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Original Research Article

Retinoblastoma – Typical and atypical clinical manifestations presented at tertiary eye care centre

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ABSTRACT

Aim: Purpose is to study the various typical and atypical manifestations of the retinoblastoma presented to our department.
Study Design: Prospective study.
Duration of the Study: 2 years, January 2020 to December 2021.
Methodology: All children presented with various signs and symptoms and cases with tumour suspicious manifestations were evaluated. Detailed birth history from parents, slit lamp examination, indirect ophthalmoscopy, B Scan, CT Scan Orbit (plain and contrast), MRI Orbit (plain and contrast) when tumour extension was suspected and documentation done in all cases.
Results: Atypical manifestations requires proper evaluation to exclude Pseudo retinoblastomas. Many clinical conditions will masquerade the tumour and cause confusion in diagnosis. Pseudo retinoblastomas which reported in our study were commonly PHPV and Coats disease. One case of Retinoblastoma was also presented like Ocular cysticercosis with inflammatory signs in anterior and posterior segment, oral steroids were given, vitreous seeds which were present in anterior chamber disappeared after steroids and fundus showed creamish white lesion filling the entire vitreous cavity. Masquerades will cause delay in the diagnosis, which can lead to extension of tumour.
Conclusion: Diagnosis is not easy, most of the times in children particularly when media is not clear, delay in diagnosis may require enucleation where globe salvage may not be possible, sometimes intracranial extension of the tumour will increase the mortality.

1. Introduction

Retinoblastoma is the most common primary intraocular tumour of childhood. Accurate diagnosis at an early stage is very important for the patient survival, globe salvage and visual acuity. Retinoblastoma can be heritable or non heritable, one in 15,000 live births is affected. Unilateral and bilateral presentations are seen, in our study two-thirds of cases were unilateral, one third of the patients presented with bilateral presentation. Single large tumour or multiple small tumours were reported. Analysis of cancer related genes helps in early detection of the tumour and also predicts the risk of other associated cancers. Now a day there is increase in number of the cases with atypical manifestations probably due to COVID-19 or environmental pollution.

White reflex in the eye is always not retinoblastoma, Retinoblastoma always will not present as white reflex in the eye. Common tumour in children. Though we have many management options today, in developing countries like India most of the children requires enucleation due to extended tumour. Delayed presentation is common in India. We like to present the typical and atypical manifestations of retinoblastoma which were reported in our institute

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during the two years' duration. Diagnosis of retinoblastoma requires meticulous workup. Studies from India showed a two- to three-fold higher incidence of tumours of the eye (majority of which will be retinoblastoma in children).[1]

Most of the retinoblastoma cases arise in Asia (53%), followed by Africa (29%), Latin America (8%), North America (3%), and Europe (6%).[2] Poverty, illiteracy and lack of facilities to higher centres is responsible for this high rate of advanced disease in developing countries.[3] Apart from clinical examination like indirect ophthalmoscopy, Imaging and B Scan are novel methods to identify the tumour.

In this article we want to present the various typical and atypical clinical manifestations of retinoblastoma, demographic profile of the patients presented to our institute.

2. Materials and Methods

All children presented with various manifestations underwent detailed examination. Apart from birth history other ocular and systemic examination done. Fundus examination in fully dilated pupils, B Scan, CT Scan Orbit done in all cases where tumour was suspected. MRI Orbit done when required to exclude extra ocular extension. Documentation done in all cases to check for the prognosis of tumour.

Prospective study done, patients presented to retina department from January 2020 to December 2021 were studied in detail for 2years.

3. Results

Pseudo retinoblastomas are common in that age group, confusion in diagnosis is due to masquerades which will delay the confirmation of diagnosis, child may require enucleation due to extension of the tumour. Chances of globe salvage will be reduced due to delayed diagnosis, if workup is insufficient removal of eyeball due to pseudo retinoblastoma will cause damage to the child. Meticulous workup for protection of child eye and health care is very important. Survival rate in low income countries is reported to be 40% and upper, middle income countries 79%.

