Retinoblastoma is the most common intraocular malignancy of childhood, yet overall it is relatively rare, affecting 1 in 18,000 to 30,000 live births. The prognosis for life is 92 percent if the tumor is detected early; however, greater than 95 percent mortality is documented for cases with advanced presentation. This paper discusses incidence, diagnosis, histopathology, and treatment of retinoblastoma.

RETINOBLASTOMA (Rb) is the most common primary malignant ocular tumor of childhood with a 92 percent cure-rate if detected early; however, greater than 95 percent mortality is documented with presentation in an advanced stage. The incidence of the disease appears to be remarkably similar throughout the world, as it has been reported that one retinoblastoma occurs in every 18,000 to 30,000 live births. There is no significant preponderance with regard to race and sex distribution.

Population studies have noted a difference in age at presentation for unilateral and bilateral retinoblastoma patients (13 months vs 24 months). Bilaterally affected ones and those individuals with a positive family history for retinoblastoma are evaluated at a younger age (11 months vs 15 months).

Chromosomal studies have indicated that 5 percent of retinoblastoma patients have a deletion in the long-arm (Q 1-4 band) of chromosome 13. Those patients harbor a host of other abnormalities, including mental retardation, extra digits, failure to thrive, and imperforate anus.

The average age at diagnosis of retinoblastoma is 17 months and 90 percent of all cases present by age 4. Leukokoria is the symptom most frequently observed by parents, followed by strabismus. The differential diagnosis of leukokoria includes larval granulomatosis, uveitis, Coats' disease, angiomatosis retinae, persistent hyperplasia of the primary vitreous (PHPV), retrolental fibrosis (RLF), retinal folds, hemorrhage, myelinated nerve fibers, coloboma, high myopia, and cataract.

DIAGNOSIS OF RETINOBLASTOMA

The approach to ruling out Rb in a patient is multidisciplinary and should involve the following modalities in the proper sequence.

Ultrasonography

Ultrasonography is most useful in eyes with opaque media where direct visualization of the fundus is impossible. Retinoblastoma is one of several pathologic conditions that has specific acoustic characteristics.

1. Solid Lesions. Retinoblastomas are solid intraocular tumors that appear as mass-occupying lesions with topographic B-scan echography and produce stationary nonmobile A-scan patterns. With eye movements, the vitreous produces highly mobile, low reflective echoes, while solid tumors move harmoniously with the globe.

2. Internal Calcifications. The calcium deposits within the lesions are highly reflective and produce overloaded spikes on A-scan echography and a thick, prominent echographic appearance on B-scan topography. With decreasing attenuation, these calcifica-
tions become more prominent and sharply delineated.

3. Echographic Shadowing. The calcium deposits and the coarse internal structure of the lesions highly reflect the ultrasonic beam, producing a shadow effect, which masks the remaining ocular and orbital structures. The echographic beam, however, is transmitted above and below the lesion.

These three main criteria are pathognomonic for retinoblastoma and are extremely important for the detection, differentiation, and diagnosis of these lesions (Figure 1). Other findings such as internal vascularity and secondary retinal detachment are also important in establishing the diagnosis.

Echography can be used to rule out Rb in leukokoria cases, where retinopathy of prematurity, persistent hyperplastic primary vitreous, endophthalmitis, and Coats' disease can be clearly differentiated. Standardized ultrasonography is also useful for follow-up of given treatment, as the size of the tumor can easily be measured.

At the King Khaled Eye Specialist Hospital (KKESH), out of 30 consecutive cases, 29 (96%) had detectable calcifications. Most, if not all, retinoblastomas, have certain amounts of calcification that, properly examined, can be detected and echographically displayed. Although other intraocular pathologies may produce calcifications, such as choroidal osteomas, choroidal hemangiomas, phthisis bulbi, and old organized vitreous hemorrhage, the combination of the acoustic criteria in retinoblastoma, and the clinical history, age, and eye examination help establish the correct diagnosis. Ultrasongraphy is important in the diagnosis of retinoblastoma, in following the disease process and the efficacy of treatment, and in ruling out other causes of leukokoria.

