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Nevoid Basal Cell Carcinoma Syndrome

Nevoid Basal Cell Carcinoma Syndrome (NBCCS), also known as Basal Cell Nevus Syndrome or Gorlin Syndrome, is a rare genetic disorder, affecting between 1 in 56,000 and 1 in 164,000 people worldwide. It is mainly known for causing early-onset multiple basal cell carcinomas (BCCs), which are a type of skin cancer. People with this syndrome may also develop jaw cysts and have other problems involving the skin, bones, and central nervous system.

The syndrome was first described by Dr. R.J. Gorlin in 1960, and since then, it has been recognized as a complex condition with a variety of symptoms. NBCCS is most often passed down from parent to child in an autosomal dominant manner, which means a child has a 50% chance of inheriting the condition if one parent has it. However, about one-third of cases are caused by spontaneous mutations, meaning the condition can occur even without a family history.

Etiology and Genetic Basis

NBCCS is caused by mutations in the PTCH1 gene, which is located on chromosome 9q22.3. The PTCH1 gene encodes a protein called Patched 1, which is an important part of the Hedgehog signaling pathway. This pathway helps control how cells grow, develop, and differentiate. When the PTCH1 gene is mutated, it disrupts the normal functioning of the Hedgehog signaling pathway. This leads to uncontrolled cell growth and the formation of neoplastic lesions, especially basal cell carcinomas (BCCs). These abnormal growths are the hallmark of NBCCS.

Although most cases of NBCCS are inherited from a parent, about one-third of patients have no family history of the condition. This suggests that their cases are caused by de novo mutations—mutations that occur for the first time in the affected individual, rather than being passed down from a parent.

Clinical Manifestations

Nevoid Basal Cell Carcinoma Syndrome (NBCCS) is primarily characterized by the early development of multiple basal cell carcinomas (BCCs), which can appear as early as childhood or adolescence. This is a key feature that distinguishes NBCCS from typical BCCs, which generally occur in older adults due to sun exposure. In individuals with NBCCS, BCCs can develop as early as 3 to 4 years old, with patients typically having an average of 8 BCCs. However, some may develop hundreds or even thousands of BCCs over their lifetime. The incidence of BCCs in NBCCS is influenced by factors like skin type, sun exposure, and a history of radiation. People with fair skin

are more likely to develop multiple BCCs, while those with darker skin tones, such as Black individuals, tend to develop fewer skin cancers.

In addition to BCCs, other skin-related features commonly associated with NBCCS include palmoplantar pits, which are small, permanent indentations on the palms and soles. These often appear during childhood or adolescence. Individuals with NBCCS may also develop epidermal cysts, moles, or skin tags, which tend to appear with age. Another critical diagnostic feature is the presence of odontogenic keratocysts, which are cysts that form in the jaw, usually in early childhood, and can persist into adulthood. These jaw cysts are frequently asymptomatic, but they can lead to pain, swelling, and tooth displacement, potentially requiring surgical intervention.

NBCCS also affects the skeletal system, with common abnormalities such as scoliosis (curved spine), spina bifida (a defect where the spine doesn't fully close), Sprengel deformity (abnormal positioning of the shoulder blades), and syndactyly (fusion of fingers or toes). Additionally, abnormal calcification in the falx cerebri, a membrane in the brain, 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. Some may develop medulloblastomas (a type of brain tumor), meningiomas (tumors that grow in the brain's protective layers), or brain cysts. While these issues are rare, medulloblastomas are more common in children with NBCCS, affecting about 1 to 4% of those with the condition. Brain calcifications (abnormal deposits of calcium) can also appear in certain areas of the brain. These calcifications can be seen through X-rays or MRI scans.

In addition to brain-related issues, people with NBCCS often have eye problems. Many individuals with this syndrome have cataracts (cloudy areas in the eye) at birth, crossed eyes, and bulging eyes. These eye issues can usually be treated with medical care or surgery, helping to manage the symptoms.

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.

X-rays, MRI scans, and ultrasound are important tools for identifying calcifications (calcium buildup in the brain), jaw cysts, and other bone problems. These tests help doctors see inside the body and detect abnormalities that may not be visible during a regular physical exam.

In some cases, genetic testing can be used to confirm the diagnosis, especially when the symptoms are unclear or seen in babies. However, genetic testing is not done routinely because it may not always detect the condition, especially in cases where symptoms are mild or not fully developed.

Management and Treatment

The management of NBCCS involves a team of healthcare providers working together to address both the skin and internal issues related to the condition. A key part of treatment is early detection and management of BCCs. People with NBCCS need regular visits to a dermatologist, usually every 3 months, to check for new tumors while they are still small and treatable.

There are several ways to treat BCCs:

- **Topical treatments**: Creams like fluorouracil and imiquimod help to treat small skin lesions by modifying the immune response to fight the tumors.
- **Surgical treatments**: Larger or deeper tumors may need surgery, including electrodessication and curettage (scraping the tumor and burning the area), excision (cutting out the tumor), or Mohs micrographic surgery (removing layers of skin until the cancer is gone).
- **Radiation therapy** is usually avoided, as it can worsen skin damage and increase the risk of developing more BCCs.

In addition to skin care, genetic counseling is important for patients considering having children, since NBCCS is passed down in an autosomal dominant manner. This means there is a 50% chance of passing the condition to each child.

Patients with NBCCS should also be monitored for other health issues that can occur with the syndrome, including brain tumors, heart fibromas, and ovarian cysts. Treatment for these

problems will depend on how severe the symptoms are. Regular check-ups help doctors detect and manage these complications before they become more serious.

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.

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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