MONOZİGOTİK İKİZDE BİLATERAL MULTİFOKAL SPORADİK RETİNOBLASTOMA

BILATERAL MULTIFOCAL SPORADIC RETINOBLASTOMA IN A MONOZYGOTIC TWIN

Murat KAYA, İlknur AKYOL

Department of Ophthalmology, Faculty of Medicine, Atatürk University, Erzurum

Özet

Bilateral retinoblastoma tanısı konan 18 aylık bir olgu, monozigotik ikizlerden biriydi ve ayrıca kardeşinde de bilateral lökokori mevcuttu. Monozigosite aynı kan grupları ve HLA tipleri ile, multifokal retinoblastoma tanısı enüklee edilen gözlerin histopatolojik incelemesi ile teyit edildi. İkizlerin ve ebeveynlerinin sitogenetik analizleri yapıldı ve karyotiplerinde sayısal veya yapısal anomaliler tespit edilmedi. İkizlerin herikisin de bilateral multifokal retinoblastoma olmasına rağmen pedigri analizi hastalığın familial tip olmadığını gösterdi. Bu olguların genetik etiyolojisini açıklayan muhtemel hipotez, literatürün ışığı altında tartışılmıştır.

Anahtar kelimeler: *Monozigotik ikizler, Retinoblastoma, Genetik*

Summary

An 18-month-old girl was diagnosed as bilateral retinoblastoma. The patient was a pair of monozygotic twin and her sibling had also bilateral leukokoria. The monozygosity was confirmed by same blood subgroups and HLA type. The diagnosis of retinoblastoma was confirmed histopatologically after enucleation of sibling eyes. Cytogenetic analysis of twins and parents were performed and no numerical or structural anomalies were observed in their karyotypes. Although the twins both have bilateral multifocal retinoblastoma, the pedigree analysis showed that the disease was not familial type. The probable hypotheses to explain the genetic etiology of the cases were discussed in the light of the literature.

Key words: *Monozygotic twins, Retinoblastoma, Genetics*

Figure 1. *Bilateral Retinoblastoma, Right Eye With Exophytic Pattern and Left Eye With Endophytic Pattern of Tumor Growing.*

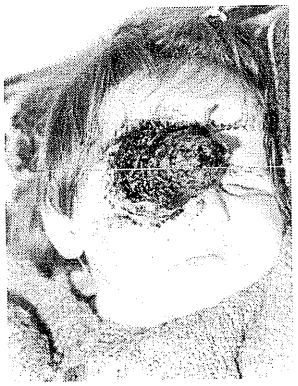


Figure 2. *Her Sibling Had Bilateral Leukocoria.*

Introduction

Retinoblastoma is a rare hereditary intraocular malignancy in childhood with an incidence of about 1 in 20.000 live births (1). Loss, or mutation in tumor suppressor gene in retinoblastoma locus (RB1), located in the 13q14, may play an important role in the etiology of retinoblastoma. About 40 percent of all cases inherit at least one mutant allele at the RB1 locus through germline. The disease, thereby can be assessed as heritable or familial. In heritable form, an additional somatic mutation occurs in normal allele and the development of tumor initiates in a single cell. Structural deletion or other mechanisms, such as mitotic recombination or nondisjunction in remaining normal allele of RB1 locus is described as loss of heterozygosity (LOH). The other 60 percent of cases are non-heritable or sporadic type whose both alleles in a single retina cell have been inactivated by somatic mutations. While the hereditary form emerges bilaterally and multifocal with early onset, in sporadic form, tumor is usually unilateral, unifocal and the onset age is later than in heritable form because the mutation chance in two alleles is a rare event (2). In present case, the monozygotic twin siblings have had bilateral multifocal retinoblastoma eventhough no family history of retinoblastoma and no evidence of chromosomal abnormalities. Consequently, we accepted it as an interesting event to discuss the genetic etiology of retinoblastoma.