Computed Tomography

Computed tomography (CT) with contrast reveals calcific ocular findings in 96 percent of the cases in a series of 27 retinoblastomas reviewed at KKESH. CT has proven to be probably the most useful diagnostic aid to detect retinoblastoma and rule out or confirm extrascleral and intracranial involvement. Additionally, CT serves as a valuable adjunct in diagnosis, particularly where ultrasound is equivocal. In 17 cases where ultrasound and CT were correlated, agreement occurred in 15; false negatives with ultrasound occurred in 2. One patient had no calcification but a definite intravitreal mass lesion. Without calcification, the differential diagnosis includes Coats' disease, PHPV, RLF, Norrie's disease, long-standing retinal detachment (RD), sclerosing endophthalmitis, and exudative vit-
reoretinopathy. Representative CT scans of the eye with retinoblastoma are depicted in Figures 2 and 3.

Figure 2. Computed tomography reveals calcification of a large retinoblastoma filling most of the vitreous in the left eye without optic nerve or extrascleral involvement.

Figure 3. Contrast-enhanced CT of a partly calcified retinoblastoma in the right eye with extensive orbital involvement, suprasellar extension, and proptosis of the eye.

Bone Scan

CT alone appears adequate to determine the extent of intracranial metastasis without brain isotope scanning or electroencephalogram. However, bone isotope scanning with \(^{99m}\)Tc is a more sensitive test to evaluate bone metastasis than radiography of long bones. For this reason, in addition to ultrasound and CT, bone scanning is a recommended aspect of the workup.

Examination under Anesthesia

Examination under anesthesia provides the necessary opportunity to easily complete the metastatic survey with lumbar puncture and bone marrow aspiration and examine both eyes with 360° scleral depression to the ora. If available, photographic documentation of lesions with the hand-held Kowa Camera or the contact MIRA Equatorplus Camera is desirable. Intraocular Rb is classified according to Reese and Ellsworth and indicates prognosis for salvaging the eye.

Group I (very favorable)

- A. single lesion - < 4 DD at or behind equator
- B. multiple tumors - < 4 DD at or behind equator

Group II (favorable)

- A. solitary lesion 4-10 DD in size at or behind the equator
- B. multiple tumors 4 DD in size or behind the equator

Group III (doubtful)

- A. any lesion anterior to the equator
- B. solitary tumors larger than 10 DD behind the equator

Group IV (unfavorable)

- A. multiple tumors, some larger than 10 DD
- B. any lesion anterior, extending to the ora serrata

Group V (very unfavorable)

- A. massive tumors involving more than one half the retina
- B. vitreous seeding
Most Rb's Group IV-V come to enucleation and it is imperative that a long (approximately 10 mm) section of optic nerve be obtained, as direct extension to the central nervous system (CNS) occurs through this route.

**Histopathology**

Retinoblastoma is composed of neuroblastic cells. Some of these cells are poorly differentiated, while others are well differentiated and exhibit photoreceptor capability with formation of rosettes and/or fleurettes. Another highly characteristic feature of retinoblastoma is the sleeves of viable cells along small blood vessels, but as the tumor cells become displaced more than 90 to 100 microns away from the nutrient vessels, they undergo ischemic coagulative necrosis. Calcification occurs almost constantly within the necrotic areas (Figure 4).

Figure 4. The upper two thirds shows typical pattern of retinoblastoma. Sleeves of viable cells around small blood vessels. The displaced tumor cells, away from the nutrient vessels, are pale-staining and necrotic. At the bottom, many rosettes are present. Hematoxylin-eosin X20.

Those well-differentiated retinoblastomas with rosettes and/or fleurettes usually have a better prognosis than poorly differentiated tumors. Another important feature about rosettes and/or fleurettes is their radio-resistance. Accordingly, incomplete shrinkage of the lesion may be noted after radiotherapy.

A total necrotic tumor with dense calcification is called histopathologically a regressed retinoblastoma. Such tumors are often seen in dessicated eyes.

Retinocytoma has been described recently as another rare variant of retinoblastoma. It is considered benign because it is a small placoid, noninvasive lesion. Furthermore, it is composed entirely of benign-appearing cells with numerous fleurettes and no evidence of necrosis or mitotic activity. The clinical counterpart of retinocytoma is retinoma.

**TREATMENT OF RETINOBLASTOMA**

The treatment of retinoblastoma is often comprised of multiple modalities. Indications for different techniques follow criteria based upon size, location of tumor, and bilaterality.

