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Retinoblastoma: The Clinical, Pathological And Radiological Presentation In Indian Children

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Abstract:
Purpose : *To assess the clinical, pathological and radiological features of tumor progression in Indian children suffering with retinoblastoma.*
Methods: *A prospective analysis of all the patients diagnosed with retinoblastoma at Department of Ophthalmology, Maharani Laxmi Bai Medical College, Jhansi from December 2013 to February 2016 was performed. The main outcome measures included clinical and histopathological findings, radiological features and treatment options.*
Results: *Fourteen patients presented with retinoblastoma during the study period. The mean age at presentation was 22.57 ± 10.8 months (range six to fourty months). Five patients presented with bilateral retinoblastoma (35.7 %). The ratio of unilateral to bilateral cases was 1.8:1. The mean duration of symptoms before presentation was 2.5 ± 3.2 months (range three days to 12 months). Eleven patients (78.6 %) presented with leukocoria. Five patients (35.7 %) presented with leukocoria as their only symptom. The patients underwent either enucleation (84.6 %) or exenteration (7.7 %) of at least one eye.*
Conclusion: *In our study unilateral retinoblastoma was more prevalent. The majority of the patients presented with leukocoria and were treated with enucleation.*
Keywords: *Retinoblastoma, Clinico-histopathology, Radiology*

I. Introduction

Retinoblastoma is the most common ocular malignant neoplasm of childhood [1]. It is bilateral in approximately 35% of cases [2], and occasionally patients with such a neoplasm have an associated independent primary midline intracranial neoplasm that is almost always a pineoblastoma [2]. The incidence of retinoblastoma is approximately one case per 15000–20000 live births, which amounts to 9000 new cases each year. There is no gender or racial predilection, and 90% of cases are diagnosed in patients under three years of age [3]. Biallelic mutations of the RB1 tumor suppressor gene likely predispose retinal progenitor cells to tumor growth [4]. In the heritable form, the first mutation is constitutional, and the second is somatic, which causes bilateral disease in the majority of patients. In the nonheritable form, both allelic mutations are somatic, limiting disease to one eye with delayed presentation compared to those with the heritable form [5].

The most common initial sign of retinoblastoma is leukocoria, where the light emanating through the pupil is white light reflecting off the tumor instead of red light reflecting off the retina. Other signs of retinoblastoma may include decreased vision, strabismus, redness, pain, high pressure in the eye, cellulitic-like periocular inflammation, pseudohypopyon, and proptosis in late disease [5]. On fundoscopic exam, four patterns of growth can be seen. In the endophytic growth pattern, tumors are well visualized and extend from the deep retinal layer into the vitreous with vessels coursing into the mass. With exophytic growth, tumors extend from the retina outward into the subretinal space, with vessels coursing over the tumor. This growth pattern can be associated with retinal detachment, and total tumor extent may be underestimated. The third pattern is the most common, representing a mix of exophytic and endophytic growth. Extensive retinoblastoma can metastasize into the CNS and present with symptoms of meningitis. The fourth pattern, diffuse infiltrating retinoblastoma, accounts for 1-2% of retinoblastomas and usually arises from the anterior retina in older children. This form usually does not form a mass or contain calcium. The resultant pseudohypopyon and floating vitreal tumor cells can be easily mistaken for uveitis or endophthalmitis and has thus been termed a masquerade disease. The absence of pain, conjunctival hyperemia, synechia (anatomic adhesions), cataract, and vitreous fibrosis suggests retinoblastoma rather than inflammation. Diffuse retinoblastomas start anteriorly and may enter the anterior chamber and fill the vitreous cavity but usually do not extend to the optic nerve. Spontaneous regression of tumor results in a shrunken, nonfunctioning globe [6].

Historically, retinoblastoma was grouped into categories based on the Reese-Ellsworth classification system (groups I–V). The International Intraocular Retinoblastoma Classification System (IIRC) separates retinoblastomas into groups (A–E) based on prognosis, which is related to the extent of intraocular disease at diagnosis. More recently, the International Retinoblastoma Staging System (IRSS), proposed by a consensus of clinicians to separate retinoblastomas into stages based on management approach, has become popular [6]. Based on the IRSS classification, Stage 0 eyes can be treated conservatively. Stage I eyes are enucleated with complete histologic resection, and Stage II eyes are enucleated with residual microscopic tumor. Stage III eyes have regional extension, including local lymph nodes, while Stage IV patients have metastatic disease (hematogenous, CNS, multiple lesions) [7]. The Tumor, Node, and Metastasis (TNM) classification system is generally used for extension of retinoblastoma beyond the eye.

Radiologic imaging can be used to help confirm the diagnosis and determine staging. The vast majority of nondiffuse type retinoblastomas appears nodular with calcifications, and presence of these calcifications distinguishes retinoblastoma from other intraocular lesions. CT evaluation of retinoblastoma typically demonstrates a hyperattenuating mass in the posterior globe with calcifications. On ultrasound, retinoblastomas are irregular masses that are more echogenic than vitreous and contain shadowing calcifications. Orbital ultrasound can detect calcifications in up to 95% of cases and can confirm the clinical diagnosis of retinoblastoma [8]. Conventional 1.5 T MR has not been considered as sensitive for detection of calcifications, but higher field-strength MR units and newer susceptibility-weighted sequences have increased its sensitivity. MR is the study of choice for known retinoblastoma cases with clinical symptoms concerning for extraocular spread of disease and for followup evaluations. Radiologic imaging is less sensitive and specific for determining the diffuse infiltrative pattern of disease, but this may show an anterior plaque without a discrete mass or calcifications. Ophthalmic imaging modalities, including ultrawide field photography, angiography, and spectral domain optic coherence tomography, aid in the diagnosis of this subtype of retinoblastoma. Enhancement is uniform with diffuse retinal thickening; however, micronodules may be visualized via US or MR with rare extension posteriorly through the choroid or into the optic nerve[9].

