OASIS DERMATOLOGY GROUP

Ph: (956) 971 - 0404
www.oasisderm.com

Gorlin Syndrome

Nevoid Basal Cell Carcinoma Syndrome (NBCCS), also known as Basal Cell Nevus Syndrome or Gorlin Syndrome, is a rare genetic disorder primarily characterized by the early onset of multiple basal cell carcinomas (BCCs), jaw cysts, and various other abnormalities affecting the skin, bones, and central nervous system. First described by dentist R.J. Gorlin in 1960, the syndrome has since been recognized as a complex condition with a broad spectrum of clinical manifestations. Although NBCCS is most commonly inherited in an autosomal dominant manner, approximately one-third of cases arise due to spontaneous mutations. The disorder affects between 1 in 56,000 and 1 in 164,000 individuals globally, with no significant gender predilection.

Etiology and Genetic Basis

NBCCS is caused by mutations in the PTCH1 gene, located on chromosome 9q22.3, which encodes the Patched 1 receptor involved in the Hedgehog signaling pathway. This pathway plays a critical role in cellular differentiation, growth, and development. Mutations in PTCH1 result in dysregulated Hedgehog signaling, leading to abnormal cell proliferation and the formation of neoplastic lesions, particularly BCCs. While most cases are inherited, approximately one-third of patients have no family history of the condition, indicating the presence of de novo(new) mutations.

Clinical Manifestations

The hallmark of NBCCS is the development of multiple BCCs, often appearing in childhood or adolescence, in stark contrast to the typical onset of BCCs in older adults due to sun exposure. BCCs in NBCCS typically manifest in individuals as young as 3–4 years old, with patients having an average of 8 BCCs; however, some may develop hundreds or even thousands over their lifetime. The incidence of BCCs is influenced by skin type, sun exposure, and radiation history. Fair-skinned individuals are more prone to developing numerous BCCs, whereas those with darker skin tones, such as Black individuals, tend to develop fewer skin cancers.

In addition to BCCs, patients with NBCCS often present with palmoplantar pits (small, permanent indentations on the palms and soles), epidermal cysts, and moles or skin tags. These features typically appear with age, often during childhood or adolescence. Skeletal abnormalities, such as odontogenic keratocysts (jaw cysts), are a critical diagnostic feature and often represent the first clinical sign of the syndrome. These cysts form in early childhood and persist through the third decade of life. While these cysts are frequently asymptomatic, they can cause pain, swelling, and displacement of teeth, leading to possible complications that require surgical intervention .

Other common skeletal features of NBCCS include scoliosis, spina bifida, Sprengel deformity (anomalous scapular positioning), and syndactyly (fusion of fingers or toes). Abnormal

calcification in the falx cerebri (brain membrane) is often visible on imaging studies and is considered a hallmark radiographic feature of NBCCS.

Neurological and Ophthalmic Manifestations

Neurological involvement is common in NBCCS. Abnormalities such as medulloblastomas, meningiomas, and cysts within the brain are present in a small percentage of cases. Medulloblastomas, which typically occur in children, are associated with a higher risk in those with NBCCS, occurring in 1–4% of affected individuals. Additionally, brain calcifications, most commonly in the tentorium cerebelli and interclinoid ligaments of the sella turcica, can be identified on skull X-rays or MRI scans.

Ophthalmologic concerns are also prevalent in NBCCS, with affected individuals showing a higher incidence of cataracts at birth, strabismus (crossed eyes), and exophthalmos (bulging eyes). These issues are generally manageable with appropriate medical or surgical intervention.

Diagnosis

NBCCS is diagnosed clinically based on the presence of major and minor criteria, as outlined in the diagnostic guidelines. A diagnosis is made when a patient fulfills either two major criteria or one major and two minor criteria:

- ***Major Criteria***:
  - More than two BCCs or one BCC diagnosed before age 20.
  - Jaw cysts (odontogenic keratocysts).
  - Three or more skin pits on the palms or soles.
  - Calcification of the falx cerebri on brain imaging.
  - Rib deformities.
  - A first-degree relative with NBCCS.
- ***Minor Criteria***:
  - Enlarged head circumference (macrocephaly).
  - Congenital malformations (cleft lip/palate, coarse facial features, ocular hypertelorism).
  - Structural anomalies (Sprengel deformity, syndactyly).
  - Abnormal bone findings (spinal malformations, cysts in hand/foot bones).
  - Ovarian fibromas.
  - Medulloblastoma or other brain cancers.

In addition to clinical examination, imaging studies such as X-rays, MRI, and ultrasound are crucial for identifying calcifications, jaw cysts, and other skeletal abnormalities. Genetic testing can confirm the diagnosis, particularly in ambiguous or infantile cases, though it is not routinely performed due to low sensitivity.

Management and Treatment

The management of NBCCS requires a multidisciplinary approach to address both the cosmetic and systemic manifestations of the syndrome. The mainstay of treatment focuses on the early identification and management of BCCs. Regular dermatologic surveillance, typically every 3 months, is essential to detect new tumors at an early, manageable stage. Lesions can be treated with various modalities, including:

- Topical treatments such as fluorouracil and imiquimod (immune response modifiers).
- Surgical options, including electrodessication and curettage, excision, or Mohs micrographic surgery, are considered for larger or more invasive lesions.
- Radiation therapy should generally be avoided, as it can exacerbate skin damage and increase the risk of developing further BCCs.

In addition to dermatologic care, genetic counseling is recommended for patients considering having children, as NBCCS is an autosomal dominant condition. Patients should also be monitored for other potential complications, such as brain tumors, cardiac fibromas, and ovarian cysts, which may require intervention based on the severity of symptoms.

Prevention and Lifestyle Modifications

Given the increased risk of skin cancer, individuals with NBCCS must adopt stringent sun protection strategies. This includes the use of sunscreen, protective clothing, and wide-brimmed hats when outdoors. Limiting sun exposure and avoiding tanning beds are critical in minimizing the risk of new BCC development. Furthermore, individuals with NBCCS should be educated on the importance of avoiding radiation exposure, which can exacerbate their condition.

Psychosocial Support

Living with NBCCS can present significant psychological challenges due to the need for frequent medical visits, recurrent surgeries, and visible scarring. It is essential for healthcare providers to offer psychosocial support, and organizations such as the Gorlin Syndrome Alliance provide resources for patients and families coping with the emotional burden of the disease.

Conclusion

Nevoid Basal Cell Carcinoma Syndrome is a rare, genetically inherited disorder with a wide range of clinical manifestations, including early-onset basal cell carcinoma, jaw cysts, skeletal abnormalities, and neurological complications. Early detection and regular surveillance are essential to manage BCCs and prevent the development of more severe complications. A multidisciplinary approach involving dermatology, genetics, ophthalmology, and neurology is key to ensuring comprehensive care and improving the quality of life for affected individuals.

References

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