# RETINOBLASTOMA IN UPPER EGYPT (1981–1991)

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We conducted a retrospective study on 78 children with retinoblastoma who were admitted, diagnosed and treated at the Ophthalmology Department of Assiut University Hospital (AUH) in the period between October 1981 and November 1991. Forty-seven children were male and 31 female, forming a male/female ratio of 3:2. The tumor was unilateral in 68 (87%) and bilateral in 10 children (13%). Retinoblastoma was primary in 67 (86%) and recurrent in 11 cases (14%). The mean age at diagnosis in males with unilateral and bilateral retinoblastoma was 36 months and 17 months respectively, while it was 33 months in females with unilateral tumors. Bilateral retinoblastoma was seen in only two females, aged 3 and 4 years. The first presenting symptoms were leukokoria (44.9%) and proptosis (39.7%). Echography showed a solid mass, with moderate to high refractile echoes, an orbital shadowing, and normal axial length of the globe. Retinoblastoma was treated by primary enucleation (50.0%), exenteration (16.7%), irradiation (3.8%), and chemotherapy (2.6%); in 25.6% of cases the parents refused treatment. The late presentation by the patients, and the deficiency in specialized centers for the management of retinoblastoma in our region of the world worsen the prognosis, both for life and for vision.

***Key words:*** retinoblastoma, leukokoria, proptosis, echography, enucleation

Retinoblastoma is the most common intraocular malignancy of childhood, comprising 3% of registered cases of malignancies in children under 15 years of age[1]. The chromosomal region 13q 14 regulates the development of normality. If both chromosomes have a 13q 14 deletion (a homozygous condition), retinoblastoma results[2]. The incidence of retinoblastoma is approximately 1:18,000 live births; however, some series have reported an increased incidence over the last few decades[3–5].

The aim of the present study is to report the clinical features, mode of presentation, echographic criteria, and treatment of retinoblastoma in our region during the period between 1981 and 1991.

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## Subjects and Methods

In the time from October 1981 to November 1991, seventy-eight Egyptian children with retinoblastoma were admitted to the Ophthalmology Department of Assiut University Hospital (AUH). The series comprised 88 eyes with retinoblastoma, 6 atrophic eyes, and 62 normal eyes.

All children suspected of having retinoblastoma were thoroughly examined. This was carried out under general anesthesia, including slit-lamp biomicroscopy using the operating microscope, examination of the vitreous and the retina using the Goldmann 3-mirror contact lens, and thorough indirect ophthalmoscopy including use of the scleral indentation technique. The observed findings were carefully recorded on retinal diagrams. Echography was performed whenever it was possible to do so, commonly under the hypnotic effect of chloral hydrate. Computerized tomography (CT-scan) was done in order to confirm

the presence of intraocular calcification, and to exclude extrascleral or intracranial extension of the retinoblastoma. Histopathological examination of the tumor, and the optic nerve stump in enucleated globes, was done routinely.

## Results

During a period of 10 years (1981–1991), 78 children with retinoblastoma were admitted to the eye department of AUH, which is a referral hospital in Upper Egypt. Table 1 shows the age and sex distribution of these cases at their first time of presentation at our hospital. Forty-seven were male and 31 female, a male/female ratio of 3:2. Retinoblastoma was unilateral in 68 (87%) and bilateral in 10 children (13%). The mean age for males with unilateral retinoblastoma was 36 months (range 8 months to 6 years), and with bilateral tumor 17 months (range 3 months to 3 years). The mean age for females with unilateral retinoblastoma was 33 months (range 2 months to 6 years). Bilateral retinoblastoma was found in two females, aged 3 and 4 years.

TABLE 1. *Age and sex distribution of patients with retinoblastoma at their first presentation.*

| Age (years) | Male | Female | Total | % |
|---|---|---|---|---|
| 0–1 | 6 | 6 | 12 | 15.4 |
| 1–2 | 13 | 5 | 18 | 23.1 |
| 2–3 | 12 | 10 | 22 | 28.2 |
| 3–4 | 11 | 7 | 18 | 23.1 |
| 4–5 | 4 | 1 | 5 | 6.4 |
| 5–6 | 1 | 2 | 3 | 3.8 |
| Total | 47 | 31 | 78 | 100 |

Table 2 shows the distribution of 88 retinoblastomas among 156 eyes of 78 children. The tumor was unilateral in 68 eyes (77.3%), of which retinoblastoma was primary in 57 (84%) and recurrent (after previous enucleation) in 11 eyes (16%). Bilateral retinoblastoma was found in 20 eyes (22.7% of all involved eyes), and the tumor was primary in all of these. There were six atrophic globes, and 62 fellow eyes were found to be normal. A family history of retinoblastoma was found in one male with unilateral tumor, and one female with bilateral tumors.

