Gorlin-Goltz Syndrome: A Comprehensive Analysis of the Clinical, Genetic and Therapeutic Manifestations of a Rare and Complex Disease

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ABSTRACT

Gorlin-Goltz syndrome, also known as basal cell nevus syndrome or nevoid basal cell carcinoma syndrome, is a rare and heterogeneous genetic disease with a varied clinical presentation involving multiple systems and organs. This comprehensive review aims to provide an in-depth understanding of this syndrome from a medical and scientific perspective.

Gorlin-Goltz syndrome is characterized by an inherited predisposition to the formation of skin and skeletal tumors, as well as the development of jaw cysts, cleft palates, facial deformities, ocular malformations and other anomalies. At the genetic level, this syndrome is linked to mutations in the PTCH1 gene, which regulates the hedgehog signaling pathway, playing a crucial role in the regulation of cell growth and differentiation.

Early and accurate diagnosis of Gorlin-Goltz syndrome is essential to prevent serious complications, such as advanced basal cell carcinomas and facial disfigurement. Molecular diagnostic strategies and therapeutic options, including reconstructive surgery, hedgehog pathway inhibitor therapy, and multidisciplinary patient management will be addressed.

This review will also explore the psychological and social impact on patients and their families, as well as advances in genetic and therapeutic research that may open new perspectives for the management and prevention of this complex disease. Ultimately, detailed knowledge of Gorlin-Goltz syndrome is essential to improve the quality of life of those affected and to promote future research in this evolving field.

INTRODUCTION

Gorlin-Goltz syndrome, also known as basal cell nevus or nevoid basal cell carcinoma, is a rare clinical entity of a genetic nature characterized by a wide range of systemic and dermatologic manifestations of varying magnitude and severity. This autosomal dominant condition is associated with mutations in the PTCH1 gene, a key component of the hedgehog signaling pathway, which is crucial in the regulation of cell development and proliferation.1

This clinical entity manifests in significant phenotypic variability, ranging from craniofacial and skeletal malformations to the formation of multiple cutaneous basal cell tumors. Additional clinical manifestations include maxillofacial deformities, cleft palate, intracranial calcifications and ophthalmologic alterations. In addition, odontogenic cysts and ribasomas can present a diagnostic challenge.1,2

In the present context, a multidisciplinary approach is imperative for the evaluation and follow-up of affected patients, including dermatologists, maxillofacial surgeons, geneticists and ophthalmologists, in order to provide comprehensive care that encompasses both the medical and surgical aspects of the disease. Early diagnosis is critical for the implementation of preventive and therapeutic strategies to mitigate potential complications, including the development of advanced basal cell carcinomas and their sequelae.2

This article aims to provide a comprehensive and up-to-date review of Gorlin-Goltz syndrome, ranging from the genetic
and molecular basis to the most recent diagnostic modalities and therapeutic options. It will also focus on the psychosocial impact of this disease on affected individuals and their families, as well as on the advances and future perspectives in the research of this complex medical entity.  

Ultimately, a thorough and up-to-date knowledge of Gorlin-Goltz Syndrome is essential for the comprehensive and optimal management of patients, thus promoting high quality care and contributing to the development of future research in this evolving field.

**EPIDEMIOLOGY**

Gorlin-Goltz Syndrome (GGS), also called Basal Cell Nevus Syndrome or Basal Cell Nevus Carcinoma, is an extremely rare medical entity of genetic origin, with an autosomal dominant inheritance pattern, implying vertical transmission of the disease with a 50% probability in each generation. The precise incidence of SGG varies according to the populations and geographic regions studied, ranging from approximately 1 in 50,000 to 1 in 256,000 births, which emphasizes its highly infrequent nature.

The genesis of SGG is predominantly associated with mutations in the PTCH1 (Patterned 1) gene, located on chromosome 9q22.3. This gene plays a critical role in the regulation of the hedgehog signaling pathway, a cellular communication system crucial for embryonic development, tissue homeostasis and cell proliferation. Mutations in PTCH1 result in an abnormal activation of this pathway, triggering a cascade of events that culminate in the formation of cutaneous basal cell tumors and other clinical manifestations characteristic of SGG.

