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Basal cell nevus syndrome (Gorlin syndrome): genetic insights, diagnostic challenges, and unmet milestones

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ABSTRACT

In this article, we present three clinical case reports on Basal Cell Nevus Syndrome (Gorlin Syndrome). Gorlin syndrome is an inherited medical condition with challenges that manifest in multiple body systems and complicate early diagnosis. We examine the epidemiology of the disease and benefits of genetic testing, molecular pathophysiology, and advancement in the molecular-based therapy of Basal Cell Nevus syndrome. The goal of this paper is to shed light on both unmet challenges and advancements in the management of Gorlin syndrome and to provide a new clinical perspective and guidance for future research.

Furthermore, the FDA approved Hedgehog pathway inhibitors Vismodegib and Sonidegib designed for advanced basal cell carcinoma have opened a new door for treatment that may ultimately decrease the number of surgeries for a patient with Gorlin syndrome. The role of these agents in syndromic odontogenic keratocyst has not been studied extensively, but one study found that hedgehog pathway inhibitors decrease the size of syndromic odontogenic keratocyst.

Ideal surgical treatment that balances low recurrence rates with low impact on one's quality of life for syndromic odontogenic keratocyst is another unanswered question for oral and maxillofacial surgeons. Per survey studies, treatment options practiced for syndromic odontogenic keratocyst range from marsupialization to segmental osteotomy. Future studies performed should take a comprehensive long-term approach with at least three years of follow-up in order to determine the most appropriate treatment.

1. Introduction

The discovery of basal cell nevus syndrome, like that of many other syndromes, began simply as an initial report by an observant clinician in 1894. It was not followed up until the 1960s, when it was defined as a distinct entity by Drs. Goltz and Gorlin, whose name is now linked with the condition. In the decades that followed, many case reports were published, which led to a refinement of the diagnostic criteria for this syndrome. In addition, scientists have expanded our understanding of the molecular pathophysiology of this syndrome and the genetic mutations behind it [1,2].

In Gorlin and Goltz's initial report, only multiple basal cell nevi, odontogenic keratocyst, and a few skeletal anomalies were highlighted as clinical features of the syndrome. Today, the spectrum of this syndrome includes neurological, endocrine, ophthalmic, and genital manifestations.

The burden of Basal Cell Nevus Syndrome (BCNS) with respect to most patients' quality of life centers on the treatment of multiple and recurrent odontogenic keratocysts (OKC) as well as basal cell carcinomas. Among its many possible skeletal manifestations, the most notable are bifid ribs and vertebral anomalies.

In this article, we initially present three clinical case reports, then focus on the specific aspects of this syndrome: epidemiology, challenges complicating early diagnosis, benefits of genetic testing, molecular pathophysiology, and advancement in molecular-based therapy. The goal of this paper is to shed light on both unmet challenges and advancements in the management of Gorlin syndrome

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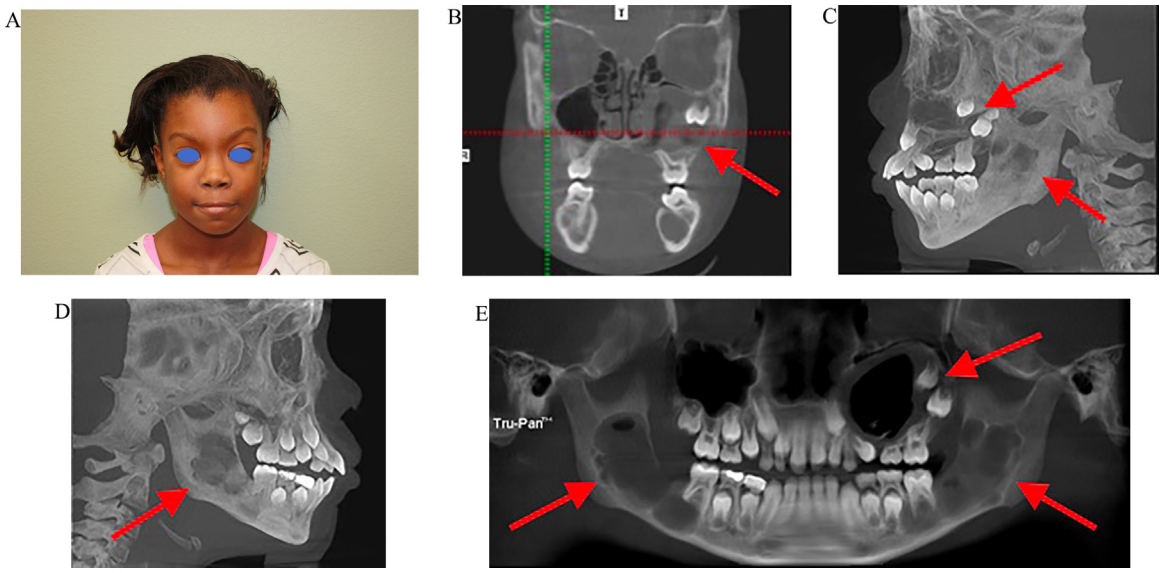

