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A REVIEW ON RETINOBLASTOMA: MOST COMMON PRIMARY INTRAOCULAR MALIGNANCY IN CHILDHOOD

Ophthalmology

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ABSTRACT

Retinoblastoma is the most common primary intraocular cancer of childhood.The most common presenting age is less than 3 years. Retinoblastoma is sporadic in 94% cases, and in about 6% cases it is familial. Leukocoria is the most common presenting feature of Retinoblastoma, whereas strabismus, painfull blind eye and loss of vision are some other clinical features. A complete ophthalmic evaluation including dilated fundus examination under anesthesia should be done and by the use of different imaging modalities diagnosis of retinoblastoma should be made and confirmed. Most importantly, the exentions of the disease should be taken into the consideration, so that the best management can be delivered to the patient. Different modes of managenent of retinoblastoma are Enucleation of eye, cryotherapy, laser phototcoagulation, thermotherapy, external beam radition, brachytherapy, and systemic chemotherapy. First priority of management is to preserve the life of the child next is to presser the vision and then to minimize the complications.

KEYWORDS

RETINOBLASTOMA, RB1 GENE, ENUCLEATION.

Retinoblastoma (RB) is the most common primary intraocular cancer of childhood (1, 2), with Worldwide Incidence from 1 in 15,000 to 1 in 18,000 live births (3). It does not show any predilection for specific race or gender. It can affect one or both eye and chance of getting the disease in right is same as of the left eye.

About 80% cases are diagnosed before the age of 3 years, in which unilateral cases are diagnosed at the age of 14-16 months and bilateral at 29-30 months.

Retinoblastoma is bilateral in about 25–35% of cases (4), and unilateral in 65-75% cases.

In bilateral RB, all the cases have multifocal disease and 5 is the mean number of tumors that are distributed between the two eyes, however in unilateral disease, multifocal disease is found only in 15% of the cases(5).

GENETICS

Retinoblastoma is sporadic in 94%,and familial in 6% of the cases (4, 6).

Sporadic Retinoblastomas (nonheritable form) are unilateral and here both mutational events occur in a single retinal cell after fertilization (somatic events).

Bilateral retinoblastomas involve germinal mutations in all cases.

Rb1

Heritable genetic form of retinoblastoma is due to mutation in RB1 gene present on chromosome 13. RB1 was the first tumor suppressor gene to be cloned (7). RB gene is located on long arm of chromosome13 band 14.2(8).

Alfred knudson found that heritable retinoblastomas were more commonly seen in younger children and were often bilateral and multifocal, whereas nonheritable retinoblastomas more commonly occurred in older children and were unilateral (9).

In " Knudson Two Hit" hypothesis (in hereditary retinoblastoma), he explained that it requires two genetic injuries in two alleles to produce retinoblastoma, and if only one of the two gene copies remains active, there will be no retinoblastoma as the function of RB gene as tumor suppressor will remain intact. Therefore, if both the copies will get inactivated leading to sufficient loss of function, allowing unbridled cell proliferation the disease will occur.

Inherited retinoblastomas may be associated with Pineoblastoma and other malignant midline supratentorial primitive neuroectodermal tumors (PNET) with a dismal result. Concurrent occurrence of retinoblastoma and PNET is known as trilateral retinoblastoma (10). Survival of trilateral retinoblastoma has increased over the decades (11).

MYCN

Somatic amplification of the MYCN oncogene is responsible for some cases of non-hereditary unilateral retinoblastoma, which are early-onset, and aggressive. MYCN amplification are found only in 1.4% of retinoblastoma cases, but in a research, it was found to be present in 185 of infants of less than 6 months of age. For MYCN retinoblastoma median age is 4.5 months, whereas for non-familial unilateral cases it is 24months (12).

CLINICAL FEATURES

Most common presenting feature of retinoblastoma is leukocoria (a white pupillary reflex that is sometimes referred to as a cat's eye reflex), followed by strabismus, painfull blind eye and loss of vision (13). Other less common signs and symptoms are faltering growth, or developmental growth, squint (cross-eyed or wall eyed).In advanced disease eye enlargement is the common finding.

Fundoscopy shows translucent or a white fluffy retinal mass.

In case of strabismus there is involvement of macula resulting in diminished vision (13).

Growth pattern of retinoblastoma;

1. Endophytic

In endophytic pattern of growth tumor grows into the vitreous cavity. Retinal vessels are not seen over the tumor surface.

2. Exophytic

In exophytic pattern of growth tumor grows towards the subretinal space. Retinal detachment are usually found here and retinal vessels are seen over the tumor surface.

3. Diffuse infilterating tumor

Seen more commonly in older children where tumor diffusely involves the retina and instead of mass, it causes a placoid thickness of retina.