4. Discussion

Pawius in 1597 described retinoblastoma tumour as fungus hematodes and advised enucleation as the primary mode of management. The discovery of ophthalmoscope in 1851 helped in describing the clinical features of retinoblastoma. Initially it was thought to be derived from the glial cells, it was called a glioma of the retina by Virchow (1864). Flexner (1891) and Winter Steiner (1897) believed it to be a neuroepithelioma because of the presence of rosettes. Later it was thought that tumour originated from the retinoblasts and the American Ophthalmological Society officially accepted the term retinoblastoma in 1926.

Cumings and Sorsby suggested that the histological difference is noted in unilateral and bilateral presentation, unilateral cases originated from the outer nuclear layer of the retina whereas bilateral cases had extensive diffuse origin.

Retinoblastoma originates in a photoreceptor cell of the retina and is associated with a mutation in the RB1 gene.

In our study we want to describe the various clinical presentations of retinoblastoma in children.

Total number of cases presented with tumour suspicious manifestations during two years' period were 21 cases, 16 patients were finally confirmed as cases of Retinoblastoma after proper evaluation. Remaining 5 cases were Coats disease, PHPV and Retro lental fibroplasia. Out of 16 cases male children were 13 cases and female children were.[3]

The Indian Council of Medical Research (ICMR) has reported a rise in the incidence of retinoblastoma cases in several hospital-based cancer registries in India. In South India our institute is a tertiary eye care centre where referrals from many surrounding neighbouring states patients were reported. According to other studies in India mortality is high with 24% due to advanced stage presentation.

Usually heritable retinoblastomas manifest before 3 years of age, between 18 months to 3 years, they are bilateral, in our study heritable retinoblastomas reported only in one child with bilateral presentation and family screening revealed isolated solitary tumours in both eyes of mother in the mid periphery. Though bilateral presentation noted in three children, family screening revealed one parent with both eyes retinoblastoma. Familial Retinoblastomas requires screening from birth to till the age of 4 years, after 4 years of age risk of retinoblastoma is reduced because it is tumour which develops from primitive retinal cell, these cells disappear after birth, retinoblastoma rarely arises at an older age.

A small incidence probably about 5 to 10% of all cases of sporadic unilateral affection, are in fact incompletely expressed germinal mutations for bilateral retinoblastoma.[4]

Retinoblastoma originates in the retinal tissue can present as endophytic tumour in the vitreous cavity or exophytic tumour into the sub retinal space, sometimes can present as diffuse infiltrative growth in the peripheral retina. Most of the times both endo and exophytic growth seen which causes exudative retinal detachment with vitreous and sub retinal tumour seeding.

4.1. Atypical manifestations of retinoblastoma

The term "diffuse infiltrating retinoblastoma" was introduced by Ashton (1958) to describe a form of retinoblastoma which did not produce a tumour mass within the retina.[5]

Diffuse infiltrating retinoblastoma is one clinical presentation seen in 2% of all retinoblastoma cases

presenting as a flat infiltration of the retina, with small tumoral mass. Diffuse spread of tumour cells in the vitreous, iris, trabecular meshwork and anterior chamber often occurs. Usually presents plaque like lesion which lacks calcification.

The clinical presentation of diffuse infiltrating retinoblastoma may mimic intraocular inflammation: the main clinical presentation was redness, vision reduction and pain. The most common clinical signs were vitreous cells, pseudo hypopyon and an increased intraocular pressure of more than 21 mm Hg. I want to describe one case which was diffuse infiltrating type presented in 5 years old girl with inflammatory signs in left anterior chamber, vitreous seeding's in anterior chamber on iris, (Figure 1) pseudo hypopyon, media was not clear due to anterior chamber inflammation, b scan revealed low to medium dense dot like echoes completely filling the vitreous cavity with no calcification. CT Scan done to exclude the retinoblastoma, but radiological imaging was not much informative, so planned to observe thinking that ocular toxocariasis, started on anti-helminthic drugs and oral steroids after paediatrician opinion, patient reviewed after 4 weeks, all the anterior inflammatory signs along with vitreous seeding's were disappeared but fundus still not visible due to vitritis, patient lost follow up due to some tragic incident in her family, reported back after 10 months with complaints of pain, again imaging repeated, b scan showed optic nerve infiltration, enucleation planned in addition to systemic chemotherapy.