The epidemiological relevance of this disease lies in its association with high disease burden and potential fatal consequences. Individuals affected by SGG are at constant risk of developing multiple basal cell carcinomas throughout their lives, exposing them to substantial morbidity and mortality risk. In addition, craniofacial and skeletal malformations, as well as ocular and oral anomalies, impose a significant burden on patients’ quality of life, underscoring the need for a multidisciplinary approach that encompasses not only medical but also psychological and social aspects.

Furthermore, GGS exemplifies an interesting clinical and genetic paradigm, enriching our understanding of the relationship between genetic alterations and complex clinical manifestations. This syndrome has also served as a model for ongoing ophthalmologic surveillance in patients with GGS.

**CLINIC**

Gorlin-Goltz syndrome (GGS), also called nevoid basal cell carcinoma syndrome or basal cell nevus, is a medical entity characterized by a diverse and complex spectrum of clinical manifestations affecting multiple organ systems. This syndrome, with autosomal dominant transmission due to mutations in the PTCH1 gene, reveals considerable phenotypic heterogeneity and requires a multidisciplinary approach for proper evaluation and management.

Cutaneous manifestations:

One of the cardinal manifestations of SGG are basal cell skin tumors, which can arise throughout the patient's lifetime. These tumors, characterized by their slow progression and malignant potential, manifest as nodular lesions, papules, plaques or ulcers that predominantly affect sun-exposed areas such as the face, neck and extremities. Their recurrent occurrence and the need for frequent surgical excisions constitute a significant burden for patients.

Ophthalmologic manifestations:

GGS is associated with various ocular abnormalities, including keratoconus, cataracts, iris coloboma, and strabismus. These alterations may affect visual acuity and require ophthalmologic interventions, underscoring the need for ongoing ophthalmologic surveillance in patients with GGS.

Skeletal Malformations:

Skeletal malformations can include bifurcated or fused ribs, spinal abnormalities such as scoliosis and kyphosis, and supernumerary or fused toes, which can affect function and require orthopedic interventions.

Neurological manifestations:

Some individuals with GGS may have intracranial calcifications, which, although usually asymptomatic, may require radiological follow-up and neurological evaluation. These clinical manifestations illustrate the complexity and variability of Gorlin-Goltz syndrome. Regular medical surveillance and a multidisciplinary approach are essential for the early diagnosis and comprehensive management of patients, with the aim of preventing serious complications and improving the quality of life of those affected by this rare but significant medical entity.

**DIAGNOSIS**

The diagnosis of Gorlin-Goltz syndrome (GGS), also known as nevoid basal cell carcinoma syndrome or basal cell nevus, is based on careful clinical and genetic evaluation, given the complexity and heterogeneity of its clinical manifestations.
The diagnostic process encompasses multiple facets to achieve diagnostic certainty that is definitive and accurate.7 Clinical evaluation: The initial evaluation involves a thorough review of the patient's medical history and a thorough physical examination aimed at identifying the characteristic manifestations of SGG. This includes looking for cutaneous basal cell tumors, craniofacial and skeletal malformations, ophthalmologic abnormalities, such as keratoconus, as well as oral abnormalities, including odontogenic cysts and cleft lip. In addition, other findings, such as supernumerary digits and intracranial calcifications, should be investigated.8 Dermatological evaluation: Since cutaneous basal cell tumors are a cardinal feature of GTS, dermatologic evaluation is essential. Skin biopsies are performed to confirm the presence of these tumors and undergo histopathological analysis to verify their basalo-lcellular nature.8 Genetic study: Once the diagnosis of SGG is suspected, genetic testing to identify mutations in the PTCH1 gene is strongly recommended. Direct DNA sequencing and sequence analysis of PTCH1 exons are common approaches to detect pathogenic mutations. Inheritance studies in family members may also be necessary to confirm autosomal dominant transmission.8 Diagnostic Imaging: Diagnostic imaging, such as X-rays, CT scans and MRI scans, can be useful in evaluating skeletal malformations, intracranial calcifications and other anatomical abnormalities associated with GTS.8 Ophthalmologic evaluation: Ophthalmologic evaluation, including specific tests such as keratometry and anterior segment evaluation, is necessary to detect ocular abnormalities, such as keratoconus, that are characteristic of SGG.8 Overall, the diagnosis of GGS requires a comprehensive approach encompassing clinical, dermatologic, genetic, and imaging aspects, with special attention to the identification of PTCH1 mutations for accurate confirmation. Early detection and accurate diagnosis are critical for the implementation of appropriate management strategies and the prevention of serious complications associated with this complex medical entity.8

