

Prenatal genetic diagnosis of retinoblastoma – clinical correlates on follow-up

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Retinoblastoma is the most common malignant intraocular tumor in pediatric age group if undetected leads to ocular mortality. Prenatal diagnosis is an emerging technology to detect fatal diseases in utero such that subsequent management is planned to reduce the ocular morbidity. We describe a case demonstrating the importance of prenatal diagnosis in a child with a strong family history of retinoblastoma and importance of a long-term clinical follow-up in these cases.

Key words: Linkage analysis, retinoblastoma, prenatal diagnosis

Retinoblastoma is a hereditary disease, 40% of the cases are inheritable.^[1] All bilateral retinoblastoma and about 15% unilateral retinoblastoma are caused by a germinal mutation.^[2] Germline mutation could be familial or could be manifest *de novo*. About 60% of patients with retinoblastoma have unilateral involvement.^[3] Mutations in the *RB1* gene are responsible for almost all cases of retinoblastoma, a small percentage (5%) of retinoblastomas are caused by deletions in the region of chromosome 13 that contains the *RB1* gene.^[4]

Case Report

A 22 weeks pregnant woman came to us for advice regarding the chance of offspring getting retinoblastoma as her first child had bilateral retinoblastoma. The other offspring was 1 year and 9 months old at the time of presentation with a history of leukocoria in the left eye. She was diagnosed to have bilateral retinoblastoma; Group B in the right eye and Group D in the left eye (International Classification of Retinoblastoma classification). Systemic chemotherapy (four cycles) and external-beam radiation therapy failed to control the tumor

in the left eye and hence the left eye underwent enucleation with ball implant, 8 months after presentation. The right eye was salvaged with good tumor control and the preservation of vision [Fig. 1].

A cytogenetic analysis done at that time revealed male karyotype with 13q14 deletion in the father, and the mother was normal. The child had female karyotype with 13q14 deletion. Parental screening with ophthalmoscopic examination was done. While the mother was found to be normal, the father revealed a retinoma in his right eye.

As direct screening by mutational analysis is time-consuming and needs more sample, prenatal cord blood was taken for molecular linkage analysis for retinoblastoma.^[5] The fetus was found to have the defective *RB1* allele inherited from the father [Fig. 2] and hence the parents were counseled accordingly. Serial ultrasounds were done to look for intraocular tumor (calcification).^[5]

The child was born at 34 weeks and the first ophthalmic evaluation done on the 2nd day of life was normal. The child underwent periodic monthly examination under anesthesia until 2 years of age. At 28 months of age, she developed a tumor (Group A) in the inferonasal retinal periphery of the right eye that was treated with cryotherapy [Fig. 3]. The tumor was regressed following treatment. The child continued to be under bi-monthly clinical follow-up. Visual assessment with Lea symbol charts showed the visual acuity of 20/20 in both eyes. At a recent follow-up at 7 years of age, the fundus was stable, and visual acuity maintained in both the eyes.

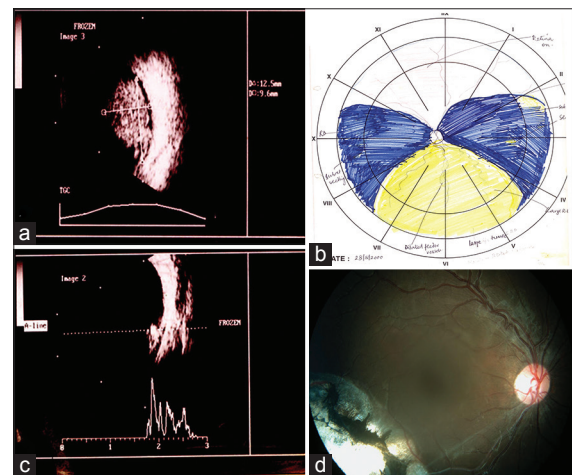


Figure 1: Clinical findings in the sibling showing bilateral retinoblastoma (a) Ultrasound B scan of the left eye showing large tumor in visit 1 (b) Fundus drawing of the left eye showing tumor coded by yellow color (c) Ultrasound B scan of the right eye showing tumor. (d) Post treatment regressed tumor in the right eye at last follow up (7 years follow-up)