The treatment of retinoblastoma is complex and involves a multidisciplinary team, including pediatric oncologists, ophthalmologists, diagnostic and interventional radiologists, radiation oncologists, ocular pathologists, and geneticists. The available treatment options include enucleation , chemoreduction, selective intraarterial and systemic chemotherapy, laser photocoagulation, focal cryotherapy, transpupillary thermotherapy, plaque brachytherapy, and external-beam radiation therapy (EBRT). Enucleation is the treatment of choice for advanced retinoblastoma with no potential for visual salvage. Historically, chemotherapy was reserved for extraocular or metastatic disease with adjuvant chemotherapy after enucleation. Discovery that patients who underwent EBRT are at an increased risk of developing secondary malignancies led to a paradigm shift in retinoblastoma treatment [10]. Now, systemic chemotherapy is used for chemoreduction, followed by laser coagulation, thermochemotherapy, cryotherapy, transpupillary thermotherapy, or plaque radiotherapy for treatments that spare the eye. Multiagent chemotherapy usually includes a combination of carboplatin and vincristine with or without etoposide. Studies have shown that for retinoblastomas in Reese-Ellsworth groups I–III, systemic chemotherapy in combination with local ophthalmic therapies (cryotherapy, laser photocoagulation, thermotherapy, and plaque radiation therapy) can avoid the need for enucleation or EBRT [10–11]. Some trials have demonstrated that treatment of large tumors with systemic chemotherapy in conjunction with localized therapies may be preferable, as they can provide vision and globe salvage with some benefits over enucleation [12] . Toxicities from chemotherapy include cytopenias (89%), neutropenic fever (28%), infection (9%), gastrointestinal symptoms, dehydration, and vincristine neurotoxicity (40%)[11].

More aggressive therapy is needed for Reese-Ellsworth groups IV and V, as advanced cases with diffuse vitreous seeding are extremely difficult to treat. Subconjunctival carboplatin and intravitreal carboplatin have been used in cases of diffuse vitreal seeding in Reese-Ellsworth group Vb eyes without evidence of seeding at 37 month followup[13]. This treatment also has improved disease control as has higher doses of carboplatin with etoposide or vincristine and combining vincristine, etoposide, and carboplatin. Cryotherapy is effective for small (<3 mm apical thickness and <10 mm basal dimension) peripheral tumors, and a triple freeze-thaw technique is used with a tumor control rate of up to 90%. Multiple sessions of focal laser photocoagulation can be used alone for tumors less than four disc diameters. Thermotherapy with infrared radiation may also be used. When the aforementioned local treatments fail, brachytherapy is ideal for small, discrete, and accessible tumors. In a large study, plaques with radioactive ruthenium 106 or iodine 125 had a 79% tumor control rate at 5 years [14]. Proton beam radiation therapy, electron beam therapy, and intensity-modulated radiation therapy are modalities of EBRT used to reduce the dose of radiation used. Typically, a total dose of 40–45 Gy is delivered over 20–25 treatments over 4-5 weeks. The risk of secondary malignancies in retinoblastoma patients has been reported with some modalities of treatment, especially EBRT. Infusion of selective intraarterial chemotherapy (SIAC) is currently the new trend in retinoblastoma treatment. SIAC has been used for the primary treatment of unilateral and bilateral retinoblastoma in IIRC groups C and D with reported cures after one and two cycles of

chemotherapy without major adverse events [14]. In patients with advanced retinoblastoma (Reese-Ellsworth group 5a and b) that failed prior intravenous chemotherapy, SIAC with simultaneous carboplatin, topotecan, and melphalan has resulted in eye-sparing treatment in 75% of patients at 24 months follow up. Recurrence rates were 35%, necessitating adjuvant local treatment; however, patients were all alive without evidence of metastatic disease in follow up.

II. Materials And Methods

A 26 months prospective analysis of all the patients diagnosed with retinoblastoma at Department of Ophthalmology, Maharani Laxmi Bai Medical College, Jhansi from December 2013 to February 2016 was performed. A detailed history of each patient that included presenting complaints, history and duration of present illness, family history, treatment history, age, sex, and place of residence was taken. All patients were subjected to an external ocular examination.The state of the lids/adnexa, extraocular movement, and presence or absence of vitreous seeding were noted. Visual acuity was also recorded. Anterior segment evaluation was performed via Slit-Lamp Biomicroscopy. Fundus evaluation after full pupil dilation was performed with both direct and indirect ophthalmoscopy. When tumors were present, their size, quadrant, number, and location were noted. IOP was measured.

Following diagnosis of retinoblastoma, the available treatments included enucleation, exenteration, cryotherapy, photocoagulation, radiotherapy and chemotherapy. Enucleation was indicated by tumor size greater than or equal to one half of the total retinal diameter. All patients with bilateral retinoblastoma received photocoagulation at the Higher center. The patients were referred to an oncology unit for chemotherapy and radiotherapy. A complete histopathological analysis was performed on all enucleated/exenterated specimens. Specimens were classified according to the cell type (well versus poorly differentiated), optic nerve infiltration and orbital infiltration. Clinical records were reviewed for the patient's age at time of the diagnosis of the ocular tumor, length of the latent period from diagnosis of retinoblastoma to discovery of the intracranial tumor. Laboratory records were also analyzed for the presence of tumor cells in cerebrospinal fluid (CSF) acquired via lumbar puncture. The CT scans or MR images were reviewed for the appearance of a primary or metastatic neoplasm in the brain as well as for spinal metastases. The brain was evaluated mainly for mass lesions in the pineal and suprasellar regions and for curvilinear or nodular areas of contrast enhancement suggestive of leptomeningeal tumor dissemination. For metastases to the subarachnoid space of the spinal cord, MR images of the spine and CT myelograms were assessed. All data utilized in this study was collected via chart review and then entered onto a standardized form. Data was subsequently entered into Microsoft Excel 2007. All statistical analysis was performed with data analysis software. Descriptive statistics were represented as mean ± standard deviation. All the tests were two-sided and the P values of less than 0.05 were considered statistically significant. There was no financial interests from the authors' side.

