC)

NBCCS is a hereditary condition that makes persons more susceptible to a high risk of developing BCC. BCC primarily affects individuals with fair skin, accounting for 90 % of cases (Flowers et al., 2023).

These lesions commonly appear as nodular or superficial growths, predominantly on the thorax and cervicofacial region, including the periorbital area, eyelids, nose, malar eminences, and upper lip as shown in figure 18. Although sun exposure, particularly ultraviolet B (UVB) radiation, is likely to exacerbate BCC, it is unnecessary. This is evidenced by BCC's frequent occurrence in non-photoexposed areas, such as the trunk. Exposure to radiation therapy is also a risk factor for BCC development (Lo Muzio, 2008).

GS poses a significant concern in the development of BCC. The number of BCCs in affected individuals varies greatly, ranging from a few to several hundred.

The clinical presentation can encompass a spectrum from clear to dark papules with a stiff texture and plane surface to pigmented and ulcerated plaques in different sizes (Bresler et al., 2016; John & Schwartz, 2016).
Research has documented that BCC generally occurs between puberty and age 35. However, cases of BCC occurring in early childhood, between the ages of two and four and ranging up to 65 years old (Jones et al., 2011).

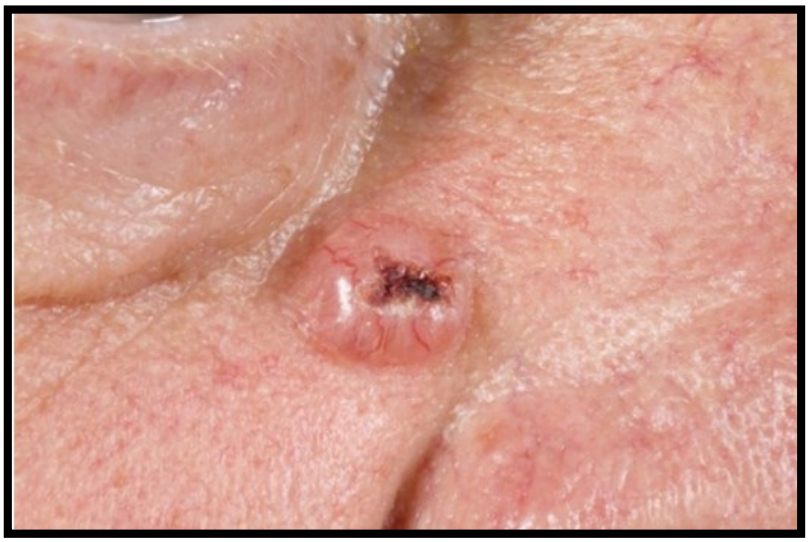


Figure 18: Basal cell carcinoma located on the right cheek. Adapted from (M. G. H. C. Reinders, 2019).

5.3. Odontogenic keratocysts

5.3.1. Introduction

OKC, an epidermoid cyst, arises from the dental laminal epithelium and results from dysregulated signal transduction, growth factors, cell cycle, and cytokines (Nilius et al., 2019).

OKC accounts for 14.3% of the total cases of odontogenic tumors and is ranked third in frequency in the category of cystic lesions by the WHO (World Health Organization) (P. Chen et al., 2022). It predominantly affects males between the ages of 40 and 50 and is located in 70% of cases in the area of the ramus and angle of the mandible (Geleț u et al., 2023).

OKC is a characteristic feature of NBCCS or GS. Sporadic cases occur mainly between the ages of 20 and 30, with a discrete male preponderance (Geleț u et al., 2023). NBCCS is a syndrome characterized by multiple OKs that can be detected early in life. Diagnosing OKCs early is vital as they are the most common initial manifestation of NBCCS, and the primary treatment typically revolves around them (Ünsal et al., 2023).

5.3.2. Keratocyst reclassification

WHO classified this pathology as a neoplastic lesion due to its locally aggressive behavior, high proliferation index with supra-basal expression of P53 (Tumor protein 53), and the frequency of alterations in the PTCH1 found in 80% of cases, whether sporadic or syndromic (Doll et al., 2018).

Since these genetic abnormalities were found in other congenital cysts in 2017, WHO changed the odontogenic keratocystic tumor back to the odontogenic keratocyst (OKC); this fact reflects the extensive and continuous investigation of this disease that has been carried on (Chen et al., 2022).

5.3.3. Radiological signs

OKC can be detected in any region of the jaws, but they tend to occur more frequently in the ramus and angle of the mandible. These cysts typically have well-defined, hardened

borders. They can be mistaken for ameloblastoma or dentigerous cysts associated with an unerupted tooth.

From a radiographic perspective, over 80% of them appear unilocular but can have several locations as seen in figure 19 (Bresler et al., 2016). The presence of multiple lesions is typically linked to NBCCS as shown in figure 20. (Boffano et al., 2021; Geleţu et al., 2023).

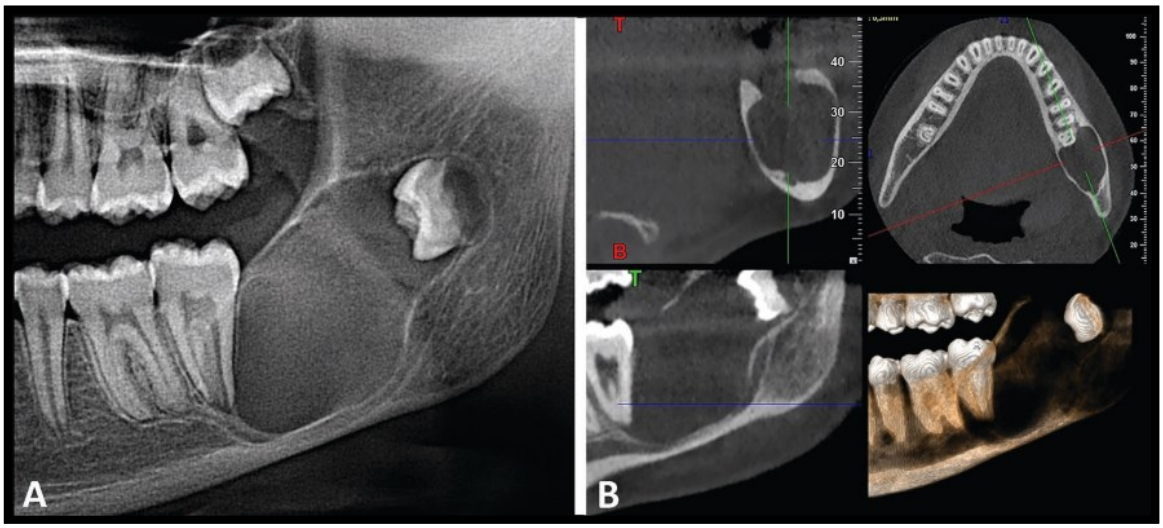


Figure 19: Radiological aspects of OKC. Adapted from (Borrás-Ferreres et al., 2020).

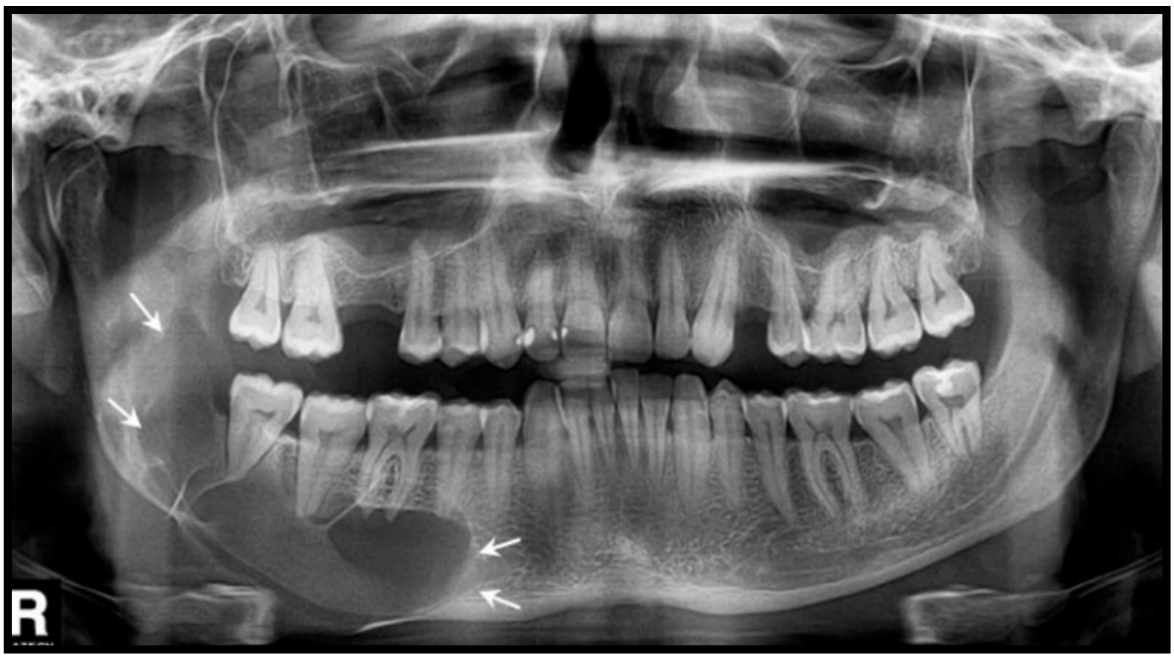


Figure 20: Multilocular OKCs. Adapted from (Geleţu et al., 2023).

5.3.4. Histological description

OKC is lined by a 5- to 10-layer Malpighian epithelium with parakeratotic hyperkeratosis and an undulating surface as shown in figure 21, unlike other odontogenic, which have the characteristic of being ortho-keratinized and have a low risk of recurrence (Bresler et al., 2016).
The nuclei of the basal layer have a characteristic palisading appearance, and normal mitoses are possible.

Keratin debris fills the lumen. Satellite cysts are present in the wall. The proliferation index is not negligible, and P63 (Tumor protein 63) and P53 are expressed by the suprabasal cells (Chen et al., 2022).

Reclassified as a congenital cyst by the WHO in 2017, OKC is the third most common odontogenic cyst after inflammatory cysts (50%) and dentigerous cysts (20%) (Woo, 2024).