ROUTES OF SPREAD

Retinoblastoma can easily spread through the optic nerve especially when the lamina cribrosa is breached (13). Other modes of spread are through sclera, choroid, and orbit through contiguous route; C.S.F. may spread the disease into subarachnoid space of brain and spinal cord. Through hematogenous route it may spread into the bone marrow, or liver; lymphatics can lead to involvement of aqueous venous channels, or conjunctiva(14).

DIAGNOSIS OF RETINOBLASTOMA

A through clinical evaluation with detailed history should be done, and it should be supplemented with B-scan ultrasonogrphy which can show round or irregular intraocular mass with high internal reflectivity which is due to intralesional calcification. A complete ophthalmic evaluation including a dilated fundus examination under anesthesia should be done along with the measurement of intraocular pressure and anterior segment evaluation for neovascularization and signs of inflammation (13).

Computed tomography (CT) scan can detect pinealoblastoma in case of trilateral retinoblastoma and it also describes the extraocular extension of retinoblastoma (13).Calcification within the tumor is best seen with CT.

Magnetic resonance imaging (MRI) is indicated in case optic nerve is also involved or intracranial extension is suspected (13).

Fluorescein angiography can also be done.

BIOPSY (PATHOLOGY)
Macroscopically it is soft and fragile, whereas the microscopic feature depends upon the degree of differentiation of the tumor cells.

Undifferentiated elements have round, small, densely packed cells, with hypochromatic nuclei and scanty cytoplasm.

Differentiated elements include Flexner-Wintersteiner rosettes, Homer Wright rosettes(15), and fleurettes from photoreceptor differentiation (16).

MANAGEMENT

First priority is to preserve the life of the child next is to presser the vision and then to minimize the complication.

Various treatment options available for retinoblastoma are:

1. Enucleation of the eye-
Primary enucleation is done in cases of unilateral disease present with advanced intraocular disease when tumor characteristics cannot be visualized, and with this cure rates of 95% are found (13).

Enucleation is the last modality and done after all the methods have been tried.

2. Cryotherapy-
Cryotherapy causes damage to the vascular endothelium with formation of secondary thrombosis and tumor tissue infarct due to rapidly freezing it.

It can be primarily used for small peripheral or recurrent tumors. Cryotherapy is done for small equatorial and peripheral retinal tumors of size upto 4mm (basal diameter) x2mm (thickness) (4, 13).

Complications of cryotherapy are retinal tear and retinal detachments. Synergistic effects of cryotherapy and chemotherapy can be seen when Cryotherapy is administered 2–3 h prior to chemotherapy (13).

3. Laser photocoagulation-
Done only for small posterior tumors, an argon or diode laser or a xenon arc is used to coagulate all the blood supply to the tumor.

Complications of laser photocoagulation are retinal detachment, retinal hole, retinal traction, retinal vascular occlusion, and preretinal fibrosis.

4. Thermotherapy-
In thermotherapy, focused heat generated by infrared radiation is applied to tissues at subphotocoagulation levels to induce tumor necrosis (17). This is also used for small tumors.

Temperature range of 40 to 60 °C should be maintained as to avoid retinal vessels damage.

Common complications of thermotherapy are retinal traction, retinal detachment, focal iris atrophy, and focal paraxial lens opacity.

5. External beam radiation (EBR)-
Indicated in case where primary chemotherapy and local therapy has failed or in a case chemotherapy is contraindicated (13).

5. Brachytherapy-
It involves placement of radioactive implants, usually on sclera adjacent to the base of a tumor for trans-scleral irradiation of the tumor (18). Most common radioactive materials used here are Ruthenium 106 and Iodine 125.

It can be used as primary treatment or, in patients with small tumors or in patients where initial therapy including EBR therapy got unsuccessful.

The common complications are radiation papillopathy, and radiation retinopathy (18).

5. Systemic chemotherapy (chemoreduction)
Used to reduce the tumor volume and currently it has become an integral part of the management of retinoblastoma.

A potential complication of chemoreduction is the development of secondary non-ocular cancers. Cases of acute myelogenous leukemia have been reported in children who have received chemotherapy for their initial disease (19).

Other alternatives of systemic chemotherapy are intra-arterial chemotherapy where drug is administered locally via a thin catheter threaded through the groin, through the aorta and the neck, directly into the optic vessels (20) and Nano-particulate chemotherapy which is used to reduce the adverse effects of systemic chemotherapy, here subconjuctival injection of nanoparticle carriers containing chemotherapeutic agents are given. In developed countries it has shown safe and good results (21,22).

PROGNOSIS

With the advancement in the management of retinoblastoma, survival of patients has dramatically improved , with survival of more than 90% in developed countries(23),and mortality is still as high as 50% in the developing nations(24,25).

With identification of risk factors and use of adjuvant therapy leading to reduction in systemic metastasis, survival rates can be further improved.

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