**Cryotherapy**

Cryotherapy may be utilized in tumors < 4 DD in size located anteriorly or in the periphery, with an 88 percent cure rate. The technique is three freeze-thaw-freeze cycles to the tumors; however, follow-up examinations under anesthesia are necessary to ensure regression of the tumor, as reactivation in previously treated lesions may occur up to 8 months after treatment.

**Photocoagulation**

Xenon marks placed concentric to the tumor are useful only in cases where the surrounding retinal pigment epithelium is not altered. However, location is the key in the selection of photocoagulation, as posterior pole tumors less than 4 DD (6 mm) in size respond best.

**Radiation**

In Groups IV and V Rb, radiation therapy may be a viable alternative to enucleation, or an adjunct to postoperative management with the following indications:

1. Treatment of tumor in one or both eyes where the extent of uninvolved retina is consi-
dered to give a good chance of vision after tumor irradiation.

2. Treatment of a less affected eye after enucleation of a more severely affected eye in the hope that some vision will remain.

3. Treatment of bilaterally severely affected eyes where a decision cannot be made as to which eye should be enucleated and which eye should be treated.

4. To irradiate residual or recurrent orbital tumor after enucleation.

5. Palliation of extraorbital metastatic tumor.

Radiotherapy can be combined with other forms of local ocular therapy such as photocoagulation or cryotherapy. It can also be combined with systemic chemotherapy.33

The method of radiotherapy depends on the amount and location of the tumors. When the tumor is small, involving less than 12 mm of the retina, and where the lesion is unsuitable for treatment with photocoagulation or cryotherapy, it is possible to administer local radiation with a radioactive applicator.34 This procedure has the advantage of limiting high dose radiation to the part of the eye containing the tumor and also minimizing the risk of radiation complications. A scleral applicator is chosen which will encompass the area of the tumor base with at least a 1 mm margin around, impregnated with radioactive cobalt 60 or iodine 125 seeds. This plaque is sutured over the appropriate area and left in place to deliver 4,000 rads to the apex of the tumor over several days.35 The applicator is then removed and the eye is followed for tumor response. Radioactive applicators cannot be utilized if the tumor involves the macula, or retina near the optic nerve head.34,35

Groups I, II, and III tumors require a dose of 3500 rads in 3 weeks with 3 fractions per week. Groups IV and V tumors require 4500 rads in 4 weeks, also using 3 fractions per week.5,31

If necessary, external radiotherapy can be supplemented with local therapy such as photocoagulation, cryotherapy or radioactive applicators for residual tumor.5,31,34

Metastatic tumor is treated in a palliative fashion, depending on the prognosis for the child. If the central nervous system (CNS) has been invaded with tumor cells in the cerebrospinal fluid (CSF), irradiation can be given to the whole brain.5

Ocular complications of radiotherapy have been markedly reduced since the advent of megavoltage x-ray machines. However, there still remains the possibility of vascular damage to the retinal endothelium. It has been estimated that the risk of complications from radiotherapy is about 10 percent with external beam therapy delivered at a dose level of 3500 rads administered over 3 weeks with 3 fractions per week.36 Should a second course of radiotherapy be necessary and cumulative doses approach 8,000 rads, the incidence of radiation-induced vasculitis increases dramatically to 80 percent.23,36

Chemotherapy

Retinoblastoma is a relatively slow-growing tumor and its metastases occur either via choroidal blood vessels exiting the eye into the orbit and circulation, or through direct extension into the optic nerve to the CNS.21 Abramson reported metastatic disease to be present at an average age of 12.4 months after the diagnosis of ocular retinoblastoma, and the average survival until death was an additional 5.8 months.6,21

In the management of children with retinoblastoma, enucleation or local therapy (photocoagulation and/or cryotherapy) is usually enough.3,30 Occasionally, radiation therapy and chemotherapy are used to complement the role of surgery. The primary indication for the use of chemotherapy is the management of extrascleral disease extension, including metastatic disease to the bone, bone
marrow, lymph nodes, and liver. Other indications for chemotherapy as an adjuvant include Reese-Ellsworth Group V disease with a high risk potential for metastatic disease. This category includes the following features: rubeosis iridis, undifferentiated histology, choroid involvement, retinal pigment epithelium involvement, and extension to the anterior segment or beyond the cribiform plate. In selected cases, chemotherapy may be combined with either photocoagulation or cryotherapy in order to avoid radiation therapy or enucleation of the affected eye. Effective agents include Adriamycin, daunomycin, cyclophosphamide, ifosfamide, vincristine, vinblastine, VP16, VM26, cisplatinum, and melphalan. Well-designed clinical trials are needed to determine the best combinations and effect of these agents.