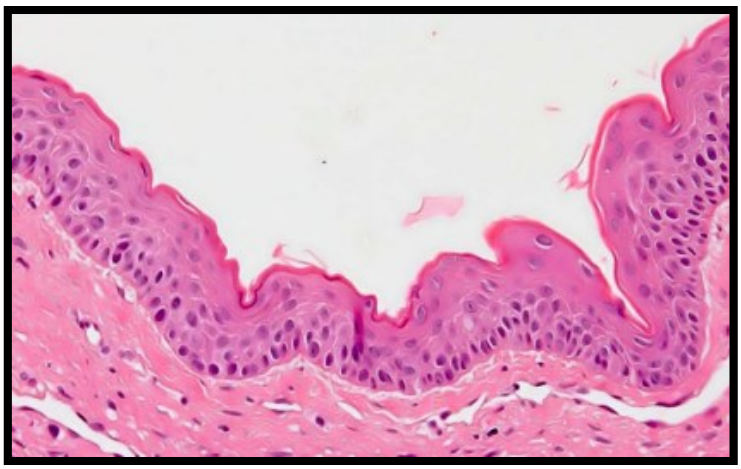


Figure 21 : Histological image displays Malpighian epithelium parakeratotic hyperkeratosis and undulating surfaces (H-E 10×). Adapted from (Borghesi et al., 2018).

5.3.5. Immunohistochemistry

To rule out other cystic lesions, primarily dentigerous cyst or radicular cyst, Immunohistochemistry (IHC) highlights specific indicators of OKC, namely the expression of cytokeratins 17 and 19 and elevated expression of Proliferating cell nuclear antigen (PCNA) and Antigen Kiel 67 (Ki-67), which indicate the aggressive and recurrent nature of OKC (Bresler et al., 2016).

5.3.6. Epidemiology

OKC represents 11% of jaw lesions of the same nature and is commonly linked to GS in individuals aged 10 to 20 (Giovacchini et al., 2020).

Indeed, this manifestation is present in 44-92% of patients affected by this syndrome, and most often, the cysts in question are numerous; their frequency varies from a single one to around thirty, with an average of 5 OKC (Lo Muzio, 2008; Verkouteren, 2023).
Research indicates that the occurrence of OKCs decreases after the age of 30 (Verkouteren, 2023).

The most affected regions are the mandibular regions (77%) and the maxilla regions (23%) (Boffano et al., 2021).

The molar-ramus region is the most frequently affected site in the mandible, accounting for 44% of cases. The incisor-canine region is the second most common site, with a prevalence of 18%. On the other hand, the incisive-canine region (15%) is the most impacted area in the maxilla, followed by 13% for the tuberosity molar region, with only a few cases reported for localization in the premolar region (Lo Muzio, 2008).

5.3.7. Origin

Most OKCs (60%) arise from the dental laminal epithelium, categorizing them as odontogenic keratocysts of primordial origin. OKCs are classified as dentigerous-origin because they arise from the reduced enamel epithelium of the dental follicle, accounting for forty percent of cases. (Figure 22(a)) (Belmehdi et al., 2016).

The clinical distinction is important because recurrences are more frequently observed after treating the primordial-origin keratocyst (Shuster et al., 2012).

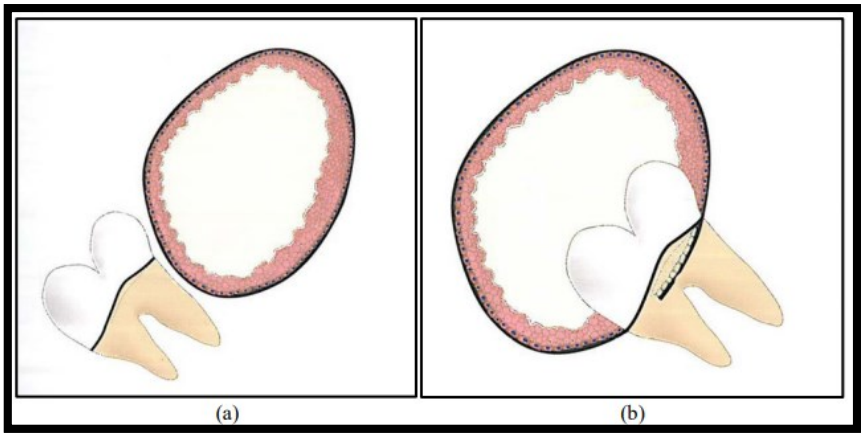


Figure 22: The origin of odontogenic keratocysts: (a) Primordial; (b) Dentigerous origin. Adapted from (Belmehdi et al., 2016).

5.3.8. Clinical evolution

The majority of keratocysts do not cause any symptoms. Pain, inflammation, spontaneous fistulation, or discomfort are possible. In the more aggressive forms, vestibular and lingual table expansion occurs late with this lesion (unlike ameloblastoma), as it mainly tends to invade the cancellous bone (Ruhin-Poncet et al., 2011).

However, this causes some vestibular or lingual cortex expansion and may result in rupture. Involvement of the inferior alveolar nerve occurs late (Oginni et al., 2023)

OKC grow within the medullary cavity of the bone in an anteroposterior direction, resulting in noticeable expansion of the bone (Belmehdi et al., 2016).

5.3.9. OKC and ameloblastoma

It is important to distinguish between OKCs and ameloblastomas, as both conditions can appear as unilocular or multilocular and can lead to bone expansion (Geleţu et al., 2023). OKC rarely causes resorption of adjacent tooth roots unlike other lesions of dental origin such as ameloblastomas (Borghesi et al., 2018).

Moreover, both conditions manifest in the same age group and prefer the posterior part of the mandible, often recurring frequently. Conventional radiographs and CT cannot distinguish between ameloblastoma and OKC. Consequently, histological evaluation, supplemented by MRI, is the primary method for determining this differential diagnosis. (Oginni et al., 2023).

5.3.10. Differential Diagnosis

OKC that is linked to an impacted tooth has the potential to imitate a dentigerous cyst. A multilocular OKC located in the posterior part of the mandible or ramus may resemble an ameloblastoma.

Moreover, if an OKC is located near the apex of a tooth or affects an area where teeth are missing, it could be mistakenly identified as a radicular cyst. Ameloblastoma, radicular cysts, and dentigerous cysts are the most frequently encountered odontogenic lesions when distinguishing an OKC from other conditions (Borghesi et al., 2018).

5.4. Cleft lips and palate

Orofacial clefts are the most congenital malformations in humans, with over 371 associated disorders. Cleft lip has been distinguished from cleft palate, with a ratio of 1:800 for cleft lip alone or with cleft palate and 1:2500 for isolated cleft palate.

These malformations are believed to be primarily caused by genetic and environmental factors (Lambrecht & Kreusch, 1997).

The presence of an evident association with Gorlin syndrome has been estimated at 5% in the literature, indicating the apparent involvement of this syndrome in these malformations (Ong, K. R., & Farndon, 2019).

5.5. Paresthesias

Paresthesias are associated with the growth of OKC and arise when the cyst grows to a size that is large enough to put pressure on or move a nerve element, resulting in paresthesia.It can also occur as a post-operative consequence following removing a sizable cyst close to a nerve (Geleţu et al., 2023).

5.6. Dental anomalies

NBCCS presents other dental anomalies, encompassing impacted teeth, malocclusions, dental ectopia/heterotopia, and tooth agenesis as seen in figure 23. Furthermore, deformed teeth and missing teeth (present in 30% of cases) are present. In addition, persons affected

with GS are more prone to caries than their family members not impacted (Ong, K. R., & Farndon, 2019).

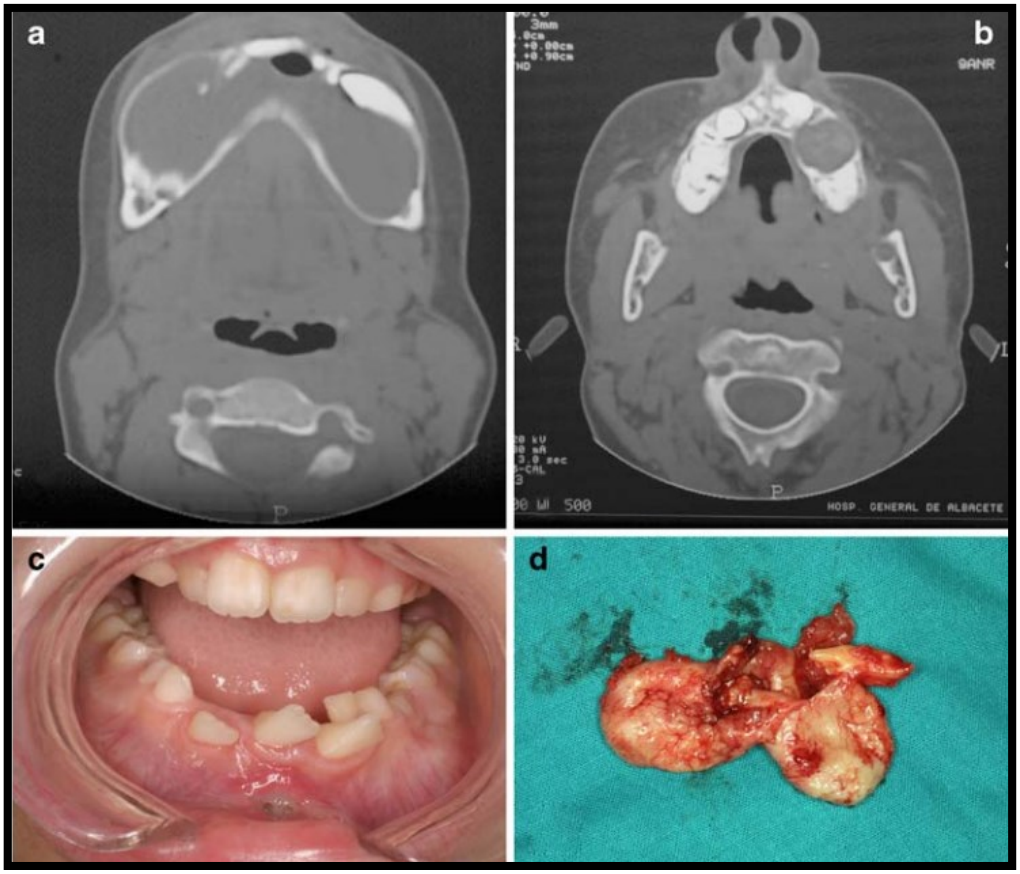


Figure 23: (a) Xray view of the mandibular KOT. (b) Maxillary KOT. (c) An intraoral examination reveals misalignment of the teeth inside the affected area. (d) Surgical resection fragment. Adapted from (García De Marcos et al., 2009).

6. Management of Gorlin syndrome

6.1. Role of the Dentist

In patients with GS, odontogenic keratocysts manifest much earlier than in individuals without the syndrome. They often serve as the initial indication of Gorlin syndrome in 78% of cases and can be identified in patients under the age of ten. Unlike other conditions where OKCs typically occur between 20 and 30, they arise much younger in GS.

The role of dentists is crucial in recognizing these early signs, enabling prompt diagnosis, and facilitating a multidisciplinary approach to managing the condition effectively (Mehta et al., 2014).

