Familial Retinoblastoma
With Unilateral and Unifocal Involvement in 2 Families

Retinoblastoma is a malignant ocular tumor of childhood that occurs in approximately 1 in 18,000 children. Approximately 40% of patients with retinoblastoma have inherited a germ-line mutation of the RB1 gene (gene map locus 13q14.1-q14.2) (OMIM 100180), and approximately 85% of them develop bilateral tumors. We report on the cases of 2 children from 2 different families; all 4 of these children developed unilateral unifocal retinoblastoma despite no family history of retinoblastoma.

Methods. This is a retrospective report of 2 families without a history of retinoblastoma in which both children in each family developed unilateral retinoblastoma.

Results. Two sets of siblings (n=4) developed unifocal unilateral retinoblastoma and neither family had a history of retinoblastoma. The first affected sibling in each family was male and received his diagnosis at age 11 months in family 1 and at age 10 months in family 2. Both second-affected siblings were female and received their diagnosis at age 3 months. On initial examination all of the patients were observed as having leukokoria, except for the younger sibling in family 2 whose tumor was found on surveillance examination. Three children underwent enucleation. In all of the cases, histopathologic examination confirmed the diagnosis of retinoblastoma and the unifocal nature of the tumor. The older sibling in family 1 underwent external beam radiation therapy and subsequent iodine 125–labeled plaque radiotherapy for limited local recurrence. Systemic chemotherapy was not considered because it first became available a decade later. No subsequent tumors developed in the contralateral eye of any child through an average follow-up of 14 years.

Family 1. An 11-month-old boy with no abnormal medical history had been observed at age 6 months to have a “cat’s eye glow” in his left eye. Family history was noncontributory except for a paternal uncle who had a “retinal scar” and “lazy eye.” Examination revealed a unifocal tumor classified as Reese-Ellsworth (RE) group Ia unilateral retinoblastoma, group D in the International Classification of Retinoblastoma (ICRB) (Figure 1). Systemic evaluation revealed no evidence of metastatic disease. Fundus examination of both parents revealed no evidence of retinoblastoma. On examination the paternal uncle was seen to have a congenital nystagmus with reduced vision in both eyes and an unusual pigmented macular scar suggestive of congenital gliosis of the retina that resulted in amblyopia.

The boy’s tumor regressed with external beam radiation therapy but later recurred at the treatment margin. Supplemental 125I-plaque radiotherapy was used and achieved complete tumor regression. The boy remained tumor free through age 13 years.

This boy’s sister was seen at age 3 months with leukokoria in the left eye. Fundus examination revealed a solitary white retinal tumor classified as RE group Va-b, ICRB group D retinoblastoma (Figure 2). Baseline systemic evaluation revealed no evidence of extraocular disease. She underwent enucleation of the left eye and remained tumor free through age 12 years.

Family 2. A 10-month-old boy with no unusual medical history was...
observed at age 6 months to have leukokoria in the right eye. There was no family history of retinoblastoma. Ophthalmic examination confirmed retinoblastoma classified as RE group Va, ICRRB group E retinoblastoma. Fundus examination of the parents showed no evidence of retinoblastoma. The child was treated by enucleation of the right eye and has remained tumor free for 18 years.

This boy’s sister was seen at age 3 months for her first comprehensive eye examination. Her medical history was normal. Fundus examination of the right eye revealed RE group II, ICRRB group D retinoblastoma. Systemic evaluation revealed no metastatic disease or other tumors. She underwent enucleation of the right eye and has remained tumor free for 13 years postenucleation.

Comment. Retinoblastoma is a primary intraocular malignant neoplasm caused by mutations of the RB1 gene. The RB1 gene product, pRB, is a cell cycle regulator with tumor suppressing activities.1 Knudson et al1 hypothesized that 2 mutational events are required for the development of hereditary retinoblastoma: first, a germ-line mutation; second, a separate somatic mutation. Patients with the disease can pass on the initial germ-line mutation as a dominant trait.4 Twenty-five percent of patients with the inheritable form have a family history of the disease. Others can develop either a new germ-line RB1 mutation or inherit the mutation from an asymptomatic carrier parent.5

Both siblings in each family described in this report developed unilateral uniocular retinoblastoma despite no family history of retinoblastoma. Approximately 12% of sporadic cases of unilateral retinoblastoma involve a germ-line mutation.1 Given that retinoblastoma developed in both siblings in each family, it is unlikely that each case represents a separate new germ-line mutation. This suggests that they are more likely due to inheritance from an asymptomatic carrier parent. Although more than 90% of those who inherit a first mutation will develop a retinoblastoma, these parents could be nonpenetrant or low-penetrant carriers with retinal cells that retained their remaining wild-type RB1 allele or with initial mutations that still retained partial function.5 Underlying mechanisms of incomplete penetrance in retinoblastoma have been studied using a mathematical model only to show that collateral incidence of retinoblastoma had occurred by chance or by a hypothetical undetected intrinsic mutation but not by low-penetrant autosomal dominant inheritance.6

An asymptomatic carrier parent could also be the result of germ-line mosaicism, in which the initial mutation is only in some cells. Sippel and associates1 found that approximately 10% of families with retinoblastoma had documented mosaicism, either in the first affected child or one of the parents. In one family reported on, 2 of 3 daughters had retinoblastoma, even though all 3 had inherited the same paternal haplotype. The father’s sperm DNA showed that approximately 5% of his spermatocytes carried the mutation.1 It seems more likely that the report herein could represent cases of germ-line mosaicism similar to those of the families that were published.1

The possibility of mosaicism is important to consider when counseling parents of a child with retinoblastoma but no family history of it. Parents are usually reassured after diagnosis of a first child with retinoblastoma that the chance of having another child with the same tumor is extremely low. In these cases, one can assume that the first child of each family had either nonhereditary retinoblastoma or a new germ-line mutation. After the birth of a second child with retinoblastoma, it is more likely that at least one parent is an unaffected carrier. The current routine in oncology centers is to perform genetic testing in children with retinoblastoma and their families which unfortunately was not available when these patients were treated.

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