TABLE 2. *Distribution of 88 cases of retinoblastoma in 156 eyes of 78 children.*

| | Retinoblastoma | | | Fellow eye | | |
|---|---|---|---|---|---|---|
| | Unilateral | | Bilateral | Atrophic | Normal | Total |
| Sex | primary | recurrent | | | | |
| Male | 32 | 7 | 16 | 1 | 38 | 94 |
| Female | 25 | 4 | 4 | 5 | 24 | 62 |
| Total | 57 | 11 | 20 | 6 | 62 | 156 |

Table 3 shows the presenting symptoms as given by the parents of children with retinoblastoma at their first presentation. Leukokoria and proptosis can be seen to be by far the most frequent presenting symptoms (see Figs. 1 and 2).

TABLE 3. *Presenting symptoms in 78 children with retinoblastoma.*

| Symptom | Males | Females | Total | % |
|---|---|---|---|---|
| Leukokoria | 23 | 15 | 35 | 44.9 |
| Proptosis | 16 | 15 | 31 | 39.7 |
| Inflamed eye | 6 | – | 6 | 7.7 |
| Strabismus | 1 | 3 | 4 | 5.1 |
| Defective vision | 1 | 1 | 2 | 2.6 |
| Total | 47 | 31 | 78 | 100 |

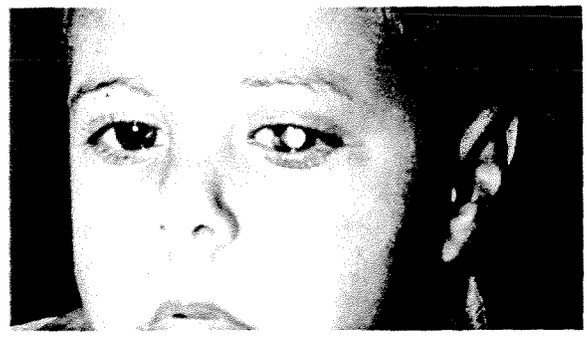

Figure 1. Leukokoria in the left eye of a child with retinoblastoma.

Figure 2. A girl with fungating retinoblastoma of the right eye.

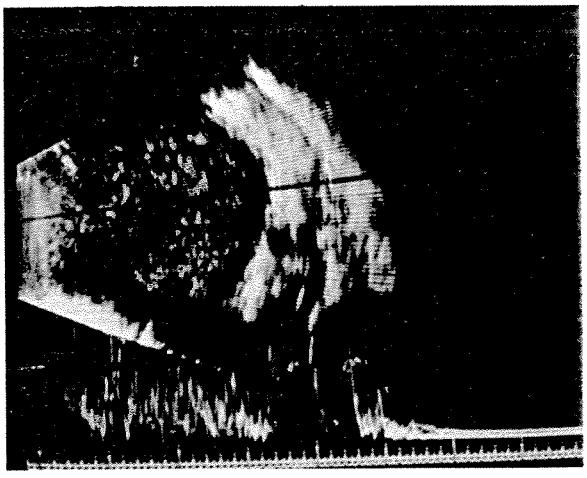

Figure 3. Echography of a case of retinoblastoma showing a vitreous mass attached posteriorly.

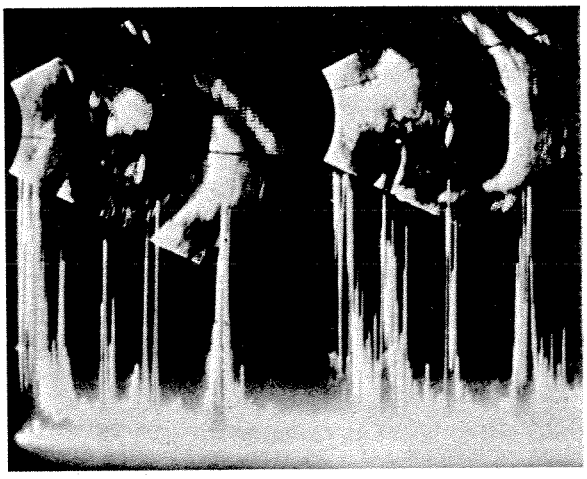

Figure 4. High amplitude refractile echoes in retinoblastoma.

