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Basal Cell Nevus Syndrome

Nevoid Basal Cell Carcinoma Syndrome (NBCCS), also known as Basal Cell Nevus Syndrome or Gorlin Syndrome, is a rare genetic disorder characterized by a predisposition to multiple basal cell carcinomas (BCCs) and a range of other systemic manifestations. The syndrome was first described by Dr. R. J. Gorlin in 1960, although evidence of its presence can be traced back to Egyptian mummies over 4,000 years old.

The condition is primarily inherited, though approximately one-third of cases occur sporadically, without a family history. NBCCS affects between 1 in 56,000 and 1 in 164,000 individuals across all races, with equal frequency in men and women.

Etiology and Pathogenesis

NBCCS is caused by mutations in the *PTCH1* gene, located on chromosome 9q22.3, which encodes the Patched-1 protein involved in the Hedgehog signaling pathway. This pathway plays a crucial role in regulating cell growth and differentiation. Mutations in *PTCH1* lead to dysregulated Hedgehog signaling, promoting the development of basal cell carcinomas and other associated abnormalities. Although NBCCS is typically inherited in an autosomal dominant manner, spontaneous mutations can occur in about one-third of cases.

Clinical Features

The hallmark feature of NBCCS is the early onset of multiple basal cell carcinomas, which typically appear in individuals in their 20s or 30s, although they can present as early as 3-4 years of age. These BCCs, a type of non-melanoma skin cancer, usually develop on sun-exposed areas, and patients with fair skin are more prone to extensive skin involvement, while those with darker skin may have fewer tumors. Patients with NBCCS can develop hundreds to thousands of BCCs, with an average of eight per individual, though the number can vary widely.

Beyond skin cancer, NBCCS is associated with other characteristic dermatological manifestations, including palmar and plantar pits (indentations on the palms or soles), epidermal cysts, and skin tags. Jawbone cysts (odontogenic keratocysts) are often the first sign of NBCCS and may be detected by a dentist. These cysts appear during childhood and can persist into early adulthood, potentially causing pain, swelling, and tooth displacement.

Other skeletal anomalies commonly observed in NBCCS include deformed ribs, scoliosis, spina bifida, and abnormalities in the fingers and shoulder blades, such as syndactyly and Sprengel deformity. Atypical facial features, including a broad face, coarse features, ocular hypertelorism (wide-set eyes), and macrocephaly (enlarged head), are common in up to 70% of patients.

Additionally, individuals with NBCCS may experience vision issues such as cataracts, strabismus, and exophthalmos.

Neurological and Other Systemic Involvements

Neurological involvement in NBCCS is frequently marked by calcifications in the brain, particularly in the falx cerebri, tentorium cerebelli, and interclinoid ligament. These calcifications can be detected on skull x-rays and are considered a significant diagnostic feature of the syndrome. Brain cysts, agenesis of the corpus callosum (a condition where the bundle of nerve fibers connecting the brain's hemispheres fails to develop), and brain tumors such as medulloblastomas and meningiomas are also seen in a small proportion of individuals with NBCCS. Cognitive impairment, including mental retardation, occurs in about 5% of cases, often related to central nervous system involvement.

Additionally, individuals with NBCCS have an elevated risk for certain cancers, including fibrosarcoma and rhabdomyosarcoma, though these malignancies are rare. Cardiac fibromas, non-cancerous growths in the heart, are occasionally found in children and can be life-threatening if they obstruct blood flow. Ovarian cysts and fibromas are present in approximately 25% of female patients but typically do not affect fertility.

Diagnostic Criteria

The diagnosis of NBCCS is primarily clinical, based on the presence of specific major and minor criteria. Major criteria include the development of more than two BCCs or a single BCC diagnosed before the age of 20, jaw cysts, the presence of three or more skin pits on the palms or soles, and calcification of the falx cerebri in the brain. Additionally, skeletal deformities such as rib malformations and a family history of NBCCS are major diagnostic indicators. Minor criteria encompass congenital malformations such as cleft lip or palate, coarse facial features, and ocular anomalies. Abnormalities detected on imaging, such as cysts in bones or spine malformations, are also considered minor criteria.

While genetic testing for mutations in *PTCH1* is available, it is not commonly performed due to its variable accuracy, particularly in cases with atypical manifestations. Genetic testing is more frequently used for early identification in infants born to parents with known NBCCS or in ambiguous cases where clinical criteria are insufficient.

Management and Treatment

The management of NBCCS revolves around early detection and treatment of basal cell carcinomas to prevent local destruction and disfigurement. Dermatological surveillance is crucial, and patients are typically advised to have regular screenings every three months, especially in the first few decades of life when BCCs are most likely to develop. Tumors can be treated with various modalities, including topical therapies (e.g., fluorouracil or imiquimod), electrodessication and curettage, excision, or Mohs micrographic surgery, the latter being the gold standard for removing skin cancers while preserving healthy tissue.

Given the increased sensitivity to sun exposure in individuals with NBCCS, sun protection is paramount. Patients should use broad-spectrum sunscreen, wear protective clothing, and avoid excessive sun exposure to reduce the risk of developing additional BCCs. Radiation therapy should be avoided as it exacerbates skin damage and increases the likelihood of skin cancer.

Other specialized care may be necessary based on the individual's specific symptoms and complications. For instance, individuals may require ongoing management by specialists in neurology, cardiology, gynecology, and ophthalmology. Genetic counseling is also recommended for patients considering having children to understand the hereditary nature of the condition and potential risks.

Conclusion

Nevoid Basal Cell Carcinoma Syndrome is a complex genetic disorder that requires multidisciplinary management to address its diverse manifestations, including multiple basal cell carcinomas, skeletal anomalies, and neurological complications. Early diagnosis, vigilant monitoring, and timely intervention, particularly in the detection and removal of skin cancers, are essential to improving the quality of life for patients with NBCCS. Ongoing research into the molecular mechanisms underlying this syndrome holds promise for more targeted therapies and enhanced management strategies in the future.

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