6.2. Treatment of keratocysts

While the objective is clear - eliminating the cyst, there is ongoing controversy regarding the surgical approach for odontogenic cysts. This controversy stems not from a lack of available techniques but the diversity of methods used over the decades. There is no consensus on a specific surgical protocol for cyst treatment (Moellmann et al., 2024).

When deciding on a treatment, it is essential to consider different factors related to the patient and the nature of the lesion. These factors include the treatment history, patient's age, involvement of soft tissue, size and location of the lesion, ability to follow up with the patient, perforations in the cortical bone if there is an associated syndrome such as NBCCS, and whether the lesion is primary or secondary.

It is also important to consider the histological characteristics of the lesion (Oginni et al., 2023). The primary goal of treatment is to reduce the recurrence rate, minimize morbidity, and, above all, eliminate the cyst (Ribeiro Junior et al., 2012).

Some authors favor an approach based on the size of the cyst, recommending excision for cysts less than 3 cm in diameter, with an expectation of bone regeneration. For cysts larger than 3 cm, treatment is less protocolized and often includes decompression followed by excision due to the high risk of postoperative infection (Oginni et al., 2023).

Surgical treatments for odontogenic cysts are generally classified into two categories: conservative treatments, such as marsupialization and decompression, aim to preserve bone architecture while eliminating the lesion, and aggressive treatments, such as enucleation with peripheral ostectomy, the use of chemical solutions, or bloc / segmental resection, involve a more invasive intervention to remove the cyst (Borrás-Ferreres et al., 2020).

There is a growing interest in developing a surgical protocol to mitigate the likelihood of recurrence. Resection, while typically having the lowest recurrence rate, is associated with risks of morbidity, such as postoperative severe complications.

Therefore, it is essential to evaluate the advantages and disadvantages of each treatment, as well as their indications and prognosis, paying particular attention to long-term outcomes (Spadari et al., 2022).

6.2.1. Surgical treatment

6.2.1.1 Marsupialization

The marsupialization technique was initially documented by Partsch in 1882 as a treatment for cystic lesions. It is a conservative treatment method commonly used for managing keratocystic lesions as seen in figure 24. Its principle consists of exposing the cyst to the oral cavity, which helps to decrease the cyst pressure and facilitate the healing process (Spadari et al., 2022).
This technique has two main indications:

- In cases where surgical enucleation poses high operative risks.
- For follicular cysts containing significant dental elements.

The advantages of marsupialization include its simplicity of execution, reduction of intraoperative complication risks, and preservation of adjacent structures. (neurovascular bundles, dental elements, maxillary sinus), Reduces the fracture's likelihood and makes removing lesions easier during enucleation (Menon, 2015).

However, this method also has drawbacks, such as slow lesion resolution and the necessity of close patient collaboration for postoperative care.

Histological examinations have revealed no evidence of remaining epithelial tissue from the cyst or its offspring in the biopsy sample obtained from the healed area of the surgical incision after the lesion has resolved (Spadari et al., 2022).

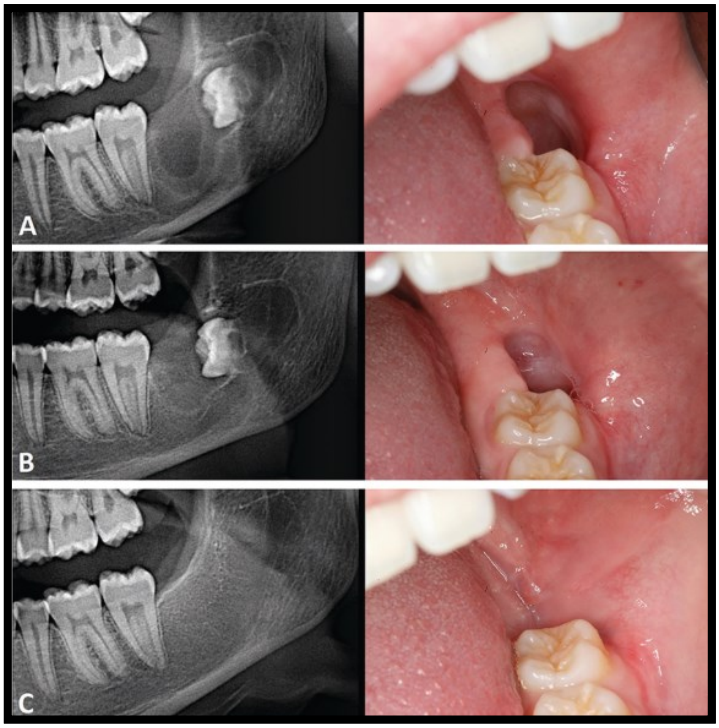


Figure 24: Radiological and clinical follow-up. A. 3 months after marsupialization. B. 6 months after marsupialization. C. 6 months after the enucleation of the cyst. Adapted from (Borrás-Ferreres et al., 2020).

6.2.1.2. Decompression

Decompression and marsupialization are sometimes mistakenly thought to be the same treatment but involve different techniques. Decompression entails creating a tiny cut in the cystic lesion and introducing a catheter to ensure continuous drainage.

This technique is designed to decrease the internal pressure of the cyst, usually followed by cystectomy after the size of the lesion decreases. By doing so, subsequent surgical steps can be undertaken without risking damage to vital anatomical structures like the inferior alveolar nerve or teeth, reducing the likelihood of a fracture.

The purposes of decompression and marsupialization are similar: exposing the cyst to the oral cavity to achieve healing. They find their interest in OKCs in young patients and large, widespread OKCs. They offer minimal invasiveness, and the procedure can be performed under local anesthesia; in case of resection, it reduces the risk of facial deformation.

Despite being considered adequate, both decompression and marsupialization may experience relapse cases during long-term follow-up (Oginni et al., 2023).

6.2.1.3. Enucleation

The approach is the total excision of the cyst during one surgical procedure. The remaining bone heals spontaneously, facilitated by bone regeneration through the inherent mechanism of blood clotting after surgery.

This approach offers the advantage of accelerated resolution of the pathology, which reduces the recovery duration. Nevertheless, when dealing with more complex keratotic tumors that have already invaded the bone and caused complications, complete excision may be challenging due to adhesions to surrounding tissues. Preserving surrounding tissues, such as teeth and nerves, can also present challenges, especially in hard-to-reach areas.

If there is a breach in the periosteal capsule, it is crucial to carefully remove the mucosa covering the cyst, as it is a potential source of recurrence as shown in figure 25. Different treatment options must be considered to avoid complications, such as extraction or endodontic treatment if the cyst is close to the teeth (Oginni et al., 2023).

There are several methods of enucleation:

- Simple enucleation involves complete extraction of the OKC from within the bone, ensuring that no visible remains are left behind.
- Enucleation using Carnoy's solution involves the application of a mixture including chloroform, ethanol, ferric chloride, and glacial acetic acid after removing the lesion. This solution cauterizes the bone walls and eliminates epithelial residues as shown in figure 27.
- Enucleation followed by peripheral ostectomy: After the enucleation procedure, a peripheral ostectomy excises any remaining bone and completely eradicates the lining epithelium as seen in figure 26.
- Enucleation followed by peripheral ostectomy and the utilization of Carnoy's solution or Modified Carnoy's solution: This technique involves the combination of enucleation followed by a peripheral ostectomy and the use of Carnoy's solution to guarantee the thorough elimination of epithelial remnants and cysts (Spadari et al., 2022).

- Enucleation is followed by applying a cryo-probe that uses nitric oxide. Set at approximately -20°C on the bone defects and the surrounding tissues if the lesion is extensive (Kaczmarzyk et al., 2012).
- Enucleation and 5-fluorouracil (5-FU) topical application for recurrent OKC leads to normal bone healing and regeneration without adverse local or systemic effects (Barua et al., 2023).

  The ease of availability and technical simplicity of applying 5-FU may make it a preferred choice over other supplementary treatments. Simply coating it onto ribbon gauze, 5% 5-FU can be placed into the bone cavity, allowing easy removal 24 hours after surgery.

  On the other hand, using Carnoy's solution considerably extends the length of the procedure due to the precautions required to prevent damage to surrounding tissues (Barua et al., 2023).

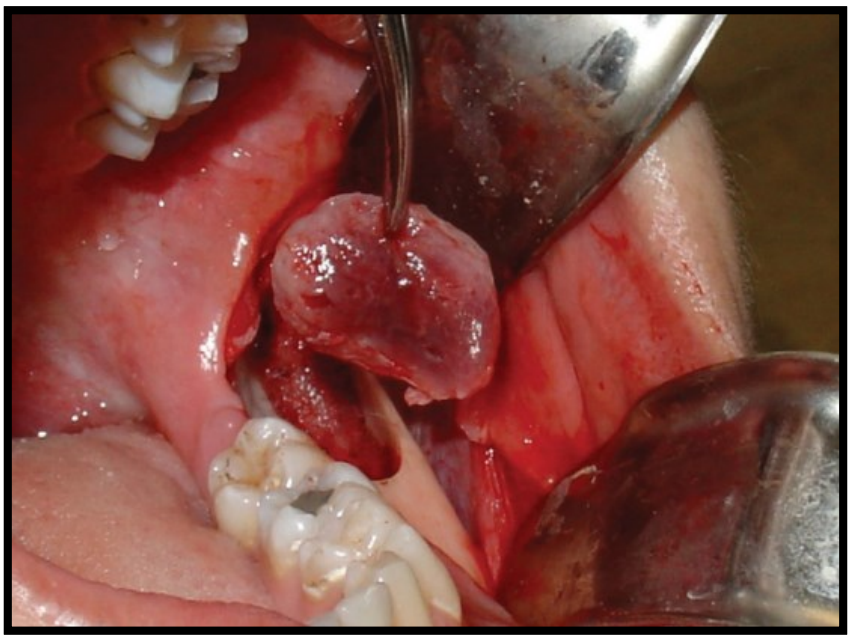


Figure 25: Enucleation. Adapted from (Ribeiro-Júnior et al., 2017).