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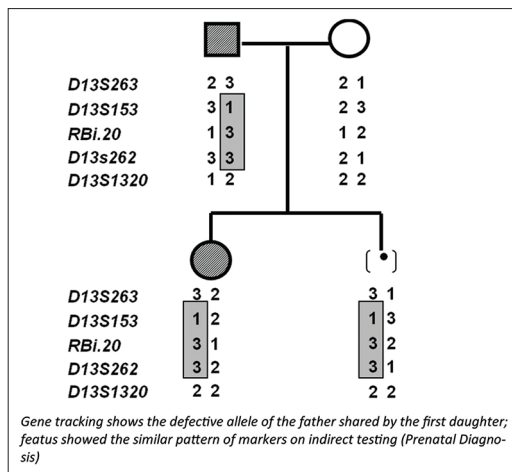


Figure 2: Gene tracking (predictive testing) in the case of familial retinoblastoma

Discussion

Prenatal diagnosis of retinoblastoma with clinical follow-up has been reported earlier,^[6] however, to the best of our knowledge, this is the first report from India to show the clinical correlate of genetic findings on a prenatal diagnosis. It is important for an ophthalmologist to determine the etiology of an unilateral case (whether it is hereditary or not) as the management of the patient (examination of fellow eye, frequency of follow-up and sometimes treatment which should be provided along with genetic counseling) may be different when compared to a bilateral case.

Prenatal genetic testing can prove useful in screening for retinoblastoma in the unborn child. In this case, already having a child with retinoblastoma (with one eye enucleated) prompted the mother to undergo a prenatal screening for the next offspring. Even though primary prevention was not possible in this situation, prenatal diagnosis with serial ultrasound scans of the fetus could help look for a tumor in the fetal eye at an early stage. If detected in utero, a fetus with retinoblastoma can be delivered early to initiate early treatment and possibly reduce the morbidity and preserve the vision. Though the child was identified to have the inherited paternal risk allele, she did not develop the tumor until 28 months of age. Hence, it is likely that these children may develop tumor at a later stage of life alarming for careful and regular long-term surveillance. Thus, prenatal diagnosis offers early detection of the tumors in the course of the disease and periodic examinations aid in eye salvage.

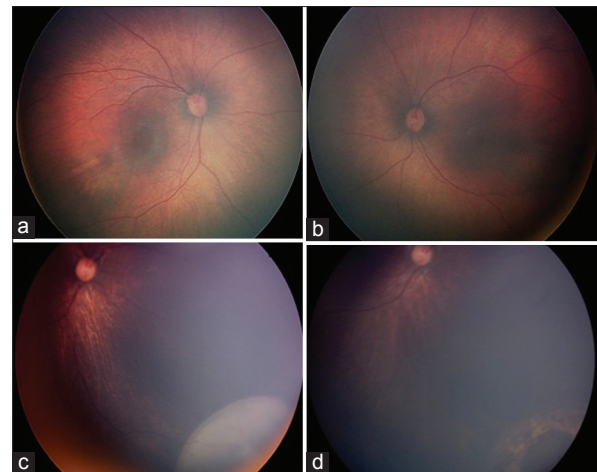


Figure 3: Fundus photographs (RetCam) of the child with defective allele detected on prenatal diagnosis (a) Fundus photograph of the right eye at 2 days of birth. (b) Fundus photograph of the left eye at 2 days of birth. (c) Fundus photograph of the right eye at 28 months showing tumor at inferonasal periphery (d) Post treatment Cryo, regressed tumor at 3 months follow-up

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Conflicts of interest

There are no conflicts of interest.

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