III. Results

Fourteen patients with retinoblastoma presented at our institute during the study period. 8 patients were male and 6 patients were female(ratio 1.33:1). The mean age at presentation was 22.57 ± 10.8 months (range six months to forty months). The mean duration of symptoms before presentation for examination was 2.5 ± 3.2 months (range : three days to 12 months). Table 1 shows the mean age at presentation and the mean duration of symptoms for male and female and the laterality of involvement. The majority of patients (71.4 %) were three years old or younger. There were no significant differences between age at presentation or duration of symptoms prior to treatment between the male and female patients ($p = 0.423$ and $p = 0.820$, respectively). Out of 14 cases, 9 (64.3%) had unilateral involvement and 5 (35.7 %) had bilateral involvement (Table 2). Fig. 1 shows clinical picture and USG B scan of a 13 months old male patient of bilateral retinoblastoma. He presented with leukocoria and proptosis (Fig.1a). The USG showed a small retinal based echogenic lesion in right eye (Fig.1b,arrow) and a large 18x16 mm heterogenous echogenic mass with calcification in left eye (Fig.1c). NCCT head with orbit of the same patient (Fig.2) showed a small hypodensity lesion in right eye (arrow) and an irregular calcification lesion in left eyeball (arrow).

All patients had a negative family history for retinoblastoma. There was no statistical difference between the proportions of males and females who developed unilateral versus bilateral retinoblastoma ($p = 0.88$).

11 patients (78.6 %) presented to the institute with leukocoria. Of these patients, 5 (35.7%) presented with leukocoria as their only symptom, and 9 had additional symptoms (Table 3). In all patients who presented with leukocoria, the mean duration of presenting symptoms was 2.6 ± 3.5 months, and in patients with leukocoria as their only presenting symptom, the mean duration of symptoms before presentation was 1.9 ± 1.6 months. 6 patients (42.9%) presented with a red eye, and this was associated with an average duration of symptoms of 3.2 months. With one exception, all patients presenting with red eye also presented with additional symptoms, including leukocoria and "other" symptoms. 5 (35.7 %) patients presented with other symptoms (e.g.

watery eye, swelling, tenderness, etc.). 2 (14.3%) patients presented with secondary glaucoma 1 month after diagnosis for retinoblastoma.

One of the cases in this study diagnosed with unilateral retinoblastoma did not undergo surgery. Cases without the histopathology scores were otherwise reflective of the rest of the patient cohort in terms of age and time to treatment. Table 4 illustrates the histopathological findings in the remaining 13 cases. Poorly differentiated and well differentiated tumors were present in nearly equal proportions in this study. 6 of the 8 patients with poorly differentiated tumors had a unilateral retinoblastoma (Table 4). This distribution of poorly differentiated, unilateral tumors versus other tumors was not statistically significant (p=0.12). Well differentiated tumors were present in near equal proportions in unilateral and bilateral cases. Patients with well differentiated tumors experienced symptoms for an average of 1.8 months before reporting to the higher center, whereas those with poorly differentiated tumors experienced symptoms for 3.4 months, but the difference was not statistically significant (p = 0.237). 3 of the 5 patients with an affected optic nerve had unilateral retinoblastoma. Patients with an affected optic nerve experienced symptoms for 4.9 months on average before reporting to the higher center, while patients with an unaffected optic nerve only experienced symptoms for 1.3 months, and this difference was statistically significant (p = 0.009). Both patients with orbital infiltration had unilateral retinoblastoma and had experienced symptoms for an average of six months before reporting to the higher center. Well differentiated tumors presented at an earlier age than poorly differentiated tumors, and patients without optic nerve infiltration presented at an earlier age than those with optic nerve infiltration. The difference in age of presentation amongst patients with well differentiated tumors versus those with poorly differentiated tumors was not statistically significant (p =0.056), but the difference in age between the patients with affected versus unaffected optic nerves was significant (p = 0.0037).

Fig.3 shows the clinical picture of a 33 months old female patient of unilateral retinoblastoma presenting with leukocoria, proptosis, dystopia and secondary glaucoma in left eye (Fig.3a) and metastatic lesions involving the left parietal (Fig.3a,arrow) and occipital regions.USG (Fig.3b) of same patient showed a large hypoechoic mass with posterior acoustic shadow and heterogemeous calcification in left eye ,also extending outside . Fig.3c depicts the Colour Doppler image of same patient showing colour flow of increased vascularity. On MRI, T2 Axial imaging (Fig.4a) of same patient delineates a heterogeneous hypointense mass in left eyeball involving the optic nerve which is also thickened suggesting tumour extension. Fig.4b shows lateral view plain digital X-ray imge showing well defined density and "sun burst" appearance (arrow) over occipital bone suggesting metastasis. Same patients MRI T2 Axial image through brain (Fig.5a) depicts well defined hyperintensity in left parietal and occipital bones, arising from both surfaces(arrow) and also extending in the extraaxial space and indenting the brain parenchyma. Fig.5b shows MRI T1 Axial image through orbit of same patient depicting a lobulated isointensity noted in left orbit pushing the deformed eyeball anteriorly and also involving the intraconal space. On MRI T2 Coronal view (Fig.5c) of same patient , there was hyperintensity mass in left parietal bone with extensions of mass seen in suprasellar region (arrow). Further images were taken from scans done for the same patient in higher center, showing (Fig.6a) FLAIR Axial image delineating the left eyeball replaced by hyperintensity mass extending into optic nerve and Contrast enhancing image (Fig.6b) depicting heterogeneous intraocular lesion replacing left eyeball. The ^{99m}Tc-MDP whole body bone scan of this patient done in higher center revealed focal area of increased radiotracer uptake noted in left parietal bone.
Fig.7a,7b and 7c show histopathology sections of 3 patients delineating multiple small round neoplastic cells arranged in sheets suggesting retinoblastoma after clinico-radiological correlation.