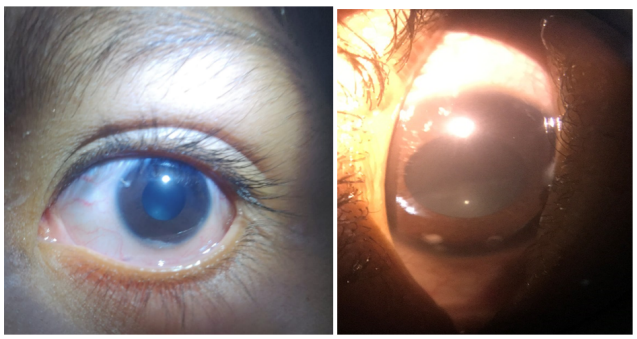

Fig. 1: Vitreous seeding's in anterior chamber

Leukocoria is the most common presenting sign and is seen in the majority of cases (56%), followed by strabismus (24%). Retinoblastoma masquerading uveitis or endophthalmitis vitreous seeding's in anterior chamber is atypical manifestation which is noted in our patient, diagnosis is delayed in this case due to atypical presentation or is it coexisting with ocular toxocariasis. Serological test revealed raised IgG and IgM values for toxocara. Previous studies reported co-existence of retinoblastoma with ocular toxoplasmosis,[6] we are reporting first case where there is co-existence of retinoblastoma with other parasite that is Toxocariasis.

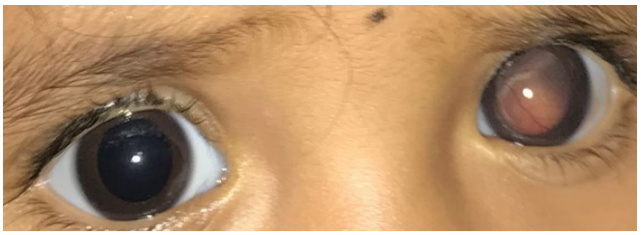

Fig. 2: LE shows retro lental mass lesion with intra lesional blood vessels

Toxocariasis is a parasitic chorio retinitis seen in children between the ages of 6 and 12 years, with a female predominance. It is usually unilateral and presents as intra retinal granulomas, lesions of the vitreous and retinal detachment. CT Scan and MRI images (plain and contrast) shows enhancement of the granulomas which looks like retinoblastoma.[7] Any tumour like lesion with inflammatory signs not responding to anti-inflammatory therapy should be considered seriously for further evaluation to exclude retinoblastoma in children.

We want to describe one more atypical manifestation of retinoblastoma in 13-year-old boy, suddenly presented with pain, protrusion of eyeball, redness, loss of vision in right eye, visual field defect in left eye, local ophthalmologist referred to higher centre, because of age and eccentric proptosis provisionally diagnosed as rhabdomyosarcoma, B Scan showed echogenic mass lesion with few high dense echoes in the lesion with after shadow effect suggestive of calcification, Visual fields of left eye advised to document the field defect.

4.2. Clinical, MRI and histological pictures of the eye ball

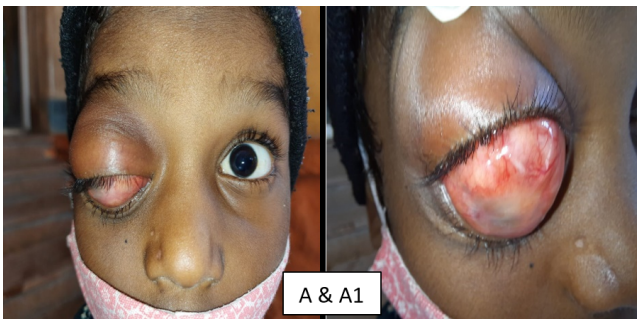

Fig. 3: Clinical photos A & A1 of the patient showing RE Proptosis

Retinoblastoma in older children is probably due to the persistence of embryonal retinoblasts, or reactivation of the tumour from previously spontaneously arrested tumour. Genetic abnormalities in older children are more complex when compared to younger children. Presentation