The recently modified MIRA Equator-Plus Camera has proved to be invaluable in documenting the regression/progression of tumors. With this equipment the capability exists to photograph 80 percent of the fundus on a single frame. The proper relationship of retinal structures and tumor location is now possible. With stereo photos comparisons are easily obtained (Fig. 5).

A need exists in the Kingdom to garner more information about this devastating disease. The opportunity for relatively pure genetic analysis of the tumor is available, as an average of two to three patients with newly diagnosed retinoblastomas present to KKESH per month. Despite the late presentation of these cases, 80 percent of children with retinoblastoma from this series are now alive and experiencing no recurrences or secondary tumors. However, the follow-up time period is, at most, 4 years.

Ultimately, the need exists to coordinate diagnosis, management, and patient follow-up care with a multidisciplinary approach. To this end, a Retinoblastoma Group has been formulated at KKESH jointly with King Faisal Specialist Hospital, Riyadh. Patients are given routine follow-up examinations. Findings are presented at the official monthly meeting. The group is comprised of pediatric ophthalmologists, retina specialists, oculoplastic surgeons, pediatricians, pathologists, radiologists, oncologists, radiotherapists, geneticists, social workers, and nursing personnel. Consultation for difficult patients is available in the interim. Direct communication between hospital facilities, through this group, has ensured proper therapeutic management of these cases and provides support when diagnostic or treatment dilemmas occur. More research needs to be completed delineating inheritance of the disease in this population, and the multidisciplinary approach provides a means of pooling cooperative efforts.

Figure 5. Mira Equator-Plus photo of a group V-A retinoblastoma. Note the superior overlying retinal detachment and the calcific, lobulated masses adjacent to the disc with surrounding tortuous retinal vasculature. This patient had retinoblastoma extension in the optic nerve, which would be expected secondary to the location of peripapillary tumor masses.
RESULTS
The Retinoblastoma Group has realized the following results:
1. Standardization of treatment;
2. Identification of patients lost to follow-up (10 patients have been retrieved outside the health-care system);
3. Concise patient management summaries.
4. Creation of an educational booklet/video for parents;
5. Psychological support to the families;
6. Genetic counseling for the parents;
7. Institution of research projects, both within the Kingdom and internationally; and
8. Increased physician and public awareness of the disease through symposia, presentations, and papers.

In conclusion, retinoblastoma is a life-threatening disease demanding prompt recognition, treatment, and close follow-up. The multidisciplinary approach offers an effective avenue of management and, combined with parent/physician education, should allow for increased longevity of the young patient.43

References


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EIGHTEENTH CENTURY OPHTHALMOLOGY IN FRANCE

Antoine Maître-Jean (1650? - 1730), the founder of French ophthalmology, was one of the first to recognize the true nature of cataract, which had been suspected by Morgagni and the Italian anatomists. In 1706 he presented his views to the Academy of Sciences at Paris and in the same year published an excellent treatise on diseases of the eye. Michel Brisseau (1677 - 1743), of Tournai, independently of Maître-Jean, showed that cataract consists of a hardening and clouding of the lens, and in 1708 "couched" or reclined, the cataractous lens in the living. He also wrote on glaucoma (Paris, 1709). The most noteworthy step in the treatment of cataract, however, is due to Jacques Daviel (1716 - 62), regarded throughout Europe as the best oculist of his time. In 1750 he began his first attempts at the extraction of cataract, an operation that had often been tried but without much success. In the single year 1752 he operated on 206 patients, with successful results in 182. Although his priority has been long and passionately discussed, it must be accepted that to him is due the credit of having invented a practical operation for the extraction of the cataract and established the technique through his teaching and example.

From Castiglioni A: A History of Medicine, p 632.