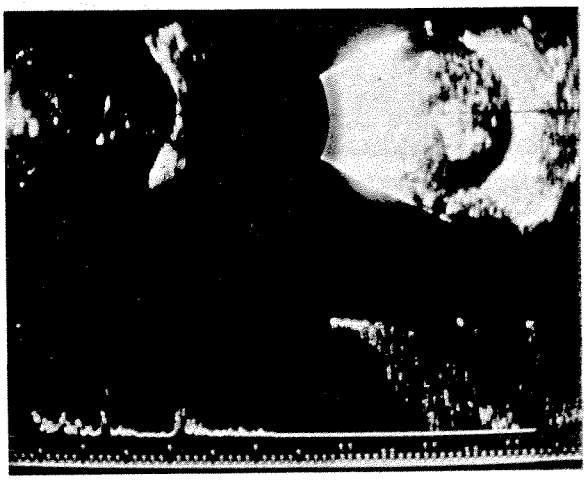

Figure 5. Orbital shadowing in a case of retinoblastoma.

We were able to do echography in 32 cases. We found a retrolental mass attached posteriorly (Fig. 3), with moderate to high amplitude refractile echoes (Fig. 4), an orbital shadowing (Fig. 5), and an axial length of the globe within normal limits (i.e. ± 17 mm).

Computerized tomography (CT-scan) was performed in 12 children. It revealed intraocular calcification (Fig. 6) and intracranial extension of the tumor (Fig. 7) in some cases.

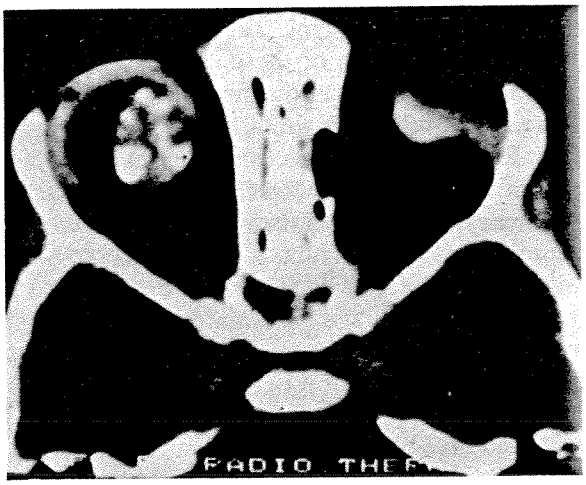

Figure 6. Computerized tomography showing intraocular calcification in retinoblastoma (right eye), and atrophic left eye.

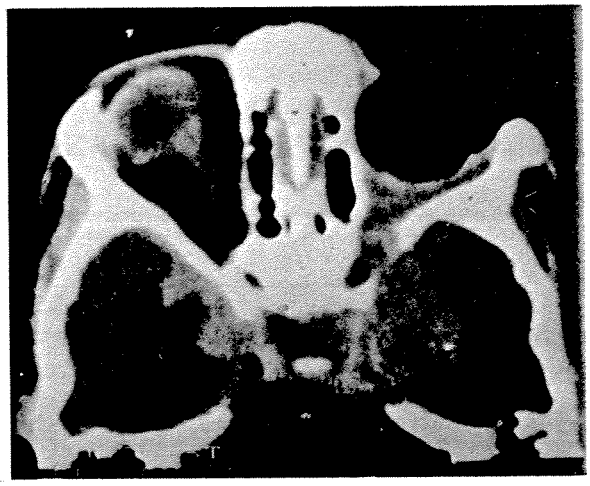

Figure 7. Computerized tomography showing intracranial extension of left recurrent retinoblastoma.

The types of treatment undergone by our patients are listed in Table 4. Primary enucleation was done in 39 cases (50.0%). We had to do exenteration on 13 cases of retinoblastoma

(16.7%); in 11 of these the indication was recurrence after previous enucleation, and 2 had extrascleral extension of the primary tumor. Chemotherapy consisting of a combination of adriamycin (10 mg/day), oncovin (1 mg/day), and endoxan (200 mg/day) was given to one male and one female with retinoblastoma and intracranial extension. One girl died before any treatment was instituted, and 20 children received no treatment, because their parents refused the proposed therapy.

