Retinoblastoma

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KEYWORDS

- Retinoblastoma • Chemotherapy • Germline mutation
- Second malignant neoplasms

KEY POINTS

- Retinoblastoma is the most common cancer of the eye in children, accounting for 3% of all childhood malignancies. Retinoblastoma affects very young children: two-thirds of the cases are diagnosed before 2 years of age, and more than 90% before 5 years.
- Two clinical forms are identified: (1) unilateral retinoblastoma, which accounts for approximately 75% of the cases; and (2) bilateral retinoblastoma, which accounts for 25% of the cases. Patients with bilateral disease carry a germline mutation of the *RB1* gene; this mutation is inherited from an affected parent in 25% of the cases, and results from a de novo mutation in utero in 75% of the cases.
- Treatment of retinoblastoma is risk adapted. Factors to be considered in the treatment decisions include intraocular and extraocular stage, laterality, and potential for vision. Ocular salvage treatments include systemic or intra-arterial chemotherapy, aggressive focal treatments (photocoagulation, thermotherapy, cryotherapy, and brachytherapy), and external beam radiation therapy.
- Children with bilateral disease are at high risk of developing second malignancies and therefore need to be followed closely. Radiation therapy is avoided whenever possible in this group of children.

INTRODUCTION

Retinoblastoma is the most common neoplasm of the eye in childhood, representing 2.5% to 4% of all pediatric cancers. The average age-adjusted incidence rate of retinoblastoma in the United States and Europe is 2 to 5 per million children (approximately 1 in 14,000–18,000 live births).[1,2] Retinoblastoma is a cancer of the very young; two-thirds are diagnosed before 2 years of age, and 95% before 5 years.[1]

Retinoblastoma presents in 2 distinct clinical forms: (1) a bilateral or multifocal, heritable form (25% of all cases), characterized by the presence of germline mutations of

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the *RB1* gene and that may be inherited from an affected survivor (25%) or be the result of a new germline mutation (75%); and (2) a unilateral or unifocal form (75% of all cases), 90% of which are nonhereditary. About 10% of germline cases are unilateral and unifocal; however, in the absence of a positive family history, it is not possible without genetic screening to determine which unilateral cases involve the germ line and are thus capable of being transmitted to the next generation.

EPIDEMIOLOGY

The incidence of retinoblastoma is not distributed equally around the world. It seems to be higher (6–10 cases per million children) in Africa, India, and among children of Native American descent in the North American continent.[3] The increased incidence in those groups occurs primarily in unilateral cases. Whether these geographic variations are caused by ethnic or socioeconomic factors is not well known. Studies from Mexico and Brazil have documented an inverse correlation between the incidence of retinoblastoma and socioeconomic index,[4–6] and in more industrialized countries an increased incidence of retinoblastoma has also been associated with poverty and low levels of maternal education.[7]

On a perhaps related note, decreased dietary intake of vegetables and fruits during pregnancy, resulting in decreased intake of nutrients such as folate and carotenoids, which are necessary for DNA methylation and synthesis as well as for retinal formation, has also been associated with an increased risk of unilateral sporadic retinoblastoma.[8] In a case-control study, the risk of developing retinoblastoma was associated with a maternal polymorphism in dihydrofolate reductase (*DHFR*19bpdel), particularly in women taking prenatal synthetic folic acid supplements.[9]

Most germline mutations in sporadic heritable retinoblastoma are paternally derived,[10] and studies have suggested an association between paternal age and occupation and the occurrence of sporadic heritable retinoblastoma.[7,11–13] Reports have also suggested an association between retinoblastoma and increased sunlight exposure,[14,15] air toxics from gasoline and diesel combustion,[16] or in vitro fertilization.[17–19] In a case-control study of sporadic retinoblastoma, radiological studies of the abdomen leading to scattered radiation exposure of the gonads were associated with an increased risk of bilateral retinoblastoma in a subsequent child.[20]

BIOLOGY

In 1971, based on the mathematical analysis of the age at presentation of bilateral (hereditary) and unilateral (mostly nonhereditary) cases of retinoblastoma, Knudson[21] proposed the 2-hit hypothesis, in which 2 mutational events in a developing retinal cell lead to the development of retinoblastoma. This hypothesis was subsequently extended to suggest that the two events could be mutations of both alleles of the *RB1* gene. *RB1*, located in chromosome 13q14, was identified and cloned in 1986.[22,23] Its product, pRb, is a key substrate for G1 cyclin-cdk complexes, which phosphorylate target gene products required for the transition of the cell through the G1 phase of the cell cycle. The active pRb functions as a tumor suppressor and is the major gatekeeper to control this critical point in growth regulation. The lack of pRb, or its inactivation, removes the pRb constraint on cell cycle control, with the consequence of deregulated cell proliferation. Biallelic loss of *RB1* function is required for tumor development; this loss is germ line and somatic for patients with bilateral disease, and somatic in patients with unilateral disease. However, additional events are required for tumor progression. Approximately two-thirds of tumors have *MDM4*/*MDM2* amplification leading to inactivation of the *p53* pathway.[24] RB1 plays an