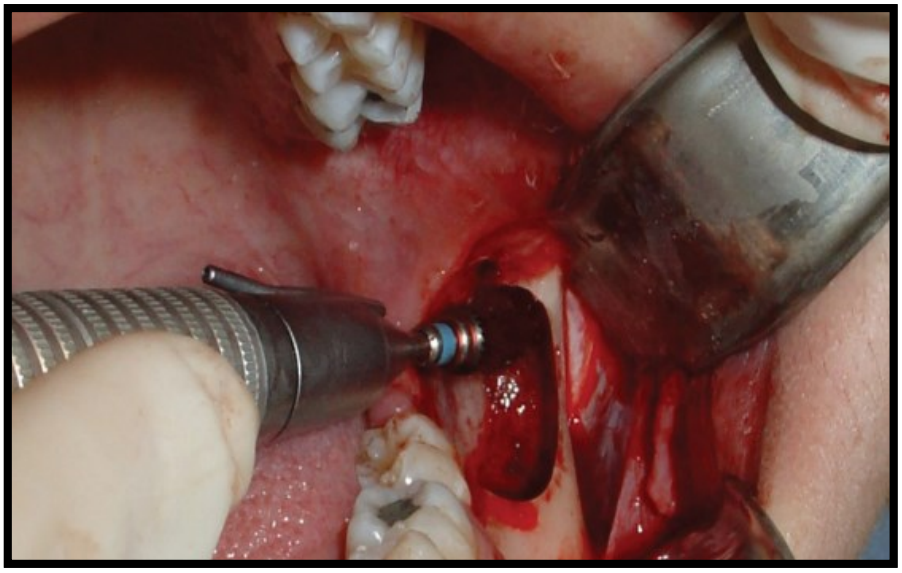


Figure 26: Peripheral ostectomy. Adapted from (Ribeiro-Júnior et al., 2017).

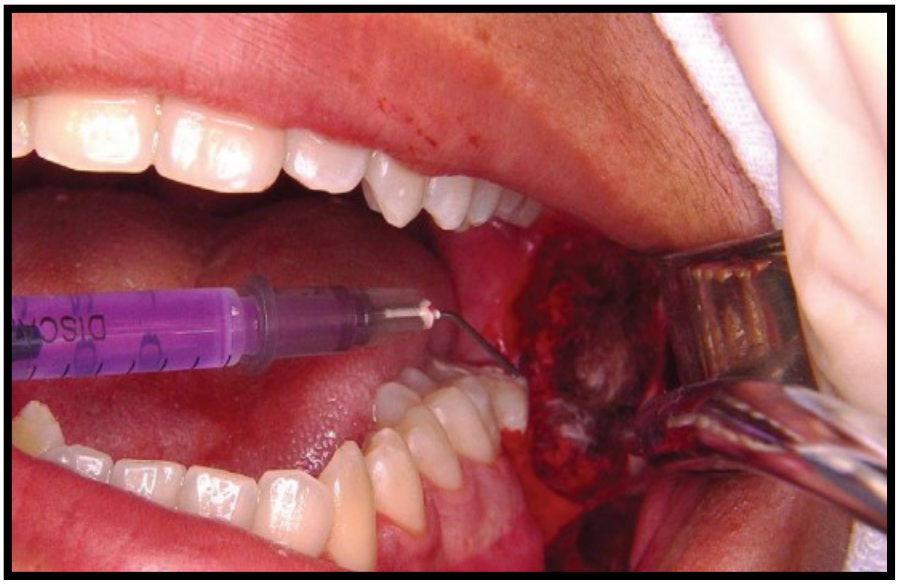


Figure 27*:* The application of Carnoy's solution. Adapted from (Ribeiro-Júnior et al., 2017).

6.2.1.4. Resection

Resection is a technique that refers to the total removal of a specific portion of the mandibular or maxillary bone without preserving its connection to the surrounding bone. Although this method shows no reappearance of keratocysts during postoperative examinations, it is associated with substantial morbidity, such as bone deformities and discontinuity in the face and mandible. Marginal resection provides a favorable option by

surgically excising lesions while keeping an undamaged bone margin to ensure integrity (Geleţu et al., 2023).

This treatment is generally not warranted for asymptomatic lesions, mainly if there is no perforation, expansion, or erosion of the cortical part of the bone. Resection should be considered only if it is extensive beyond the cortical bone, particularly recurrent tumors. Lesions confined to the medullary portion of the bone generally warrant a less aggressive approach. Lesions confined to the medullary part of the bone generally warrant a more conservative approach.

Rapid reconstruction using free flaps of the iliac wing, the fibula, or autologous bone grafts is recommended in cases where mandibular resection is necessary. For extensive, multilocular lesions, those in high-risk sites, or those prone to recurrence or malignant degeneration, a resection might be needed to prevent recurrence and expansion of the lesion (Spadari et al., 2022).

6.2.2. Surgical treatment and GS

There is a clear differentiation between OKCs linked to NBCCS and those not. OKCs of non-NBCCS origin are typically solitary and are frequently observed in adult and old individuals, primarily in the posterior mandible. They exhibit dense layers of cells covering their surface and experience a recurrence rate of approximately 61%.

In contrast, NBCCS-associated OKC is often multiple, occurs in younger patients, and is distributed equally across the jawbones. Their lining epithelium is reduced in thickness, and they experience a greater recurrence rate of about 82% (Spadari et al., 2022).

The rates of recurrence of OKCs display considerable diversity. The rates of success for different surgical procedures are as follows:

- 32-33% for marsupialization
- 30% for enucleation
- 18% for enucleation with peripheral ostectomy
- 14.5-38% for enucleation combined with cryotherapy
- 13-14.6% for decompression and cystectomy
- 9-17% for enucleation and rinsing using Carnoy's solution
- 0-8.4% for surgical resection.

Keratocysts reappear more frequently in individuals with NBCCS, often manifesting at a young age. These cysts typically show parakeratinization and can occasionally undergo neoplastic changes, potentially leading to conditions such as ameloblastomas and squamous cell carcinomas.

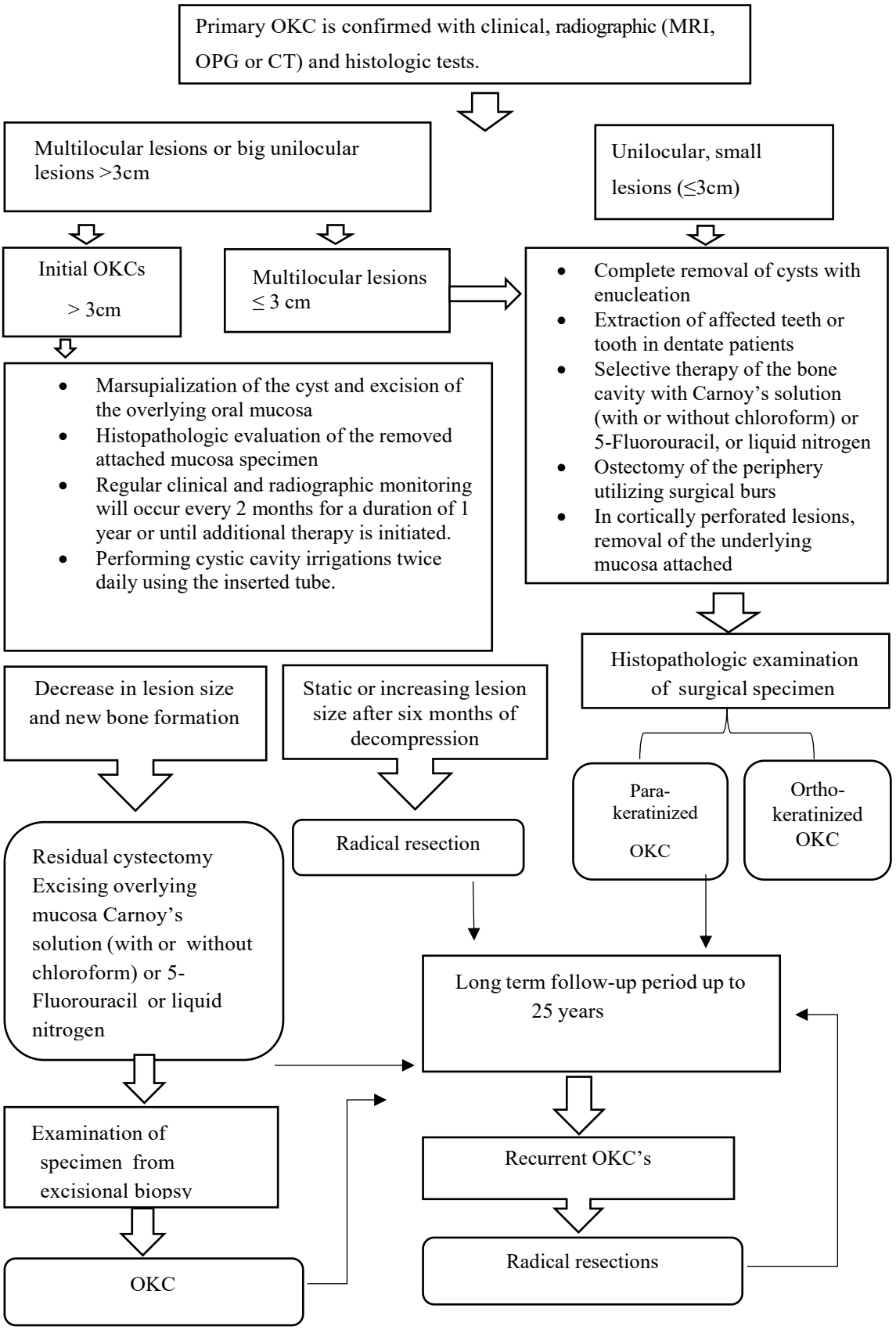
Therefore, it is essential to opt for surgical intervention and maintain vigilant monitoring to mitigate risks associated with recurrence and potential malignant transformations (Bresler et al., 2016).

The current method suggests targeted surgical protocols based on developmental aspects, histological type, and location of the lesion:

- For unilocular lesions arising within the mandible and contained within the bone without extending into surrounding soft tissues, initial treatment typically involves excising the lesion and thorough bone curettage using manual and rotating instruments. Additionally, cytotoxic substances may be applied to ensure comprehensive removal.
- The previously mentioned treatment approach can still be considered for multilocular lesions within the mandible. Nevertheless, this approach is linked to an increased likelihood of OKC reappearance, and a more aggressive treatment strategy will likely be necessary.
- Traditional removal and curettage methods often fail to completely eradicate multilocular lesions arising in the mandible and penetrating the bone cortical. A more aggressive approach may be necessary in such scenarios, involving the resection of the lesion with ample security margins.That may be complemented by quick or delayed restoration of the removed tissue section to restore functional and aesthetic integrity. Although locally aggressive, benign lesions in the maxilla require a more radical treatment approach than those in the mandible, even when they have the same morphology, histological type, and extension. This phenomenon is caused by the specific characteristics of the anatomy, which leads to faster growth and makes treatment more difficult in case of a relapse (Spadari et al., 2022).

Oginni et al. have established a treatment protocol for OKC that considers the size and number of cysts, as summarized in the figure below (Table 4).

Table 4: Decision treatment of OKCs. Adapted from (Oginni et al., 2023).



6.3. Treatment of BCCs

Managing BCCs can be difficult because every lesion needs to be treated separately. Generally, the care of BCC involves removal, curettage, and elimination. Nevertheless, the complications during the procedure can be very burdensome, particularly for patients with a high number of tumors at a young age who have NBCCS (Fisher et al., 2020).