A total of 84.6 % of the patients underwent enucleation or exenteration was done in 7.7% of patients in at least one eye (Table 5). Even in cases when leukocoria was the only presenting symptom, 80% eyes had tumors occupying more than half of the retina. One patient did not undergo any treatment following diagnosis. All bilateral eyes received photocoagulation at the higher center in the less affected eye. Exenteration was performed in one case with extraocular involvement. In bilateral cases, the eye with the more advanced disease was treated surgically. Although all bilateral patients were referred for chemotherapy and radiotherapy, only 3 of the 5 bilateral patients (60.0 %) underwent chemotherapy, 4 (80 %) photocoagulation and 1 (20 %) radiotherapy. No patient in this study was elected to undergo cryotherapy. The patients with unilateral or bilateral retinoblastoma that had infiltrated optic nerve were referred for chemotherapy. 4 of the 5 of these patients underwent chemotherapy. Orbital extension was present in one case, and this patient underwent exenteration but did not undergo chemotherapy. One patient with unilateral retinoblastoma without optic nerve infiltration also underwent chemotherapy. This accounts for the seven unilateral patients who underwent chemotherapy.

IV. Discussion

Retinoblastoma is the most common primary intraocular malignancy in children. The tumour is highly curable when confined within coats of the eye, either by globe preserving methods [early intraocular; group A-C, international classification of retinoblastoma (ICRB)] or by enucleation (advanced intraocular; group D-E,

ICRB); thus leading to a high probability of disease free survival. Once the tumour extends through the coats of the eye, it has access to the vascular channels of the orbit and to the central nervous system through the optic nerve [15].

Retinoblastoma is bilateral in about 25 to 35% of cases [16]. In our study 5 cases (35.7%) were bilateral retinoblastoma. 57.1% of patients were male and 42.9% were female. No statistical difference occurred between the proportions of males and females who developed unilateral versus bilateral retinoblastoma ($p = 0.88$). There were no significant differences between age at presentation or duration of symptoms prior to treatment between the male and female patients ($p = 0.423$ and $p = 0.820$, respectively).

The average age at diagnosis is 18 months, unilateral cases being diagnosed at around 24 months and bilateral cases before 12 months[16]. In our study, the mean age of patients was 22. 57 ± 10.8 months , being consistent with the literature, where approximately 80% of the cases are diagnosed before the age of three or four years, on average at 24 months [17]. Majority of patients (71.4 %) in this study were less than 3 years.
Studies conducted in the USA, the UK, Switzerland and Finland stated that leukocoria is the most frequent presenting symptom, found in approximately 50-60% of cases, followed by strabismus (25%) and inflammatory signs (6-10%) [18,19] . In this study, 78.6% of infants and children presented with leukocoria, followed by red eye (42.9%), secondary glaucoma (14.3%) and strabismus (7 %). Other manifestations include blindness, and when the tumor spreads extraocularly it is often characterized by an orbital mass with proptosis, and when metastasis to the central nervous system is present, headache, vomiting, anorexia and irritability may occur. In our study, only 5 out of 14 patients (35.7%) had manifestations other than leukocoria and strabismus: anorexia, apathy, growth delay, blindness, fever, nystagmus and eye secretion.

The average duration of symptoms was 2.5 ± 3.2 months and delayed diagnosis (duration of symptoms longer than six months) was a prognostic factor for poor survival. Antoneli [20], by reviewing cases of children with retinoblastoma, demonstrated that the average duration of symptoms in these patients decreased from 7.5 months (1986-1990) to 5.3 months (1991-1995). Sixty-eight percent of these patients showed a duration of symptoms shorter than six months and had a higher rate of intraocular tumor compared to those who had a duration of symptoms longer than six months.

In developing countries, rates of ocular salvage and patient survival are low since the diagnosis is frequently made at a later stage, when extraocular dissemination (EORB) has already occurred [21-22]. Ignorance on behalf of the parents, delay in referral on behalf of the general practitioner/pediatrician and refusal of medical advice have been associated with delayed diagnosis and treatment [23-25]. In developed countries, retinoblastoma is usually diagnosed in its early intraocular stages leading to high chances for preservation of vision, globe and disease free survival of the patient. Various methods have been suggested for education of the public thus leading to early detection and a better prognosis for vision and life. Chantada [21] in his recent review on strategies to manage retinoblastoma in developing countries concluded that the priorities for management of retinoblastoma in developing countries should be opposite to that in developed nations treatment of overt extraocular retinoblastoma, that with high risk histopathological features and eye preserving conservative therapy, in decreasing order of priority.