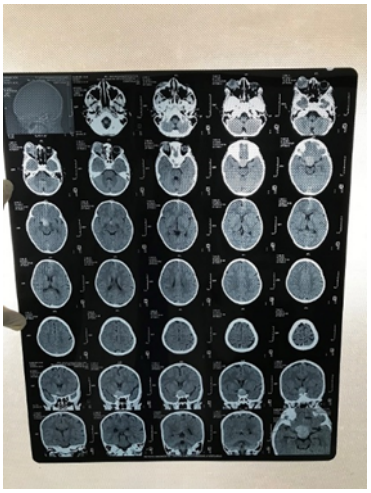

Fig. 4: MRI showing mixed density lesion from the sellar and supra sellar aspect with hyper dense areas, indenting over the brain stem with lesion causing changes along the infundibulum and optic nerve invasion and extending along the intra conal aspect of the right globe. Diffuse altered contour of the globe with protrusion of the eyeball, soft tissue peri orbital swelling, diffuse retro lental calcifications, hypo dense areas along the vitreous distortion of eyeball, no bony erosions noted, rest of the orbit is normal

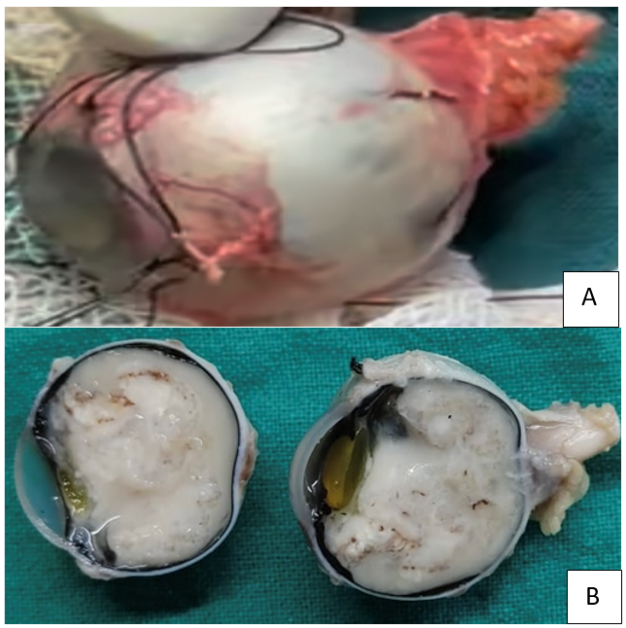

Fig. 5: A): Image is enucleated globe with long optic nerve stump; **B: I**mage show tumour involving the entire globe

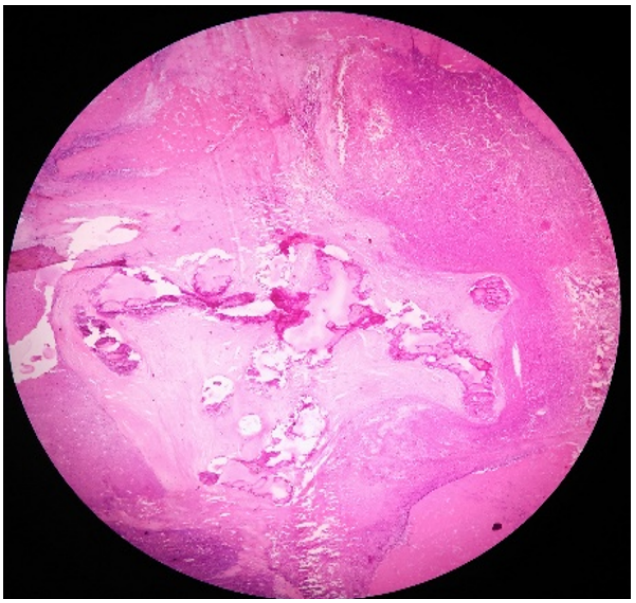

Fig. 6: HPE report 10x magnification round tumour cells suggestive of undifferentiated tumour, dark pink is the tumour tissue, light pink area is necrotic tissue with cluster of calcification