Although metastases from BCCs are rare, they can cause significant damage to tissues and potentially invade nearby organs. That poses a higher risk for people with NBCCS because of the size and number of their tumors (Flowers et al., 2023).

Several non-invasive treatment methods can be used, such as 5-fluorouracil 5% in conjunction with or without a cream containing tretinoin 0.1%, topical imiquimod accompanied or not with curettage, photodynamic therapy, oral retinoids, topical solasodine, laser, glycoalkaloids or topical tazarotene (Fisher et al., 2020).

VISMODEGIB was approved by the FDA in 2013 as the first drug to specifically target the Hedgehog pathway and directly block signaling components involved in the proliferation of BCC in patients with NBCCS (Bresler et al., 2016).

Although this therapy has had encouraging outcomes in adults, it is linked to permanent fusion of the growth plate in children. The therapeutic objectives for children are centered around attaining effective cancer management while reducing any suffering or scarring (Fisher et al., 2020).

Treatment strategies for individuals with NBCCS entail regular dermatologic exams and implementing steps to avoid BCC, including safeguarding the skin against UV radiation and phototherapy, vitamin D, and retinoids (Fisher et al., 2020; John & Schwartz, 2016). Radiotherapy is not recommended for patients with NBCCS (Bresler et al., 2016).

6.4. Treatment of cleft lip and cleft palate

A cleft can manifest as labial, labio-maxillary, uni/bilateral labio-maxillo-palatal, or isolated palatal. A multidisciplinary team brings together several specialists and enables comprehensive care for patients born with a cleft.

This team follows the child at each stage of development and establishes an optimal treatment plan that avoids unnecessary burdens on the family. Depending on the type of

cleft and the child's age, issues related to feeding, speech, ENT (Ear, Nose, and Throat), dental, orthodontic, aesthetic, and even psychological problems may need to be addressed. This care begins at diagnosis, pre or postnatally, and continues until the end of growth. It requires a multidisciplinary team that collaborates with obstetricians and geneticists.

In the following table, we will present the intervention chronology for unilateral or bilateral labial or palatal clefts as presented by the Lausanne multidisciplinary team (Hohlfeld et al., 2009).

Table 5: Timeline of the management of CLP patients by the interdisciplinary team at Lausanne. Adapted from (Hohlfeld et al., 2009).

WHEN	WHAT	WHO
Antenatal	• Information • Psychological help, if necessary	• Pediatric surgeon • Psychologist
Birth	• Information • Dietary support • Feeding plate	• Pediatric surgeon • Orthodontist
3 months	• Soft palate closure • Lip closure	• Pediatric surgeon
5-6 months	• Closure of hard palate and lip for complete cleft	• Pediatric surgeon
8months	• Lip closure on the other side	• Pediatric surgeon
18 months-3 years	• Routine check • Guidance workshop each therapy	• Pediatric surgeon
3 years	• First multidisciplinary conference • Speech therapy assessment • Psychological assessment	• Complete team
3-9 years	• Checkups every 2-3 years • Speech therapy follow-up • Orthodontic follow-up • Early secondary surgery	• Complete team • Pediatric surgeon • ENT
9 years	• Orthodontic and maxillofacial assessment	• Complete team
9-10 years	• Alveolar bone graft	• Maxillofacial surgeon • Orthodontist
12-18 years old	• Checkups every 2-3 years	• Complete team
18-20	• Final Assessment: • Genetic counseling	• Complete team

6.5. Inhibition of the hedgehog pathway and the introduction of Vismodegib

The FDA approved the medication Vismodegib in January 2013. The effectiveness of the treatment has been proven in patients with GS, as it dramatically reduces the quantity and dimensions of surgically curable BCC compared to placebo medicine (Verkouteren, 2023).

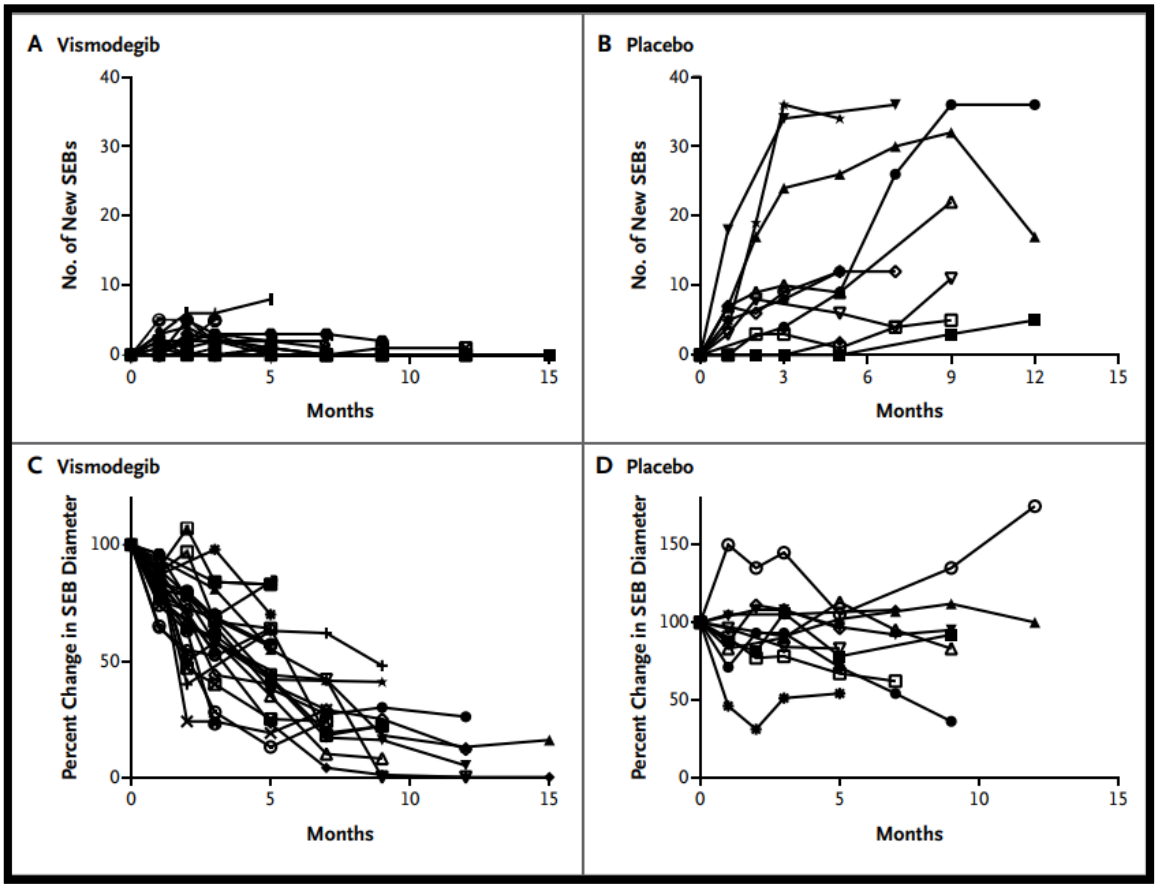


Figure 28: Basal cell carcinomas that can be treated with surgery were found in 36 patients on Vismodegib therapy. Adapted from (Tang et al., 2012).

Additionally, it has been observed that patients undergoing this treatment experience a disappearance of palmar and plantar pits, considered major diagnostic criteria for the disease (Bichakjian et al., 2018).

Histologically, this treatment reduces Hedgehog pathway signaling by 90%, and it has shown a marked decrease in the tumorigenic nature of the disease as shown in figure 28. That suggests it may act on various symptoms, including odontogenic keratocysts, potentially reducing their number and incidence (Tang et al., 2012).

III. Conclusion

Nevoid Basal Cell Carcinoma Syndrome is an autosomal dominant genetic anomaly known as Gorlin-Goltz syndrome.

The estimated prevalence in the general population varies from 1 in 50,000 to 1 in 150000 individuals, varying by race but not by gender. Numerous studies have focused on the origin of this syndrome, revealing it to be a genetic disorder. The main interest is an accurate diagnosis and, more recently, a research tool for treatment. The major challenge for healthcare specialists remains the diagnosis of this syndrome.

Indeed, specialists should have a minimum level of knowledge about the various manifestations of the syndrome to make a correct diagnosis and thus prevent complications. These complications can be diverse (dermatological, ocular, skeletal, neurological, and dental) but are often asynchronous and typically diagnosed late, exposing patients to a risk of tumorigenesis.

Dentists are mainly, if not most, concerned by this challenge due to the frequency of odontogenic keratocysts and other oral-facial manifestations, which include CLP, dental malposition, BCC, and nevi. The onset of these manifestations is often early, as confirmed by literature data and our series of clinical cases. To facilitate early diagnosis, we must learn to work closely with other healthcare specialists, particularly neurologists, radiologists, and dermatologists. Management also depends on our skills, but it remains symptomatic and often leads to recurrences.

We must remember that the significant severity associated with NBCCS is carcinogenic transformation; this highlights the criticality of promptly identifying our patient's condition and regular follow-up.

IV. Bibliography

Akbari, M., Chen, H., Guo, G., Legan, Z., & Ghali, G. (2018). Basal cell nevus syndrome (Gorlin syndrome): genetic insights, diagnostic challenges, and unmet milestones. *Pathophysiology*, *25*(2), 77–82. https://doi.org/10.1016/J.PATHOPHYS.2017.12.004

Aszterbaum, M., Rothman, A., Johnson, R. L., Fisher, M., Xie, J., Bonifas, J. M., Zhang, X., Scott, M. P., & Epstein, E. H. (1998). *Identification of Mutations in the Human PATCHED Gene in Sporadic Basal Cell Carcinomas and in Patients with the Basal Cell Nevus Syndrome*.