V. Figures And Tables

Table 1: Mean age at presentation and duration of symptoms before presentation

	Male	Female	Total Average
Mean Age at Presentation (years)	21.75±9.4	22.83±13.8	22. 29±10.4
Mean Duration of Symptoms before Presentation (months)	2.3±3.2	2.7±3.2	2.5±3.2

Table 2: Distribution of gender and laterality

Gender	Laterality		
	Unilateral (n, %)	Bilateral (n, %)	Total (n , %)
Male	5 (35.7)	3 (21.4)	8 (57.1)
Female	4 (28.6)	2 (14.3)	6 (42.9)
Total	9 (64.3)	5 (35.7)	14 (100)

Table 3: Frequency of presenting symptoms with duration of symptoms

Frequency (Percent)	Leukocoria Only	Leukocoria Total	Strabismus	Proptosis	Fungating Mass	Red eye	Other
	11 (78.6)	12 (85.7)	1 (7)	4 (28.6)	1 (7)	6 (42.9)	5 (35.7)
Mean duration of presentation (Months)	1.9 ± 1.6	2.6 ± 3.5	2.0 ± NA	4.5 ± 4.5	1.0 ± NA	3.1 ± 3.5	3.2 ± 3.4

Table 4: Histo-pathological findings with duration of symptoms and age at presentation

n=13	Poorly differentiated	Well differentiated	Optic nerve affected	Optic nerve unaffected	With orbital Infiltration	Without orbital Infiltration
Frequency (percent)	7 (53.8)	6 (46.2)	5 (38.6)	8 (61.5)	2 (15.4)	11 (84.6)
Unilateral	5 (38.6)	3 (23)	3 (23)	5 (38.6)	2 (15.4)	9 (69.2)
Bilateral	3 (23)	2 (15.4)	2 (15.4)	3 (23)	0	2 (15.4)
Mean duration of symptoms (months)	3.4±4.3	1.8±1.5	4.9±4.5	1.3±1.3	7.0±7.1	2.3±2.8
Mean age at presentation (years)	2.8±1.4	1.8±1.4	3.0±1.6	1.8±1.0	3.2±0.7	2.4±1.5

Table 5: Frequency of treatments and treatment according to laterality

Laterality n=13	Treatment				
	Enucleation (n, %)	Exenteration (n, %)	Photocoagulation (n, %)	Radiotherapy (n, %)	Chemotherapy (n, %)
Unilateral	7 (53.8)	1 (7.7)	2 (15.3)	2 (15.3)	7 (53.8)
Bilateral	4 (30.7)	0	4 (30.7)	1 (7.7)	3 (23)
Total	11 (84.5)	1 (7.7)	6 (46)	3 (23)	10 (76.8)

Figure 1: Clinical picture and USG image of a 13 months old male patient with bilateral retinoblastoma (a, b, c).

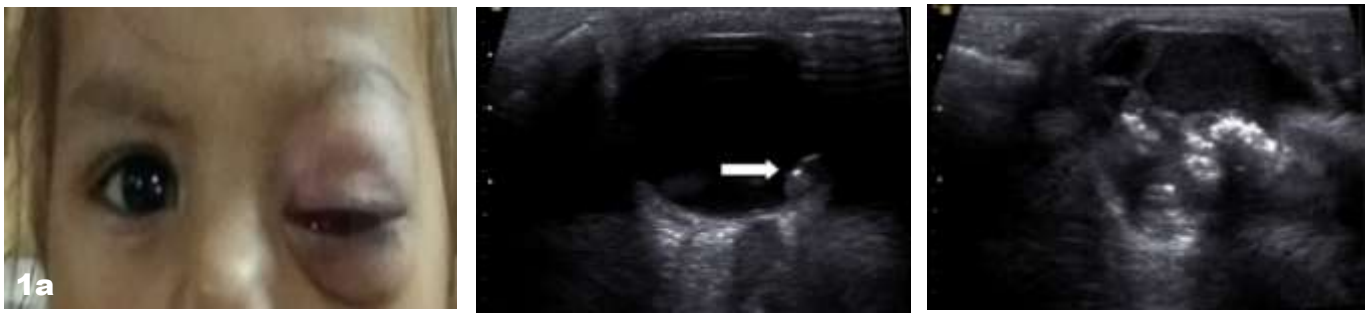


Figure 2: NCCT image of a 13 months old male patient with bilateral retinoblastoma.

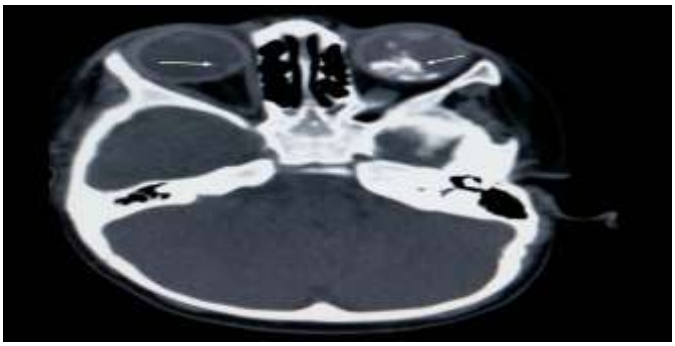


Figure 3: Clinical picture and USG image of a 33 months old female patient with unilateral (left eye) retinoblastoma.

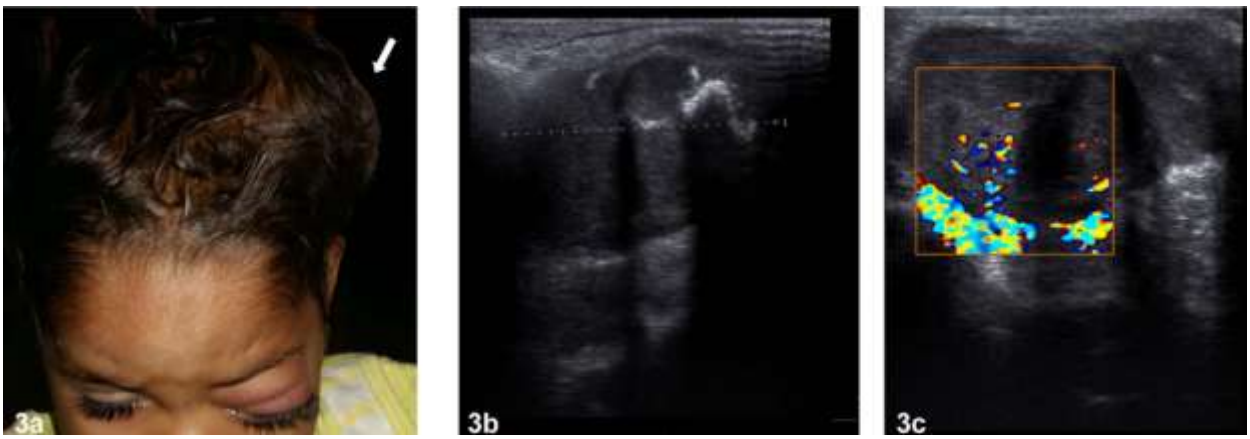


Figure 4: MRI T2 Axial and lateral view skull X-ray image of a 33 months old female patient with unilateral (left eye) retinoblastoma.

