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Gorlin syndrome: *PTCH1* Mutations

Gorlin Syndrome, also called Nevoid Basal Cell Carcinoma Syndrome (NBCCS), is caused by mutations in either the *PTCH1* gene or the *SUFU* gene. Gorlin Syndrome is characterized by the development of multiple basal cell carcinomas and jaw keratocysts. Jaw cysts frequently begin in the second decade of life and become less frequent after 30 years; jaw keratocysts usually present as painless swellings, but may lead to major tooth disruption and fracture of the jaw. Basal cell carcinomas (BCCs) usually occur from the third decade of life onward but may occur in childhood. They become more frequent with age, although 10% of individuals with Gorlin syndrome never develop a BCC. Approximately 60% of individuals have a recognizable appearance with macrocephaly, bossing of the forehead, coarse facial features, and facial milia. Some individuals will present with skeletal abnormalities (e.g. bifid ribs, wedge-shaped vertebrae). Calcification of the falx is present in more than 90% of affected individuals by age 20 years.[6,5] Cardiac and ovarian fibromas occur in approximately 2% and 20% of individuals respectively. The risk to develop medulloblastoma (primitive neuroectodermal tumor (PNET), generally desmoplastic subtype[2]) in children with Gorlin Syndrome is estimated to be <2% in individuals with *PTCH1* mutations.[4] Peak incidence is at age two years.[2,1]

A summary of the natural history and general management guidelines based on the current literature is included below for your information. General guidelines for management are based on the American Association for Cancer Research (AACR) surveillance recommendations, June 2017.[4]

Surveillance Recommendations

- Annual dermatology evaluation for basal cell carcinoma screening, beginning at age 10, with increased frequency after first basal cell carcinoma observed
- Baseline echocardiogram in infancy
- Dental exams with jaw X-ray (orthopantogram) every 12 to 18 months beginning at age 8 to evaluate for jaw keratocysts
- Ovarian ultrasound by age 18 to evaluate for ovarian fibromas prior to pregnancy
- Low risk for medulloblastoma: no radiographic screening unless concerning neurologic exam, head circumference change, or other unusual signs or symptoms
- No other tumors occur at a frequency that warrants surveillance above that offered to members of the general population

Treatment of Manifestations

Manifestations should be treated by specialists (e.g., oral surgeon, dermatologist, plastic surgeon, pediatrician, medical geneticist) experienced with the condition. Keratocysts usually require surgical excision. Early treatment of BCCs is essential to prevent long-term cosmetic problems, particularly on the face. The priorities are to ensure complete eradication of aggressive BCCs, and to preserve normal tissue to prevent disfigurement. Surgical excision is supplemented by other possible treatments including cryotherapy and laser treatment for early lesions and photodynamic therapy. Surgical treatment using Mohs' microsurgery appears particularly effective. Recent studies have shown that administration of Vismodegib, a SMO inhibitor, resulted in regression of existing tumors and prevented the appearance of new tumors in Gorlin syndrome. If medulloblastoma occurs, radiation-sparing treatment given risk of radiation-induced skin cancers.

Agents/ Circumstances to Avoid

Excessive sun exposure increases the likelihood of developing BCCs. Individuals should practice safe sun behaviors by using complete sunblock and covering the skin with long sleeves, high collars, and hats. Use of radiotherapy can lead to the development of thousands of BCCs in the radiation field and is not recommended. If the treating team believes that no other treatment modality is possible, radiotherapy should be used through as few skin ports as possible.

Implications for Family Members/ Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *PTCH1* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

References

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