Bale, A. E., & Yu, K. P. (2001). The hedgehog pathway and basal cell carcinomas. *Human Molecular Genetics*, *10*(7), 757–762. https://doi.org/10.1093/hmg/10.7.757

Barua, C. G., Ali, I., Tripathi, A., Malakar, A., & Singha, P. K. (2023). The Role of 5-Fluorouracil in Preventing Recurrence After Enucleation of Odontogenic Keratocyst: A Case Report. *Cureus*. https://doi.org/10.7759/cureus.44777

Belmehdi, A., Chbicheb, S., & Wady, W. El. (2016). Odontogenic Keratocyst Tumor: A Case Report and Literature Review. *Open Journal of Stomatology*, *06*(07), 171–178. https://doi.org/10.4236/ojst.2016.67022

Betancourt, N. J., Qian, M. F., Pickford, J. R., Bailey-Healy, I., Tang, J. Y., & Teng, J. M. C. (2022). Gorlin Syndrome: Assessing Genotype-Phenotype Correlations and Analysis of Early Clinical Characteristics as Risk Factors for Disease Severity. *J Clin Oncol*, *40*, 2119–2127. https://doi.org/10.1200/JCO.21

Bichakjian, C., Armstrong, A., Baum, C., Bordeaux, J. S., Brown, M., Busam, K. J., Eisen, D. B., Iyengar, V., Lober, C., Margolis, D. J., Messina, J., Miller, A., Miller, S., Mostow, E., Mowad, C., Nehal, K., Schmitt-Burr, K., Sekulic, A., Storrs, P., … Rodgers, P. (2018). Guidelines of care for the management of basal cell carcinoma. *Journal of the American Academy of Dermatology*, *78*(3), 540–559. https://doi.org/10.1016/j.jaad.2017.10.006

Boffano, P., Cavarra, F., Agnone, A. M., Brucoli, M., Ruslin, M., Forouzanfar, T., Ridwan-Pramana, A., Rodríguez-Santamarta, T., Carlos De Vicente, J., Starch-Jensen, T., Pechalova, P., Pavlov, N., Doykova, I., Gospodinov, D.,

Konstantinovic, V. S., Jovanovi, M., Meyer, C., Tamme, T., Andrianov, A., … Rocchetti, V. (2021). *The epidemiology and management of odontogenic keratocysts (OKCs): A European multicenter study*. https://doi.org/10.1016/j.jcms.2021.09.022

Borghesi, A., Nardi, C., Giannitto, C., Tironi, A., Maroldi, R., Di Bartolomeo, F., & Preda, L. (2018). Odontogenic keratocyst: imaging features of a benign lesion with an aggressive behaviour. In *Insights into Imaging* (Vol. 9, Issue 5, pp. 883–897). Springer Verlag. https://doi.org/10.1007/s13244-018-0644-z

Borrás-Ferreres, J., Sánchez-Torres, A., Alberdi-Navarro, J., Aguirre-Urizar, J. M., Mosqueda-Taylor, A., & Gay-Escoda, C. (2020). Therapeutic management of the odontogenic keratocyst. An energetic approach with a conservative perspective and review of the current therapeutic options. *Journal of Clinical and Experimental Dentistry*, *12*(8), e794–e799. https://doi.org/10.4317/jced.56722

Bouyssi-Kobar, M., De Asis-Cruz, J., Murnick, J., Chang, T., & Limperopoulos, C. (2019).HHS Public Access. *Journal of Pediatrics*, *23*(12), 13–2. https://doi.org/10.1158/1078-0432.CCR-17-0595.Cancer

Bree, A. F., & Shah, M. R. (2011). Consensus statement from the first international colloquium on basal cell nevus syndrome (BCNS). *Am. J. Med. Genet. Part A*, *155*(9), 2091–2097. https://doi.org/10.1002/ajmg.a.34128

Bresler, S. C., Padwa, B. L., & Granter, S. R. (2016). Nevoid Basal Cell Carcinoma Syndrome (Gorlin Syndrome). *Head and Neck Pathology*, *10*(2), 119–124. https://doi.org/10.1007/s12105-016-0706-9

Briscoe, J., & Thérond, P. P. (2013). The mechanisms of Hedgehog signalling and its roles in development and disease. *Nature Reviews Molecular Cell Biology*, *14*(7), 418–431. https://doi.org/10.1038/nrm3598

Bubshait, D. K. (2022). A review of polydactyly and its inheritance: Connecting the dots. *Medicine (United States)*, *101*(50), E32060. https://doi.org/10.1097/MD.0000000000032060

Carlson, E. R., Oreadi, D., & McCoy, J. M. (2015). Nevoid Basal Cell Carcinoma Syndrome and the Keratocystic Odontogenic Tumor. *Journal of Oral and Maxillofacial Surgery : Official Journal of the American Association of Oral and*

Maxillofacial Surgeons, *73*(12), S77–S86. https://doi.org/10.1016/j.joms.2015.04.037

Chen, P., Liu, B., Wei, B., & Yu, S. (2022). Brief Communication The clinicopathological features and treatments of odontogenic keratocysts Peng. In *Am J Cancer Res* (Vol. 12, Issue 7). www.ajcr.us/

Chen, X., Tukachinsky, H., Huang, C. H., Jao, C., Chu, Y. R., Tang, H. Y., Mueller, B., Schulman, S., Rapoport, T. A., & Salic, A. (2011). Processing and turnover of the Hedgehog protein in the endoplasmic reticulum. *Journal of Cell Biology*, *192*(5), 825–838. https://doi.org/10.1083/jcb.201008090

DeLair, D. F., & Soslow, R. A. (2016). Gynecologic Manifestations of Less Commonly Encountered Hereditary Syndromes. *Surgical Pathology Clinics*, *9*(2), 269–287. https://doi.org/10.1016/j.path.2016.01.008

Epstein, E. H. (2008). Basal cell carcinomas: Attack of the hedgehog. *Nature Reviews Cancer*, *8*(10), 743–754. https://doi.org/10.1038/nrc2503

Evans, D. G., Farndon, P. ; A., Adam, M. P., Feldman, J., & Mirzaa, G. M. (2002). *Nevoid Basal Cell Carcinoma Syndrome*.

Evans, D. G., Farndon, P. ; A., Adam, M. P., Feldman, J., & Mirzaa, G. M. (2024). *Nevoid Basal Cell Carcinoma Syndrome*.

Evans, D. G., & Farndon, P. A. (2018). Nevoid Basal Cell Carcinoma Syndrome Summary Diagnosis Suggestive Findings. *GeneReviews® [Internet]*, 1–21. https://www.ncbi.nlm.nih.gov/books/NBK1151/

Evans, D. G., Oudit, D., Smith, M. J., Rutkowski, D., Allan, E., Newman, W. G., & Lear, J. T. (2017). First evidence of genotype-phenotype correlations in Gorlin syndrome. *Journal of Medical Genetics*, *54*(8), 530–536. https://doi.org/10.1136/jmedgenet-2017-104669

Evans, Ladusans, E. J., Rimmer, S., Burnell, L. D., Thakker, N., & Farndon, P. A. (1993). Complications of the naevoid basal cell carcinoma syndrome: Results of a population based study. *Journal of Medical Genetics*, *30*(6), 460–464. https://doi.org/10.1136/jmg.30.6.460

Fan, Z., Li, J., Du, J., Zhang, H., Shen, Y., Wang, C. Y., & Wang, S. L. (2008). A

missense mutation in PTCH2 underlies dominantly inherited NBCCS in a Chinese family. *Journal of Medical Genetics*, *45*(5), 303–308. https://doi.org/10.1136/jmg.2007.055343

Fazel, N. (2019). Oral Signs of Systemic Disease. *Oral Signs of Systemic Disease*, 1–266. https://doi.org/10.1007/978-3-030-10863-2

Figueira, J. A., de Souza Batista, F. R., Rosso, K., Veltrini, V. C., & Pavan, A. J. (2018). Delayed diagnosis of Gorlin–Goltz syndrome: The importance of the multidisciplinary approach. *Journal of Craniofacial Surgery*, *29*(6), e530–e531. https://doi.org/10.1097/SCS.0000000000004438

Fisher, J., Moustafa, D., Su, K. A., Bartenstein, D. W., Lilly, E., Kroshinsky, D., & Hawryluk, E. B. (2020). A pediatric approach to management of skin growths in basal cell nevus syndrome. *Pediatric Dermatology*, *37*(3), 527–530. https://doi.org/10.1111/pde.14122

Flowers, L., Sandhu, M., & Martin, K. (2023). Skin Cancer: Basal Cell Nevus Syndrome (Gorlin Syndrome). *Journal of the Dermatology Nurses' Association*, *15*(6), 268–272. https://doi.org/10.1097/JDN.0000000000000764

Fuse, N., Maiti, T., Wang, B., Porter, J. A., Tanaka Hall, T. M., Leahy, D. J., & Beachy, P. A. (1999). Sonic hedgehog protein signals not as a hydrolytic enzyme but as an apparent ligand for Patched. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(20), 10992–10999. https://doi.org/10.1073/pnas.96.20.10992

García De Marcos, J. A., Dean-Ferrer, A., Arroyo Rodríguez, S., Calderón-Polanco, J., Alamillos Granados, F. J., & Poblet, E. (2009). Basal cell nevus syndrome: Clinical and genetic diagnosis. *Oral and Maxillofacial Surgery*, *13*(4), 225–230. https://doi.org/10.1007/s10006-009-0169-1

Geleţu, G. L., Burlacu, A., Baciu, E. R., Diaconu-Popa, D., Murariu, A., Foia, L. G., Ungureanu, L., & Onică, N. (2023). Various Surgical Interventions in Treating Odontogenic Keratocyst: A Radiological Case Report. *Healthcare (Switzerland)*, *11*(3). https://doi.org/10.3390/healthcare11030416

Giovacchini, F., Bensi, C., Paradiso, D., Belli, S., Mitro, V., & Tullio, A. (2020). Factors influencing the recurrence of keratocysts: Monocentric study. *Journal of*

Oral Medicine and Oral Surgery, *26*(1), 1–7. https://doi.org/10.1051/mbcb/2019031

Gonzalez, D. M., & Medici, D. (2014). Signaling mechanisms of the epithelial-mesenchymal transition. *Science Signaling*, *7*(344), re8. https://doi.org/10.1126/scisignal.2005189

Hahn, H., Wicking, C., Zaphiropoulos, P. G., Gailani, M. R., Shanley, S., Chidambaram, A., Vorechovsky, I., Holmberg, E., Unden, A. B., Gillies, S., Negus, K., Smyth, I., Pressman, C., Leffell, D. J., Gerrard, B., Goldstein, A. M., Dean, M., Toftgard, R., Chenevix-Trench, G., … Bale, A. E. (1996). Mutations of the human homolog of drosophila patched in the nevoid basal cell carcinoma syndrome. *Cell*, *85*(6), 841–851. https://doi.org/10.1016/S0092-8674(00)81268-4

Hohlfeld, J., De Buys Roessingh, A., Herzog, G., Fabre, M., Cherpilled, J., Waridel, F., Pasche, P., Jaques, B., Broome, M., Despars, J., Despars, C., Peter, C., Zbinden, C., Fleury, L., & Bourgey, M. J. (2009). Prise en charge des fentes labio-maxillo-palatines au CHUV. *Revue Medicale Suisse*, *5*(191), 402–408.