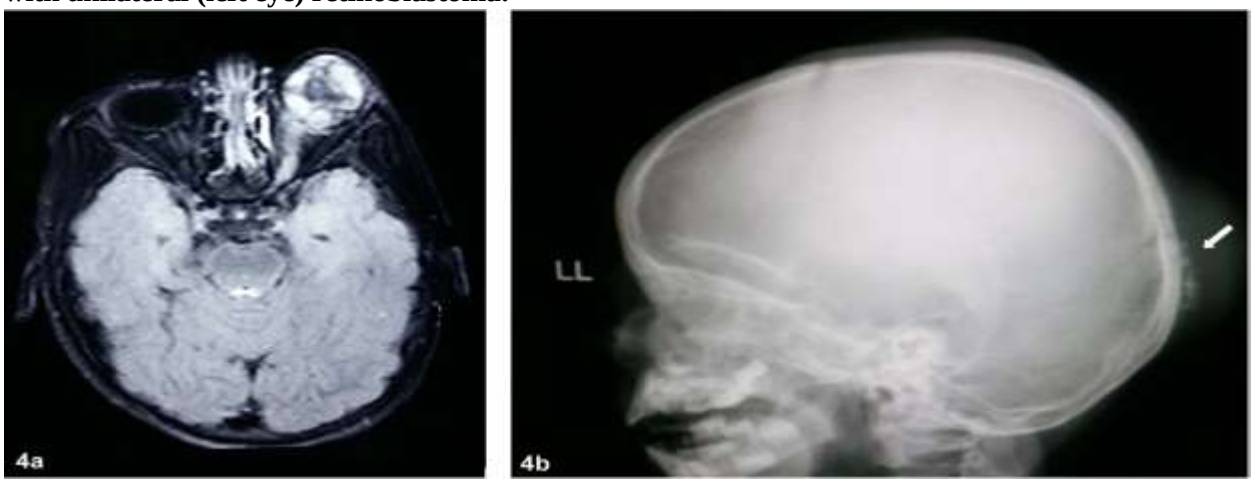


Figure 5: MRI T2 Axial image through brain, T1 Axial image through orbit and T2 Cornal view image of a 33 months old female patient with unilateral (left eye) retinoblastoma.

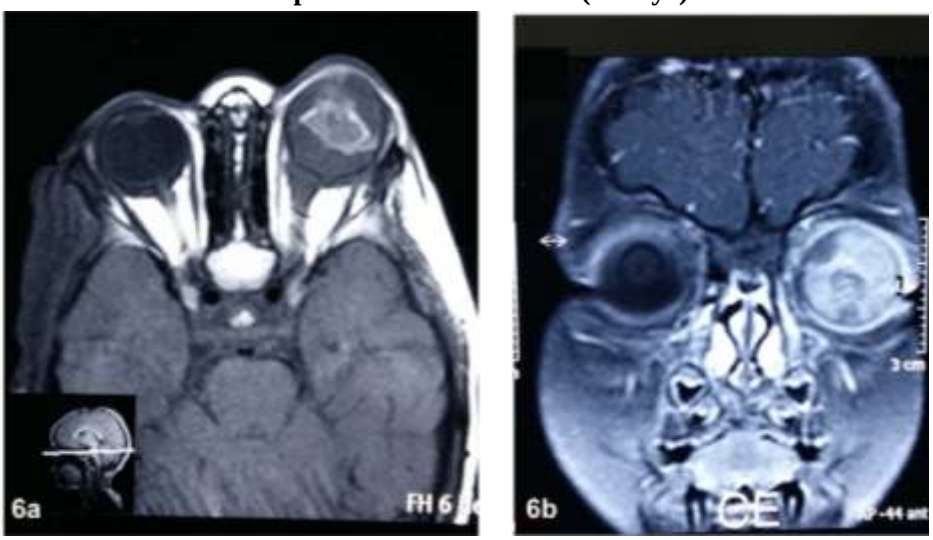


Figure 6: MRI FLAIR Axial image and Contrast enhancing image of a 33 months old female patient with unilateral (left eye) retinoblastoma.