Fig. 1. Clinical findings of a patient with Gorlin syndrome. (A) Frontal view demonstrates mild hypertelorism (A). CT images (B–D): Coronal section with left sinus obliteration (arrow) (B), radiolucent multicystic lesions in the right ramus (arrow) (C), and radiolucent multicystic lesions in the left ramus (arrow) (D). Panoramic radiography demonstrates bilateral mandibular ramus lesions and left sinus radiolucent and radiopaque lesions with an impacted tooth (arrow) (E).

Table 1
Diagnostic criteria for BCNS syndrome/Gorlin syndrome.

Major criteria:
I. Multiple (>2) basal cell carcinoma (BCC) or one BCC under the age of 20 years, or >10 basal cell nevi
II: Any odontogenic keratocyst histologically or observed on Panoramic radiograph as an area of translucency or polyostotic bone cyst
III: Palmar or plantar pits (3 or more)
IV: Ectopic calcification: lamellar (Sheet like) falx calcification or evidence of early calcification in an individual younger than 20 years
V. First-degree relatives with NBCCS
Minor criteria:
I: Congenital skeletal anomaly: Bifid, fused played, or missing ribs, or bifid, wedged or fused vertebra
II: occipital-frontal circumference >97 percentile (macrocephaly), with frontal bossing
III: Cardiac or ovarian fibromas
IV: Childhood medulloblastoma (primitive neuroectodermal tumor)
V. Lymphomesenteric or Pleural cysts
VI: Congenital malformation: Cleft lip and/or palate, polydactyly, eye anomaly (cataract, coloboma, microphthalmia,)

and to provide a new clinical perspective and guidance for future research.

2. Case reports

The following three case reports are from academic-based practices, two at University Health in Shreveport, LA and another from Thomas Jefferson in Philadelphia, PA. In all three cases the suspicion for Gorlin syndrome diagnosis was high and subsequently confirmed by genetic testing. The molecular diagnosis was performed using genomic DNA extracted from a sample of each patient's whole blood after obtaining informed consent.

Case 1: A 9-year-old female patient (Fig. 1) presented with multiple jaw cysts and painless swelling of her left cheek not associated with any other symptoms. There was no familial history of similar lesions or of any first-degree relatives with BCNS. Physical examination revealed mild frontal bossing. Panoramic X-ray illustrated three large cystic lesions, the largest residing in the left maxillary sinus associated with impacted teeth numbers 15 and 16. Both mandibular rami were 75% occupied with multilocular cysts associated with teeth numbers 17, 18, and 32. The occipital-frontal circumference of 54 cm was greater than the 97th percentile according to Nellhaus charts. The patient's interorbital distance of 38 mm was more than 10 mm above the standard deviation (25 ± 2) for her age group.

Chest X-ray revealed no evidence of bifid ribs. The patient underwent marsupialization of the left maxillary cyst, enucleation of the bilateral ramal cysts, and extraction of teeth numbers 17, 18, and 32. Histologic examination of the cyst revealed an odontogenic keratocyst. Therefore, the patient fulfills one major criterion and two minor criteria for the diagnosis of BCNS (Gorlin) syndrome (Table 1).

2.1. Molecular detection of PTCH1 mutations

Direct sequencing of all coding exons revealed a heterozygous deletion of the *PTCH1* gene. The deletion led to a frameshift mutation starting with codon leucine 87, changing it to an isoleucine residue, and creating a premature Stop codon at position 2 of the new reading frame. It is predicted that this mutation resulted in the loss of normal *PTCH1* protein function.

Case 2: An 11-year-old male patient (Fig. 2A, B) presented with a surgical history of multiple odontogenic keratocysts of the right mandible and maxilla. The patient's father (Fig. 2A, B) also had a history of multiple odontogenic cysts, which were removed at age 16. Craniofacial CT scan showed extensive dural and choroid plexus calcifications and abnormal enlargement of the subarachnoid space

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