Hooper, J. E., & Scott, M. P. (2005). Communicating with hedgehogs. *Nature Reviews Molecular Cell Biology*, *6*(4), 306–317. https://doi.org/10.1038/nrm1622

Huq, A. J., Walsh, M., Rajagopalan, B., Finlay, M., Trainer, A. H., Bonnet, F., Sevenet, N., & Winship, I. M. (2018). Mutations in SUFU and PTCH1 genes may cause different cutaneous cancer predisposition syndromes: similar, but not the same. *Familial Cancer*, *17*(4), 601–606. https://doi.org/10.1007/s10689-018-0073-7

Ingham, P. W. (2022). Hedgehog signaling. *Current Topics in Developmental Biology*, *149*, 1–58. https://doi.org/10.1016/BS.CTDB.2022.04.003

Javelaud, D., Pierrat, M. J., & Mauviel, A. (2012). Crosstalk between TGF-β and hedgehog signaling in cancer. *FEBS Letters*, *586*(14), 2016–2025. https://doi.org/10.1016/j.febslet.2012.05.011

Jen, M., & Nallasamy, S. (2016). Ocular manifestations of genetic skin disorders. *Clinics in Dermatology*, *34*(2), 242–275. https://doi.org/10.1016/j.clindermatol.2015.11.008

John, A. M., & Schwartz, R. A. (2016). Basal cell naevus syndrome: An update on

genetics and treatment. *British Journal of Dermatology*, *174*(1), 68–76. https://doi.org/10.1111/bjd.14206

Johnson, R. L., Rothman, A. L., Xie, J., Goodrich, L. V., Bare, J. W., Bonifas, J. M., Quinn, A. G., Myers, R. M., Cox, D. R., Epstein, E. H., & Scott, M. P. (1996). Human homolog of patched, a candidate gene for the basal cell nevus syndrome. *Science*, *272*(5268), 1668–1671. https://doi.org/10.1126/science.272.5268.1668

Jones, E. A., Sajid, M. I., Shenton, A., & Evans, D. G. (2011). Basal Cell Carcinomas in Gorlin Syndrome: A Review of 202 Patients. *Journal of Skin Cancer*, *2011*, 1–6. https://doi.org/10.1155/2011/217378

Kaczmarzyk, T., Mojsa, I., & Stypulkowska, J. (2012). A systematic review of the recurrence rate for keratocystic odontogenic tumour in relation to treatment modalities. *International Journal of Oral and Maxillofacial Surgery*, *41*(6), 756–767. https://doi.org/10.1016/j.ijom.2012.02.008

Kenney, A. M., & Rowitch, D. H. (2000). Sonic hedgehog Promotes G 1 Cyclin Expression and Sustained Cell Cycle Progression in Mammalian Neuronal Precursors. *Molecular and Cellular Biology*, *20*(23), 9055–9067. https://doi.org/10.1128/mcb.20.23.9055-9067.2000

Khodaverdi, S., Nazari, L., Mehdizadeh-Kashi, A., Vahdat, M., Rokhgireh, S., Farbod, A., & Tajbakhsh, B. (2018). Conservative management of ovarian fibroma in a case of Gorlin-Goltz syndrome comorbid with endometriosis. *International Journal of Fertility and Sterility*, *12*(1), 88–90. https://doi.org/10.22074/ijfs.2018.5240

Kimonis, V. E., Goldstein, A. M., Pastakia, B., Yang, M. L., Kase, R., Digiovanna, J. J., Bale, A. E., & Bale, S. J. (1997). Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. *American Journal of Medical Genetics*, *69*(3), 299–308. https://doi.org/10.1002/(SICI)1096-8628(19970331)69:3<299::AID-AJMG16>3.0.CO;2-M

Kimonis, V. E., Mehta, S. G., DiGiovanna, J. J., Bale, S. J., & Pastakia, B. (2004). Radiological features in 82 patients with nevoid basal cell carcinoma (NBCC or Gorlin) syndrome. *Genetics in Medicine*, *6*(6), 495–502. https://doi.org/10.1097/01.GIM.0000145045.17711.1C

Kristine Larsen, A., Bisgaard Mikkelsen, D., Michael Hertz, J., & Bygum, A. (2014). Manifestations of Gorlin-Goltz syndrome. *Danish Medical Journal*, *61*(5), 1–5.

Lambrecht, J. T., & Kreusch, T. (1997). Examine Your Orofacial Cleft Patients for Gorlin-Goltz Syndrome. In *The Cleft Palate-Craniofacial Journal* (Vol. 34, Issue 4, pp. 342–350). https://doi.org/10.1597/1545-1569_1997_034_0341_eyocpf_2.3.co_2

Lee, S. G., Evans, G., Stephen, M., Goren, R., Bondy, M., & Goodman, S. (2024). Medulloblastoma and other neoplasms in patients with heterozygous germline SUFU variants: A scoping review. *American Journal of Medical Genetics, Part A*, *November 2023*. https://doi.org/10.1002/ajmg.a.63496

Lo Muzio, L. (2008). Nevoid basal cell carcinoma syndrome (Gorlin syndrome). *Orphanet Journal of Rare Diseases*, *3*(1), 1–16. https://doi.org/10.1186/1750-1172-3-32/TABLES/3

Longhitano, L., Tibullo, D., Vicario, N., Giallongo, C., Spina, E. La, Romano, A., Lombardo, S., Moretti, M., Masia, F., Coda, A. R. D., Venuto, S., Fontana, P., Parenti, R., Volti, G. L., Rosa, M. Di, Palumbo, G. A., & Liso, A. (2021). IGFBP-6/sonic hedgehog/TLR4 signalling axis drives bone marrow fibrotic transformation in primary myelofibrosis. *Aging*, *13*(23), 25055–25071. https://doi.org/10.18632/aging.203779

MacDonald, D. S. (2015). A systematic review of the literature of nevoid basal cell carcinoma syndrome affecting East Asians and North Europeans. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, *120*(3), 396–407. https://doi.org/10.1016/j.oooo.2015.05.024

Mak, A. S. L., & Leung, K. Y. (2019). Prenatal ultrasonography of craniofacial abnormalities. In *Ultrasonography* (Vol. 38, Issue 1, pp. 13–24). Korean Society of Ultrasound in Medicine. https://doi.org/10.14366/usg.18031

Martinez, M. F., Romano, M. V., Martinez, A. P., González, A., Muchnik, C., Stengel, F. M., Mazzuoccolo, L. D., & Azurmendi, P. J. (2019). Nevoid basal cell carcinoma syndrome: PTCH1 mutation profile and expression of genes involved in the hedgehog pathway in argentinian patients. *Cells*, *8*(2), 1–12. https://doi.org/10.3390/cells8020144

Massimino, M., Biassoni, V., Gandola, L., Garrè, M. L., Gatta, G., Giangaspero, F., Poggi, G., & Rutkowski, S. (2016). Childhood medulloblastoma. *Critical Reviews in Oncology/Hematology*, *105*(May), 35–51. https://doi.org/10.1016/j.critrevonc.2016.05.012

Mehta, D., Raval, N., Patadiya, H., & Tarsariya, V. (2014). Gorlin-Goltz syndrome. *Annals of Medical and Health Sciences Research*, *4*(2), 279. https://doi.org/10.4103/2141-9248.129064

Menon, S. (2015). Keratocystic Odontogenic Tumours: Etiology, Pathogenesis and Treatment Revisited. In *Journal of Maxillofacial and Oral Surgery* (Vol. 14, Issue 3, pp. 541–547). Springer. https://doi.org/10.1007/s12663-014-0734-5

Mizuochi, H., Fujii, K., Shiohama, T., Uchikawa, H., & Shimojo, N. (2015). Hedgehog signaling is synergistically enhanced by nutritional deprivation and ligand stimulation in human fibroblasts of Gorlin syndrome. *Biochemical and Biophysical Research Communications*, *457*(3), 318–323. https://doi.org/10.1016/j.bbrc.2014.12.108

Moramarco, A., Himmelblau, E., Miraglia, E., Mallone, F., Roberti, V., Franzone, F., Iacovino, C., Giustini, S., & Lambiase, A. (2019). *Ocular manifestations in Gorlin-Goltz syndrome*. *6*, 1–7.

Morse, C. B., McLaren, J. F., Roy, D., Siegelman, E. S., Livolsi, V. A., & Gracia, C. R. (2011). Ovarian preservation in a young patient with Gorlin syndrome and multiple bilateral ovarian masses. *Fertility and Sterility*, *96*(1), e47–e50. https://doi.org/10.1016/j.fertnstert.2011.04.028

Nguyen, N. M., & Cho, J. (2022). Hedgehog Pathway Inhibitors as Targeted Cancer Therapy and Strategies to Overcome Drug Resistance. *International Journal of Molecular Sciences*, *23*(3). https://doi.org/10.3390/ijms23031733

Niewiadomski, P., Niedziółka, S. M., Markiewicz, Ł., Uśpieński, T., Baran, B., & Chojnowska, K. (2019). Gli proteins: Regulation in development and cancer. *Cells*, *8*(2), 1–36. https://doi.org/10.3390/cells8020147

Nilius, M., Kohlhase, J., Lorenzen, J., Lauer, G., & Schulz, M. C. (2019). Multidisciplinary oral rehabilitation of an adolescent suffering from juvenile Gorlin-Goltz syndrome - A case report. *Head and Face Medicine*, *15*(1).

https://doi.org/10.1186/s13005-019-0189-5

Oginni, F. O., Alasseri, N., Ogundana, O. M., Famurewa, B. A., Pogrel, A., & Al-Moraissi, E. A. (2023). An evidence-based surgical algorithm for management of odontogenic keratocyst. In *Oral and Maxillofacial Surgery* (Vol. 27, Issue 2, pp. 201–212). Springer Science and Business Media Deutschland GmbH. https://doi.org/10.1007/s10006-022-01064-z

Ong, K. R., & Farndon, P. A. (2019). (2019). Gorlin (Naevoid Basal Cell Carcinoma) Syndrome. *Harper's Textbook of Pediatric Dermatology, 2*, 1769–1785. https://doi.org/10.1002/9781444345384.ch132

Ossama, N., Zineb, R., Olaya, M. A., & Ihsane, B. E. N. Y. (2017). *Syndrome de Gorlin-Goltz : du diagnostic au traitement : à propos d ' une observation to treatment : a case report*. 1–7.