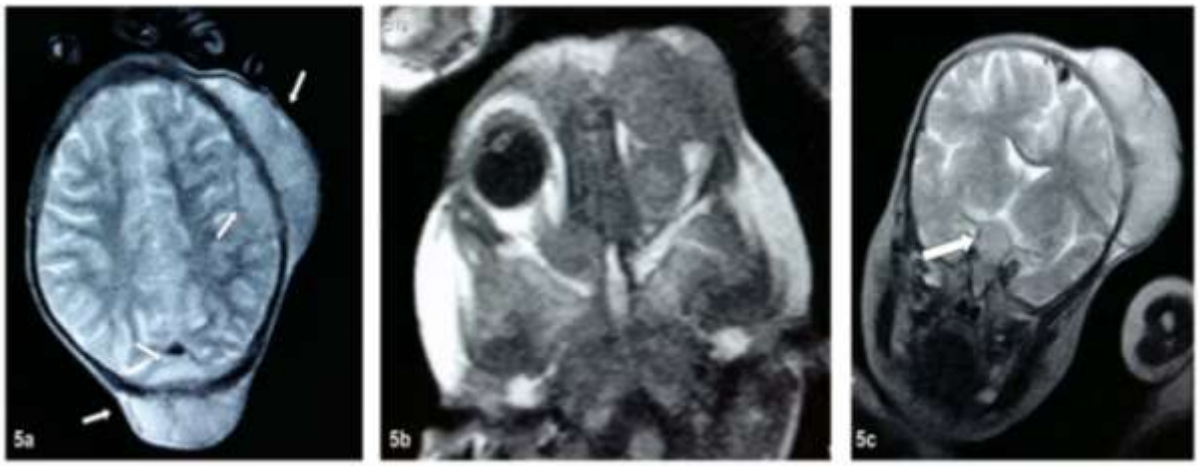
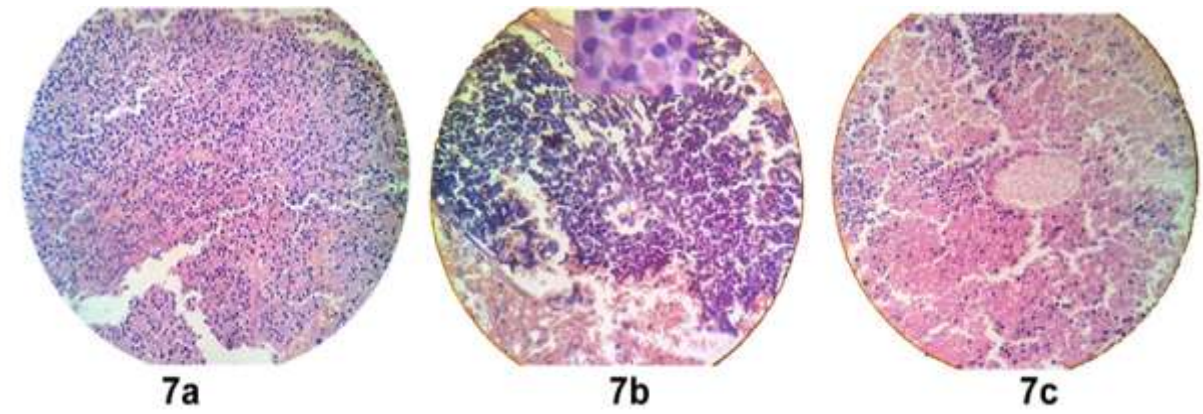


Figure 7: Histopathology section of 3 patients of retinoblastoma showing poorly differentiated small round cells (7b Closet also)



VI. Conclusion

There are very few human malignancies where definitive treatment is started without any confirmed histopathological diagnosis and imaging plays an important role in diagnosis and staging of the disease. Imaging (preferably magnetic resonance imaging) is required to confirm the diagnosis, access for local spread into the orbit through the sclera or into the optic nerve, metastasis into the central nervous system and for trilateral retinoblastoma. Chemotherapy has a variable effect on EORB, 75.0% of eyes with EORB had residual viable tumour tissue when enucleated after receiving neoadjuvant chemotherapy.

The early diagnosis of retinoblastoma is still a challenge in industrialized and in developing countries, and data by Abramson et al. [26] suggest that abnormal ocular reflex has not been investigated as recommended. Theauthors suggest that every infant/child with family history of retinoblastoma be immediately referred to a pediatric oncologist, and that every newborn infant and child with signs and symptoms such as leukocoria, strabismus, conjunctival hyperemia, proptosis, decrease in visual acuity be submitted to funduscopic examination through a dilated pupil. In addition, education programs for pediatricians, geneticists, obstetricians and ophthalmologists should be offered in order to increase the index of suspicion of retinoblastoma. Based on these facts, there is a necessity to train health professionals and inform the lay population so that they can identify the initial symptoms of retinoblastoma, especially strabismus. This may result in a larger number of cases with an early diagnosis, thus reducing the mortality of this disease.

Direct ophthalmologic visualization is most sensitive and specific for determining intraocular disease status and therapeutic response; like CT and MR imaging, such examinations typically require general anesthesia. Clinical staging includes CT and MR imaging of the orbits and brain [27]. High-resolution real-time and Doppler sonography of the orbits defines intraocular disease extent, monitors therapeutic response, and clarifies CT or MR imaging. Thus, the roles of imaging are to confirm the ophthalmologic diagnosis, determine

intra- and extraocular disease extent, and characterize tumor response [27, 28]. Assessment of optic nerve involvement and intracranial extent of disease and identification of distant metastases are particularly important in patients with retinoblastoma.

Standard therapy comprises enucleation for unilateral disease and radiation therapy with or without enucleation for bilateral disease. However, contemporary treatment for retinoblastoma is transitioning to front-line chemotherapy to improve disease control while preserving vision and minimizing adverse sequelae of enucleation and radiation therapy [29].

References

[1]. Amaoku WMK, Willshaw HE, Parkes SE, Shah KJ, Mann JR. Trilateral retinoblastoma: a report of five cases. Cancer 1996;78:858–863

[2]. Stolovitch C, Loewenstein A, Varssano D, Lazar M. Trilateral retinoblastoma. Metab Pediatr Syst Ophthalmol 1992;15:57–59

[3]. T. Kivela, "The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death," British Journal of Ophthalmology, vol. 93, no. 9, pp. 1129–1131, 2009.

[4]. . A. Dyer and R. Bremner, "The search for the retinoblastoma cell of origin," Nature Reviews Cancer, vol. 5, no.2,pp. 91–101, 2005.

[5]. H. Dimaras, K. Kimani, E. A. Dimba et al., "Retinoblastoma," Lancet, vol. 379, no. 9824, pp. 1436–1446, 2012.

[6]. E. M. Chung, C. S. Specht, and J. W. Schroeder, "From the archives of the AFIP: pediatric orbit tumors and tumor like lesions: neuroepithelial lesions of the ocular globe and optic nerve," Radiographics, vol. 27, no. 4, pp. 1159–1186, 2007.