TABLE 4. *Treatment of 78 children with retinoblastoma.*

| Treatment | Males | Females | Total | % |
|---|---|---|---|---|
| Primary enucleation | 26 | 13 | 39 | 50.0 |
| Exenteration | 8 | 5 | 13 | 16.7 |
| Irradiation | 3 | – | – | 3.8 |
| Chemotherapy | 1 | 1 | 2 | 2.6 |
| Died before therapy | – | 1 | 1 | 1.3 |
| Refused therapy | 9 | 11 | 20 | 25.6 |
| Total | 47 | 31 | 78 | 100 |

Histopathological examination of 39 excised tumors (Fig. 8) served to confirm the clinical diagnosis, and helped in planning further therapy. At the time of operation, retinoblastoma was confined to the globe in 34 eyes, two eyes showed extrascleral extension, and the optic nerve was invaded in 3 eyes.

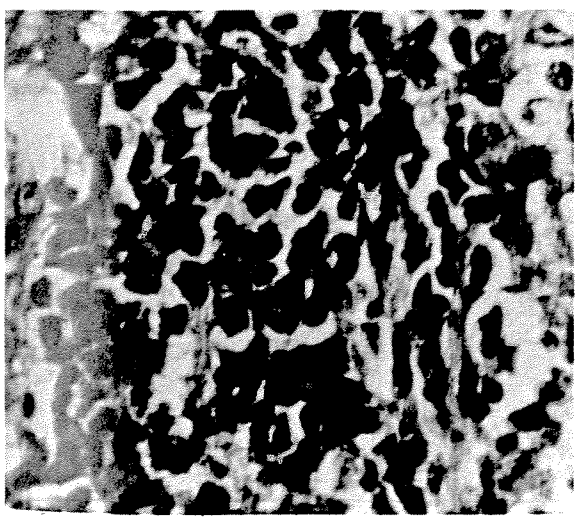

Figure 8. Histopathological specimen showing rosette formation of malignant cells in retinoblastoma (H & E × 640).

## Discussion

During the last 10 years, we admitted 78 children with retinoblastoma. Many authors[3–5] have observed a marked rise in the incidence of retinoblastoma over the last 30 to 40 years. This has been attributed to various factors: a decrease in the mortality rate due to early detection and better treatment of the disease, leading to an increased frequency of the gene in the population; and a cumulative, progressive effect of exposure to nonspecific ambient radiation, as well as other exogenous influences, resulting in a greater rate of spontaneous mutations both in the general population, and in a particularly susceptible subgroup[6]. Survival rates have improved from around 5% during the 1960s to 90% or more under favorable circumstances today[7].

In past series, there has been either no sex predilection[8], or a slight male preponderance[9,10]. We found a male/female ratio of 3:2. This was in contrast to the ratio of 0.9:1 reported in Egypt earlier[11]. Others have found the ratio of boys to girls in uniocular cases to be 1.2:1, and 3:1 in binocular cases[12], while a male/female ratio of 4:7 was recently reported for the Middle East[13].

In our present study, retinoblastoma presented earlier in females than in males (33 versus 36 months, on average, for unilateral tumors), and earlier in bilateral cases as compared to unilateral ones (17 versus 36 months, on average, for our male group). In most reports in the USA, age at diagnosis averaged 18 months[14]. Most population-based studies have noted a difference in the age at presentation for unilateral versus bilateral retinoblastoma patients, 24 versus 13 months being mentioned in a major textbook[15].

Regarding the mode of presentation, out of our 78 cases of retinoblastoma, 35 (44.9%) presented because of leukokoria, 31 (39.7%) with proptosis, 6 (7.7%) as an inflammatory condition, 4 (5.1%) with strabismus, and 2 (2.6%) with defective vision. Similar modes of presentation, but in differing proportions, were reported by other authors. Ayoub and Shoukry[16] found the most common presenting symptom to be white or yellow coloration of the pupil (in 61%), whereas in another study carried out in the Middle East[13], leukokoria was found in 77%, strabismus in 6.5%, with proptosis, inflammation and poor vision con-

stituting the remainder. In a Swedish study[17] pupillary changes accounted for 58%, squint for 19.3%, and an acutely red eye for 9% of presentations. Proptosis, our second most frequent presenting symptom (in nearly 40% of all cases), was found to occur much more infrequently in other series. The cause of this is presumably that our patients usually present much later in the course of the disease. This aspect is also stressed by the fact that 16% of retinoblastoma patients were detected merely on the grounds of family history in one study in the USA[18], and another 1% on routine pediatric examination, without any other clinical sign being present as yet, to alert the child's parents.

Our survey revealed retinoblastoma to be unilateral in 68 (87%), and bilateral in 10 children (13%). A previous study at the same hospital[19] reported 78% and 22% respectively. Other authors[12] have reported unilaterality in 82% (bilaterality in 18%) of cases, whereas 70% is the figure given for unilateral retinoblastoma in a major textbook[15].