Pan, S., Dong, Q., Sun, L. S., & Li, T. J. (2010). Mechanisms of inactivation of PTCH1 gene in nevoid basal cell carcinoma syndrome: Modification of the two-hit hypothesis. *Clinical Cancer Research*, *16*(2), 442–450. https://doi.org/10.1158/1078-0432.CCR-09-2574

Pennisi, M., Lanza, G., Cantone, M., Schepis, C., Ferri, R., Barone, R., & Bella, R. (2017). Unusual neurological presentation of nevoid basal cell carcinoma syndrome (Gorlin-Goltz syndrome). *Journal of Clinical Neurology (Korea)*, *13*(4), 439–441. https://doi.org/10.3988/jcn.2017.13.4.439

Peris, K., Fargnoli, M. C., Kaufmann, R., Arenberger, P., Bastholt, L., Seguin, N. B., Bataille, V., Brochez, L., del Marmol, V., Dummer, R., Forsea, A. M., Gaudy-Marqueste, C., Harwood, C. A., Hauschild, A., Höller, C., Kandolf, L., Kellerners-Smeets, N. W. J., Lallas, A., Leiter, U., … Garbe, C. (2023). European consensus-based interdisciplinary guideline for diagnosis and treatment of basal cell carcinoma—update 2023. In *European Journal of Cancer* (Vol. 192). Elsevier Ltd. https://doi.org/10.1016/j.ejca.2023.113254

Reinders, M. G. H. C. (2019). *The hedgehog pathway in basal cell carcinoma: target for diagnostics and therapy* (Issue 2019). https://doi.org/10.26481/dis.20190215mr

Reinders, M. G., van Hout, A. F., Cosgun, B., Paulussen, A. D., Leter, E. M., Steijlen, P. M., Mosterd, K., van Geel, M., & Gille, J. J. (2018). New mutations and an

updated database for the patched-1 (PTCH1) gene. *Molecular Genetics and Genomic Medicine*, *6*(3), 409–415. https://doi.org/10.1002/mgg3.380

Ribeiro-Júnior, O., Borba, A. M., Alves, C. A. F., de GOuveia, M. M., Deboni, M. C. Z., & da Graça Naclério-Homem, M. (2017). Reclassification and treatment of odontogenic keratocysts: A cohort study. *Brazilian Oral Research*, *31*, 1–10. https://doi.org/10.1590/1807-3107bor-2017.vol31.0098

Ribeiro Junior, O., Borba, A. M., Alves, C., De Gouveia, M., Coracin, F., & Guimarães Júnior, J. (2012). Keratocystic odontogenic tumors and Carnoy's solution: Results and complications assessment. *Oral Diseases*, *18*(6), 548–557. https://doi.org/10.1111/j.1601-0825.2012.01907.x

Rinaldi, B., Cesaretti, C., Boito, S., Villa, R., Guerneri, S., Borzani, I., Rizzuti, T., Marchetti, D., Conte, G., Cinnante, C., Triulzi, F., Persico, N., Iascone, M., & Natacci, F. (2022). Family history is key to the interpretation of exome sequencing in the prenatal context: unexpected diagnosis of Basal Cell Nevus Syndrome. *Prenatal Diagnosis*, *42*(7), 927–933. https://doi.org/10.1002/pd.6171

Robert J. Gorlin and Robert W. Goltz. (1960). gorlin1960. *The New Englad Journal of Medicine*.

Ruel, L., & Thérond, P. P. (2009). Variations in Hedgehog signaling: Divergence and perpetuation in Sufu regulation of Gli. *Genes and Development*, *23*(16), 1843–1848. https://doi.org/10.1101/gad.1838109

Ruhin-Poncet, B., Picard, A., Martin-Duverneuil, N., Albertini, A. F., & Goudot, P. (2011). Keratocysts (or keratocystic epithelial odontogenic tumors). *Revue de Stomatologie et de Chirurgie Maxillo-Faciale*, *112*(2), 87–92. https://doi.org/10.1016/j.stomax.2011.01.010

Scalia, A. C., Farulla, A., Fiocchi, F., Alboni, C., & Torricelli, P. (2018). Imaging features of uterine and ovarian fibromatosis in nevoid basal cell carcinoma syndrome. *Journal of Radiology Case Reports*, *12*(9), 21–30. https://doi.org/10.3941/jrcr.v12i9.3390

Shimkets, R., Gailani, M. R., Siu, V. M., Yang-Feng, T., Pressman, C. L., Levanat, S., Goldstein, A., Dean, M., & Bale, A. E. (1996). Molecular analysis of chromosome 9q deletions in two Gorlin syndrome patients. *American Journal of Human*

Genetics, *59*(2), 417–422.

Shuster, A., Shlomi, B., Reiser, V., & Kaplan, I. (2012). Solid keratocystic odontogenic tumor-report of a nonaggressive case. *Journal of Oral and Maxillofacial Surgery*, *70*(4), 865–870. https://doi.org/10.1016/j.joms.2011.02.140

Singh Dhull, K., Acharya, S., Ray, P., Panda, S., & Sahoo, R. S. (2013). Gorlin Syndrome with Bilateral Polydactyly: A Rare Case Report. *International Journal of Clinical Pediatric Dentistry*, *6*(3), 208–212. https://doi.org/10.5005/jp-journals-10005-1221

Smith, M. J., Beetz, C., Williams, S. G., Bhaskar, S. S., O'Sullivan, J., Anderson, B., Daly, S. B., Urquhart, J. E., Bholah, Z., Oudit, D., Cheesman, E., Kelsey, A., McCabe, M. G., Newman, W. G., & Evans, D. G. R. (2014). Germline mutations in SUFU cause Gorlin syndrome-associated childhood medulloblastoma and redefine the risk associated with PTCH1 mutations. *Journal of Clinical Oncology*, *32*(36), 4155–4161. https://doi.org/10.1200/JCO.2014.58.2569

Spadari, F., Pulicari, F., Pellegrini, M., Scribante, A., & Garagiola, U. (2022). Multidisciplinary approach to Gorlin-Goltz syndrome: from diagnosis to surgical treatment of jawbones. In *Maxillofacial Plastic and Reconstructive Surgery* (Vol. 44, Issue 1). Springer. https://doi.org/10.1186/s40902-022-00355-5

Srinivas, N., Rachakonda, S., Hielscher, T., Calderazzo, S., Rudnai, P., Gurzau, E., Koppova, K., Fletcher, T., & Kumar, R. (2019). Telomere length, arsenic exposure and risk of basal cell carcinoma of skin. *Carcinogenesis*, *40*(6), 715–723. https://doi.org/10.1093/carcin/bgz059

Svärd, J., Henricson, K. H., Persson-Lek, M., Rozell, B., Lauth, M., Bergström, Å., Ericson, J., Toftgård, R., & Teglund, S. (2006). Genetic elimination of suppressor of fused reveals an essential repressor function in the mammalian hedgehog signaling pathway. *Developmental Cell*, *10*(2), 187–197. https://doi.org/10.1016/j.devcel.2005.12.013

Tang, J. Y., Mackay-Wiggan, J. M., Aszterbaum, M., Yauch, R. L., Lindgren, J., Chang, K., Coppola, C., Chanana, A. M., Marji, J., Bickers, D. R., & Epstein, E. H. (2012). Inhibiting the Hedgehog Pathway in Patients with the Basal-Cell Nevus Syndrome. *New England Journal of Medicine*, *366*(23), 2180–2188.

https://doi.org/10.1056/nejmoa1113538

Tatsi, E. B., Kanaka-Gantenbein, C., Scorilas, A., Chrousos, G. P., & Sertedaki, A. (2020). Next generation sequencing targeted gene panel in Greek MODY patients increases diagnostic accuracy. *Pediatric Diabetes*, *21*(1), 28–39. https://doi.org/10.1111/pedi.12931

Torrelo, A., Bueno, E., Colmenero, I., Rivera, I., & Happle, R. (2013). *Received Date : 14-Jan-2013 Revised Date : 09-May-2013 Accepted Date : 02-Jun-2013 Article Type : Case Report*.

Tostar, U., Malm, C. J., Meis-Kindblom, J. M., Kindblom, L. G., Toftgård, R., & Undén, A. B. (2006). Deregulation of the hedgehog signalling pathway: A possible role for the PTCH and SUFU genes in human rhabdomyoma and rhabdomyosarcoma development. *Journal of Pathology*, *208*(1), 17–25. https://doi.org/10.1002/path.1882

Ünsal, G., Cicciù, M., Ayman Ahmad Saleh, R., Riyadh Ali Hammamy, M., Amer Kadri, A., Kuran, B., & Minervini, G. (2023). Radiological evaluation of odontogenic keratocysts in patients with nevoid basal cell carcinoma syndrome: A review. *Saudi Dental Journal*, *35*(6), 614–624. https://doi.org/10.1016/j.sdentj.2023.05.023

Verkouteren, B. J. A. (2023). *Basal cell carcinoma and basal cell nevus syndrome* [maastricht university]. https://doi.org/10.26481/dis.20230929bv

Verkouteren, B. J. A., Cosgun, B., Reinders, M. G. H. C., Kessler, P. A. W. K., Vermeulen, R. J., Klaassens, M., Lambrechts, S., van Rheenen, J. R., van Geel, M., Vreeburg, M., & Mosterd, K. (2022). A guideline for the clinical management of basal cell naevus syndrome (Gorlin–Goltz syndrome)*. *British Journal of Dermatology*, *186*(2), 215–226. https://doi.org/10.1111/bjd.20700

Visioli, F., Martins, C. A. M., Heitz, C., Rados, P. V., & Sant'Ana Filho, M. (2010). Is Nevoid Basal Cell Carcinoma Syndrome Really So Rare?: Proposal for an Investigative Protocol Based on a Case Series. *Journal of Oral and Maxillofacial Surgery*, *68*(4), 903–908. https://doi.org/10.1016/j.joms.2009.03.032

Wilke, P. I., Biermann, D., Grafmann, M., Kozlik-Feldmann, R., Papingi, D., Sachweh, J. S., Stute, F., & Olfe, J. (2023). Siblings with Gorlin–Goltz syndrome associated

with cardiac tumors: a case report and review of literature. *Orphanet Journal of Rare Diseases*, *18*(1), 1–10. https://doi.org/10.1186/s13023-023-02792-5

Woo, S.-B. (2024). Odontogenic cysts. *Oral Pathology*, 414–448. https://doi.org/10.1016/B978-0-323-82918-2.00023-8

Yamada, H., Shimura, M., Takahashi, H., Nara, S., Morishima, Y., Go, S., Miyashita, T., Numabe, H., & Kawashima, H. (2020). A familial case of overgrowth syndrome caused by a 9q22.3 microdeletion in a mother and daughter. *European Journal of Medical Genetics*, *63*(5), 103872. https://doi.org/10.1016/j.ejmg.2020.103872

Zimmerman, R. S., Jalas, C., Tao, X., Fedick, A. M., Kim, J. G., Pepe, R. J., Northrop, L. E., Scott, R. T., & Treff, N. R. (2016). Development and validation of concurrent preimplantation genetic diagnosis for single gene disorders and comprehensive chromosomal aneuploidy screening without whole genome amplification. *Fertility and Sterility*, *105*(2), 286–294. https://doi.org/10.1016/j.fertnstert.2015.10.003