[7]. G. Chantada, F. Doz, and C. B. G. Antoneli, "A proposal for an international retinoblastoma staging system," Pediatric Blood & Cancer, vol. 47, no. 6, pp. 801–805, 2006.

[8]. P. Galluzzi, T. Hadjistilianou, A. Cerase, S. De Francesco, P. Toti, and C. Venturi, "Is CT still useful in the study protocol of retinoblastoma?" American Journal of Neuroradiology, vol. 30, no. 9, pp. 1760–1765, 2009.

[9]. H. J. Brisse, L. Lumbroso, P. C. Fréneaux et al., "Sonographic, CT, and MR imaging findings in diffuse infiltrative retinoblastoma: report of two cases with histologic comparison," American Journal of Neuroradiology, vol. 22, no. 3, pp. 499–504, 2001.

[10]. B. G. Mohney, D. M. Robertson, P. J. Schomberg, and D. O. Hodge, "Second nonocular tumors in survivors of heritable retinoblastoma and prior radiation therapy," American Journal of Ophthalmology, vol. 126, no. 2, pp. 269 277, 1998. prior radiation therapy," American Journal of Ophthalmology, vol. 126, no. 2, pp. 269–277, 1998.

[11]. D. L. Friedman, B. Himelstein, C. L. Shields et al., "Chemoreduction and local ophthalmic therapy for intraocular retinoblastoma," Journal of Clinical Oncology, vol. 18, no. 1, pp. 12–17, 2000.

[12]. C. B. G. Antoneli, K. C. B. Ribeiro, F. Steinhorst, P. E. R. S. Novaes, M. M. Chojniak, and M. Malogolowkin, "Treatment of retinoblastoma patients with chemoreduction plus local therapy: experience of the AC Camargo Hospital, Brazil," Journal of Pediatric Hematology/Oncology, vol. 28, no. 6, pp. 342–345, 2006.

[13]. S. J. Smith, J. S. Pulido, D. R. Salomão, B. D. Smith, and B. Mohney, "Combined intravitreal and subconjunctival carboplatin for retinoblastoma with vitreous seeds," The British Journal of Ophthalmology, vol. 96, no. 8, pp. 1073-1077, 2012.

[14]. C. L. Shields, J. A. Shields, J. Cater, I. Othmane, A. D. Singh, and B. Micaily, "Plaque radiotherapy for retinoblastoma: long-term tumor control and treatment complications in 208 tumors," Ophthalmology, vol. 108, no. 11, pp. 2116–2121, 2001.

[15]. Finger PT, Harbour JW, Karcioglu ZA. Risk factors for metastasis in retinoblastoma.Surv Ophthalmol 2002;47(1):1-16

[16]. Shields JA, Shields CL. Intraocular tumors – A text and Atlas. Philadelphia, PA, USA, WB Saunders Company, 1992.

[17]. Hurwitz RL, Shields CL, Shields JA, Chévez-Barrios P, Hurwitz MY, Chintagumpala MM. Retinoblastoma. In: Pizzo PA, Poplack DG, editors. Principles and Practice of Pediatric Oncology. 4th ed. Philadelphia: Lippincont-Raven; 2003. p. 825-46.

[18]. Abramson DH, Frank CM, Susman M, Whalen MP, Dunkel IJ, Boyd NW. Presenting signs of retinoblastoma. J Pediatr.1998;132:505-8.

[19]. Bedford MA, Bedotto C, Macfaul PA. Retinoblastoma. A study of 139 cases. Br J Ophthalmol. 1971;55:19-27.

[20]. Antoneli CBG. Retinoblastoma: análise da evolução clínica de pacientes portadores de retinoblastoma submetidos a tratament multidisciplinar [tese]. São Paulo: Universidade de São Paulo; 1999.

[21]. Chantada GL, Qaddoumi I, Canturk S, Khetan V, Ma Z, Kimani K, Yeniad B, Sultan I, Sitorus RS, Tacyildiz N, Abramson DH. Strategies to manage retinoblastoma in developing countries.2011;56(3):341-348

[22]. Canturk S, Qaddoumi I, Khetan V, Ma Z, Furmanchuk A, Antoneli CB, Sultan I, Kebudi R, Sharma T, Rodriguez-Galindo C, Abramson DH, Chantada GL. Survival of retinoblastoma in less-developed countries impact of socioeconomic and health-related indicators. 2010;94(11):1432-1436

[23]. Chantada GL. Retinoblastoma: lessons and challenges from developing countries. Ellsworth Lecture 2011. 2011;32(4):196-203

[24]. Sitorus RS, Moll AC, Suhardjono S, Simangunsong LS, Riono P, Imhof S, V鮭lker-Dieben HJ. The effect of therapy refusal against medical advice in retinoblastoma patients in a setting where treatment delays are common.2009;30(1):31-36

[25]. Chantada G, Fandi舸o A, Manzitti J, Urrutia L, Schvartzman E. Late diagnosis of retinoblastoma in a developing country. 1999; 80(2):171-174

[26]. Abramson DH, Beaverson K, Sangani P, Vora RA, Lee TC, Hochberg HM, et al. Screening for retinoblastoma: presenting signs as prognosticators of patient and ocular survival. Pediatrics. 2003;112(6 Pt 1):1248-55.

[27]. Kaufman LM, Mafee MF, Song CD. Retinoblastoma and simulating lesions: role of CT, MR imaging and use of Gd-DTPA contrast enhancement. Radiol Clin North Am 1998;36:1101–1117

[28]. Remit FG, Slovis TL, Baker JD. Orbital sonography in children. Pediatr Radiol 1996;26:245–258

[29]. Pratt CB. Use of chemotherapy for retinoblastoma. Med Pediatr Oncol 1998;31:531–533