TREATMENT
Treatment of Gorlin-Goltz Syndrome (GGS), also known as nevoid basal cell carcinoma syndrome or basal cell nevus, is a complex, multidisciplinary process that encompasses a range of clinical manifestations and focuses on preventing serious complications and improving patients' quality of life.9 Dermatologic Surgery: The cornerstone of SGG treatment is dermatologic surgery. The cutaneous basal cell tumors that develop in these patients require meticulous surgical resection. The aim is to remove visible and histopathologically confirmed lesions while minimizing cosmetic and functional morbidity. In cases of large tumors or multiple lesions, Mohs micrographic surgical techniques may be employed to ensure complete tumor removal and preservation of surrounding healthy tissue.9 Maxillofacial and Orthodontic Surgery: Craniofacial and oral malformations may require surgical and orthodontic interventions to improve function and appearance. This may include correction of cleft palate, cleft lip, odontogenic cysts, and dental anomalies, with the goal of achieving proper masticatory function and improved facial aesthetics.9 Ophthalmologic approach: Ophthalmologic abnormalities, such as keratoconus, may require specific treatment. In mild cases, contact lenses may be used to correct visual disturbances, while in more severe cases, corneal transplantation may be necessary.10 Pharmacological therapy: In recent years, targeted drug therapy has been investigated as a therapeutic option for cutaneous basal cell tumors in the setting of SGG. Inhibitors of the hedgehog signaling pathway, such as vismodegib and sonidegib, have demonstrated efficacy in the treatment of advanced or inoperable tumors in patients with SGG.10 Surveillance and Prevention: Continuous surveillance is essential in patients with SGG because of their constant risk of developing new cutaneous basal cell tumors. Regular dermatologic follow-up is recommended to detect and treat new lesions early. In addition, the importance of avoiding excessive sun exposure and the use of sunscreen to reduce the occurrence of new tumors is emphasized.10 Psychosocial support: Given the psychological and social impact of GGS, psychosocial support and genetic counseling are integral components of treatment. Providing emotional support to patients and their families is critical to help cope with the physical and emotional demands of this disease.10 The treatment of Gorlin-Goltz syndrome is a multidisciplinary approach that requires the collaboration of dermatologists, maxillofacial surgeons, ophthalmologists, geneticists and other specialists. Comprehensive care, constant vigilance and precise therapeutic strategies are essential to optimize the management of this complex medical entity and improve the quality of life of those affected.10

CONCLUSION
Gorlin-Goltz syndrome (GGS), a rare genetic disorder of autosomal dominant transmission, stands as a medical entity of unusual complexity and scope. Throughout this comprehensive review, we have explored its heterogeneous
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clinical manifestations, underlying genetic underpinnings, and evolving therapeutic strategies.

The cardinal feature of SGG, the formation of basal cell skin tumors, prompts a predominantly surgical therapeutic approach. Dermatologic surgery, supported by Mohs micrographic surgery in selected cases, stands as the mainstay in the management of these cutaneous tumors, although not without challenges in terms of aesthetic and functional morbidity. Collaboration between dermatologists and maxillofacial surgeons is essential for a comprehensive approach to craniofacial and oral malformations, which often require surgical and orthodontic interventions.

The treatment of ophthalmologic anomalies, such as keratoconus, finds solutions in vision correction through contact lenses and, in advanced cases, corneal transplantation. In addition, targeted drug therapy, particularly inhibitors of the hedgehog signaling pathway, has emerged as a developing paradigm in the management of advanced skin tumors and represents a constantly evolving avenue of research.

Surveillance and prevention are crucial components in the ongoing care of patients with GDS. Regular dermatologic follow-up, along with sun protection education, is essential to detect and treat new lesions early. In addition, the importance of addressing the psychosocial implications of GGS and offering emotional support to both patients and their families is emphasized, given the physical and emotional burden of this disease.

Ultimately, GGS challenges the medical and scientific community to maintain constant vigilance and to make further progress in understanding its underlying genetic and molecular mechanisms. Research in this area promises to open new therapeutic perspectives and more targeted therapies. Multidisciplinary care and cross-specialty collaboration remain the cornerstone for optimally addressing this complex medical entity, with the goal of improving patients’ quality of life and reducing morbidity and mortality associated with GGS.

REFERENCES