In our present study we saw six atrophic eyes (3.8% of all eyes). There was no other apparent cause to explain this finding in these children. The detection of intraocular calcification by CT-scan in these atrophic eyes was highly suggestive of spontaneous regression of retinoblastoma. Several cases of bilateral retinoblastoma showed inert tumor in one eye, with a viable retinoblastoma in the fellow eye, while spontaneous regression occurring in both eyes was seen in only 12 out of 47 reported cases[20,21]. Many theories have been advanced to explain the finding of phthisis in eyes with retinoblastoma. The most widely accepted is that of vascular obstruction to both the tumor and the eye as a whole, caused by the growth of the tumor[22].

In our study, we found retinoblastoma to be recurrent in 11 of 78 cases (14%). These recurrences were seen after previous primary enucleation, performed during the 10-year period of our study. More than 45 cases of second primary tumors, not associated with irradiation, have been reported in patients with retinoblastoma[1,23]. A 14% incidence of second primary tumors in cases of retinoblastoma treated solely by enucleation was reported by other authors[23].

Echography was found to be a valuable tool in determining whether the vitreous cavity was filled with solid tissue, and/or whether pathologic tissue was confined to the retrolental part of the eye. Ultrasonography is a good method of determining increase in size of this tissue[24]. There are two ultrasonic types of retinoblastoma: solid and cystic. The solid type may represent the early lesion, whereas the cystic type may be characteristic of more advanced tumors with necrosis, and with seedlings of tumor floating free in the vitreous cavity[7]. We agree with others[25,26] that there are at least three criteria for the echographic diagnosis of retinoblastoma: a solid retrolental mass attached posteriorly; the presence of intratumoral calcifications; and normal axial length of the eye for its age. Moreover, calcifications in the tumor cause marked orbital shadowing[25,27]. Simulating lesions with retinal detachment do not demonstrate a mass[28].

Reese[29] and Ellsworth[14,30] emphasized that the treatment of retinoblastoma differs for each of five situations:

1) the unilateral case,
2) the bilateral case,
3) the case with residual tumor tissue left in the orbit at the time of enucleation,
4) the case with later recurrence of tumor in the orbit, and
5) the case with extension to the brain, or distant metastases.

The majority of patients in our series (87%) had unilateral single retinoblastoma (likely to be sporadic); these tumors were commonly large when the patient presented with either leukokoria or proptosis. The traditional method of dealing with such a case has been to enucleate the eye, additionally taking out as long a piece of optic nerve as possible. In the presence of a normal fellow eye, such an approach has been recommended[15,31]. Primary enucleation was indicated in 39 cases (50%) in our study. We quite agree that the most significant factor in the treatment of retinoblastoma is the stage of the disease at the time treatment is undertaken. The approach depends upon whether the tumor is confined to the eye, whether it has extended locally to the orbit, or whether metastases have already occurred[15]. We hope the access to good facilities for pediatric anesthesia, echography, and CT-scan

will assist in early detection of retinoblastoma, so that the indications for enucleation, which still forms an important line of treatment for the tumor in our region, will in time decrease. In one study reviewing the causes of enucleation in 209 cases[32], retinoblastoma was the diagnosis for 30 of these (14%). In another study[13], 47 patients underwent enucleation of one eye for retinoblastoma, and in 20 of these no additional treatment had to be given.

Although radiotherapy today is the mainstay of management of retinoblastoma[33], we used it in only three of the cases in this study (3.8%); all suffered from advanced retinoblastoma with intracranial extension. The reason for this low figure is that radiotherapy has only recently become available in our hospital, which also explains the high rate of exenterations in our series.

Chemotherapy with a combination of adriamycin, oncovin, and endoxan was used in the treatment of one male and one female with retinoblastoma with distant metastases. The use of chemotherapy in those cases in which there has been marked choroidal extension or extensive orbital disease has not been accompanied by an improved overall survival rate. The drugs used in those cases were cyclophosphamide combined with vincristine and actinomycin[31].

## Conclusion

Retinoblastoma is not uncommon in our region (about 8 cases per year). We have noticed an increase in the number of cases of retinoblastoma in this ten-year period. Cases with bilateral retinoblastoma are likely to be inherited, and the parents may benefit from genetic counselling. Access to good facilities for pediatric anesthesia, echography, and computerized tomography assist in early detection, and in differentiation of retinoblastoma from other simulating conditions. The delay in presentation, and the deficiency in specialized centers for the treatment of retinoblastoma in our region are factors that worsen the prognosis, both for vision and for life, in our patient population.

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