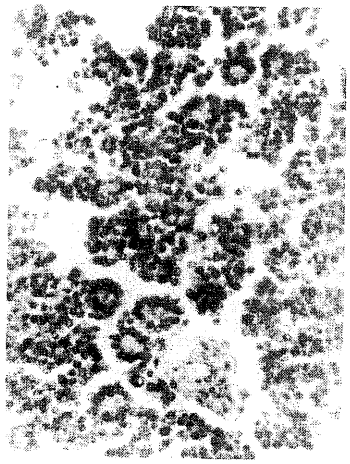
Case

An 18-months-old girl having a huge tumor 7x4x5 cm in sizes in the right orbit and leukokoria in the left eye, was diagnosed as bilateral retinoblastoma (Figure 1). The diagnosis of retinoblastoma was established pathologically after enucleation of both eyes. According to pedigree analysis, she was a pair of a monozygotic twin. The identical twinning was confirmed by the same blood subgroups and HLA types. Bilateral leukokoria was also observed in the clinical examination of her sister (Figure 2). Following enucleation of her both eyes, our results were confirmed histopathologically as retinoblastoma (Figure 3). Except the twin siblings, the parents have three healthy sons and one healthy daughter older than the patients. Ophthalmologic examinations of the parents and other siblings revealed no abnormality. High resolution chromosome analyses of the fibroblast and peripheral lymphocytes of the parents, monozygotic twins and other children were performed and no numerical or structural anomalies were observed. The family history of retinoblastoma was negative. Their pedigree analysis had also suggestion that it was not inherited.

Discussion

To our knowledge, there are a few previous reports of monozygotic twins with bilateral retinoblastoma (3,4). The concordance rate of retinoblastoma in twins was calculated as 76.56%, while for a sporadic unilateral case this risk is lower (1.6%)(5). The hereditary form of disease is suggested to be as an autosomal dominant trait. However, in several reports, a reduced penetrance was pointed out (about 90%) since the occurrence of second mutation is a matter of chance (6). The maximum risk that a carrier might pass the gene to the next child is 50 percent. There is

Figure 3. *The Flexner-Wintersteiner Rosettes Were Observed Histopathologically.*



however, a 0.5x90 percent risk for the child of acquiring a retinoblastoma because the penetrance is 90%. Naumova and Sapienza proposed that there is a sex-ratio distortion in favor of males among the patients with bilateral sporadic disease and these phenomena may be due to the inability of these males to erase the genome imprint established on the half of the genome inherited from their mothers. Germinal imprinting may be mediated by some epigenetic process such as *de novo* DNA methylation and be carried over to postzygotic stages. Such a bias would not be expected for sporadic tumors, where both mutations occur in somatic tissue (7). Although no family history of retinoblastoma and cytogenetic abnormalities in these monozygotic twins, microdeletions in locus 13q14 have been indicated in 5-10% of the reported cases(8). In some patients with normal constitutive karyotype, 13q14 rearrangements in tumor tissue were also observed (9). Various mutations of RB1 gene in DNA derived peripheral blood cells have been found in about 10 percent of the cases (10). In present cases, cytogenetic analysis alone can not answer the question of whether the retinoblastoma was inherited or whether it occurred as spontaneous mutation germline, because no chromosomal abnormalities were found in fibroblast and lymphocyte cultures. Multifocal spontaneous point mutations in retinal cells may also not be excluded. Considering there is no positive data suggesting familial trait in pedigree of cases and no cytogenetic findings in light microscope, three possible hypotheses may be proposed to explain the genetic etiology of multifocal retinoblastoma in present monozygotic cases. First, although parents are not carrier for mutant RB1 gene, at the term of fertilization, either ovum or sperm may had *de novo* mutation in one allele at the RB1 locus. So, both sisters of monozygotic twins may carry the same mutant allele inherited from the beginning. Second, one of parent may have been a germline mosaic and during gamete may develop from such cells. Lastly, as third view, an allelic mutation may occur in early postzygotic stage before splitting of the embryo. So, in early life of the twins, occurring a somatic mutation in remaining normal allele might lead to multifocal retinoblastoma in many retina cells of each sister. For determining the definite etiology, a molecular mutation screening must be performed on genomic DNA of RB1 gene of the patients and their family.

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Address for Correspondence:
Murat KAYA, MD.

Department of Ophthalmology
Atatürk University,Medical School,Erzurum