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REVIEW

Gorlin Syndrome☆

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Abstract Gorlin syndrome is a rare autosomal dominant disease caused by mutations in the sonic hedgehog signaling pathway. Of particular importance is the PTCH1 gene. The disease is characterized by the development of multiple basal cell carcinomas at young ages. These tumors may present with other skin manifestations such as palmoplantar pits and with extracutaneous manifestations such as odontogenic keratocysts and medulloblastoma. Although the dermatologist may be key for recognizing clinical suspicion of the syndrome, a multidisciplinary team is usually necessary for diagnosis, treatment, and follow-up. Skin treatment may be complicated due to the large number of basal cell carcinomas and the extent of involvement. In recent years, new drugs that inhibit targets in the sonic hedgehog pathway have been developed. Although these agents appear promising options for patients with Gorlin syndrome, their efficacy is limited by adverse effects and the development of resistance.
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PALABRAS CLAVE
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Síndrome de Gorlin

Resumen El síndrome de Gorlin es una enfermedad infrecuente de herencia autosómica dominante producida por mutaciones en genes de la vía de señalización Sonic Hedgehog, entre los que destaca *PTCH1*. Se caracteriza por el desarrollo de múltiples carcinomas basocelulares en edades tempranas, que pueden ir asociados a otras manifestaciones cutáneas como pits palmoplantares, o a manifestaciones extracutáneas, entre las que destacan los queratoquistes odontogénicos y el meduloblastoma. El papel del dermatólogo es importante en la sospecha de este síndrome, pero suele ser necesario un equipo multidisciplinar en el diagnóstico, seguimiento y en el tratamiento de estos pacientes. El tratamiento dermatológico puede

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ser complicado debido al alto número de carcinomas basocelulares y a su extensión. En los últimos años se han desarrollado nuevos fármacos que inhiben la vía Sonic Hedgehog y parecen prometedores para estos pacientes, aunque su eficacia está limitada por los efectos secundarios y la creación de resistencias.
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Introduction

Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome (Online Mendelian Inheritance in Man [OMIM]: 109400), is an autosomal dominant inherited disease that predisposes affected individuals to developmental defects and tumor formation, and multiple basal cell carcinomas (BCCs) in particular.[1] The molecular pathogenesis of this syndrome is linked to the *patched 1* gene (*PTCH1*), which encodes the PTCH1 transmembrane receptor, implicated in the sonic hedgehog (SHH) signaling pathway.[2–4] Progress in therapy for these patients has been made recently with the introduction of the SHH inhibitor vismodegib, indicated for the treatment of recurrent or locally advanced metastatic BCC.[5]

Epidemiology

Gorlin syndrome has a variable prevalence, according to published series, of between 1/30 827[6] and 1/256 000.[7] Farndon et al.[8] established a minimum prevalence of this disease of 1/57 000 inhabitants, and estimated that 1 out of every 200 patients with 1 or more BCCs has Gorlin syndrome.

The life expectancy of patients with Gorlin syndrome is 73.4 years, which is significantly less than the general population, who have a life expectancy of approximately 80 years.[9] The most frequent cause of premature death in these patients is medulloblastoma.[10]

Molecular Pathogenesis

Gorlin syndrome is an autosomal dominant inherited disease, with high penetrance and variable expressivity.[11] It is caused by loss of heterozygosity of the tumor suppressor gene *PTCH1*, which maps to chromosome 9q22.3.[2] *PTCH1* forms part of the SHH signaling pathway, and so mutations in this gene lead to overexpression of the SHH pathway.[4]

The SHH pathway was first described in *Drosophila*.[12] It is essential for development, as it intervenes in tissue polarity and stem cell populations.[13] In mammals, the pathway comprises 4 main elements (Fig. 1):

1. Hedgehog ligands (HHL) of PTCH1: Sonic hedgehog, Indian hedgehog, and desert hedgehog
2. PTCH1 receptor
3. Smoothened (SMO) signal transducer
4. Gli1, Gli2, Gli3 transcription factors[13]

PTCH1 constitutively inhibits SMO protein activity. Binding of HHL to PTCH1 suppresses inhibition of SMO by

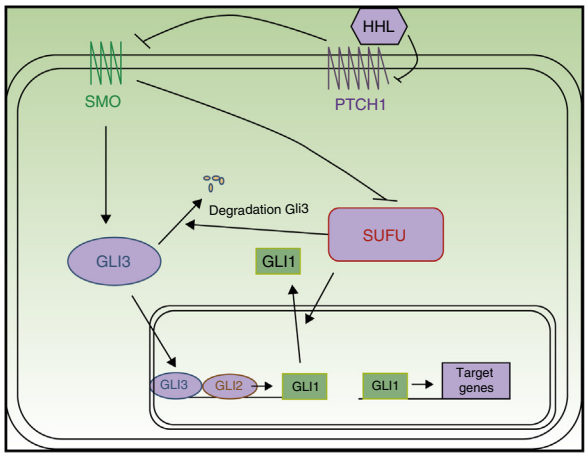

Figure 1 Schematic of the hedgehog pathway. Abbreviations: HHL, hedgehog ligands; PTCH1, Patched 1; SMO, Smoothened; SUFU, suppressor of fused.

PTCH1. Once released, SMO translocates to the end of the primary cilium to exercise its function, with resulting activation of Gli transcription factors.[14,15] The Gli proteins promote transcription of genes implicated in increased cell survival and mitosis.[16] In vertebrates, there are 3 Gli proteins. Gli1 and Gli2 have an activation function, whereas Gli3 suppresses transcription of the target genes,[14] including the *Gli* and *PTCH1* genes. A relationship has also been demonstrated between the SHH pathway and other signaling pathways such as the epidermal growth factor, insulin growth factor, transforming growth factor beta (TGF-β), mammalian target of rapamycin (mTOR)/S6K1, protein kinase receptor C 1, notch, wnt/β-catenin, and phosphonositide-3-kinase (PI3K/Akt) pathways, such that all modulate cancer pathogenesis.[4,13,14,17]

PTCH1 is mutated in between 50% and 85% of patients with Gorlin syndrome,[18,19] and these are de novo mutations in between 20% and 30%.[20] Less frequently, mutations are found in other genes of the SHH pathway.[21] Of particular note are the *suppressor of fused (SUFU)*,[22] *PTCH2*, *SMO*, and *GLI* genes.[23] The most frequently mutated gene after *PTCH1* is *SUFU*, and this mutation should be investigated in patients with a genetic test negative for *PTCH1*.[11] The presence of a *SUFU* deactivating mutation has been associated with lower penetrance and fewer major diagnostic criteria. Moreover, these patients have a higher risk of medulloblastoma and they do not present odontogenic keratocysts.[22] *PTCH2* mutations are rare in patients with Gorlin syndrome, and these patients have a milder phenotype.[23] The cases

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