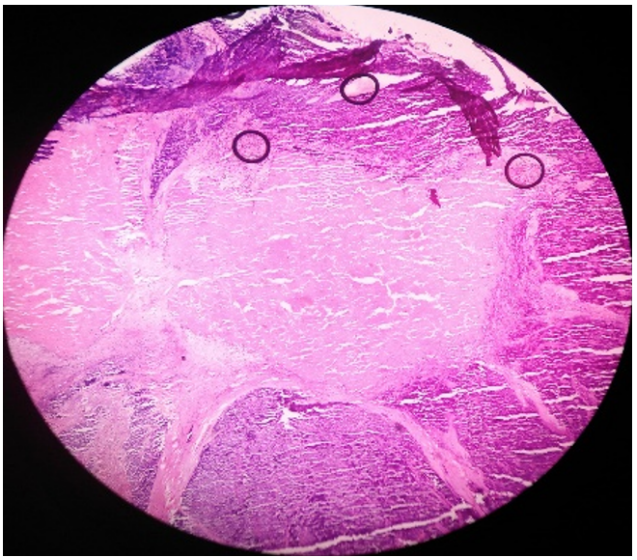

Fig. 7: 40x shows no fluorettes and rosettes, black circles are artefacts

in older children is different, may present like uveitis, orbital cellulitis, vitreous haemorrhage and neo vascular glaucoma.[8]

Role of MRI has become important tool to detect the growth pattern of the tumour, extension of the tumour, the involvement of the optic nerve and retro bulbar space, the presence of leptomeningeal spread or the existence of a second tumour[9] usually there is median delay of 21 months from the time of the initial diagnosis of the retinoblastoma

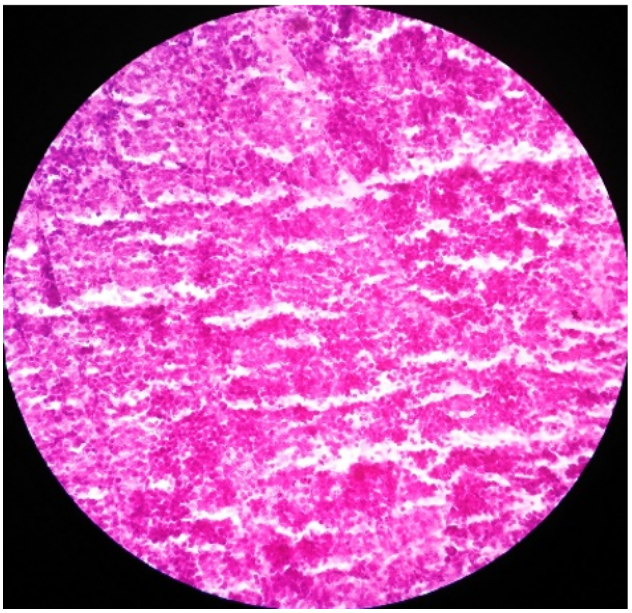

Fig. 8: Tumour tissue arranged in sheets consisting of small round blue cells with scant cytoplasm, hyper chromic nuclei, areas of dystrophic calcification, large areas of tumour necrosis seen, optic nerve infiltrated with tumour tissue, peri vascular infiltrates noted. HPE suggestive of Retinoblastoma

to identification of pineal or suprasellar involvement.[9] Advantages of MRI are many and also no risk of radiation exposure.

In older children retinoblastoma is misdiagnosed because of the rarity, they present with unusual clinical findings where diagnosis will become difficult and challenging. According to literature 3.5% to 8.5% cases diagnosed as retinoblastoma in older children. Risk of misdiagnosis is due to presentation after 5 years, other clinical manifestations like coats disease and PHPV. 17 to 31% children of retinoblastoma are misdiagnosed in older children due to age and unusual clinical manifestations.[10]

Older age retinoblastoma forms a significant percentage of retinoblastoma in developing countries, is misdiagnosed in one-third of cases, and may present at an advanced stage in 46% of cases.[11]

Calcification is one of the diagnostic marker in Retinoblastoma, calcification depends on the calcium content of the tumour, after necrosis calcification of the tumour occurs, sometimes calcification is not seen, may be extensive exudative retinal detachment or due to low calcium content of the tumour, B Scan is very sensitive in picking the calcification specks, if not detected on B Scan, CT Scan of orbit can be ordered. Other conditions where calcification seen are coats disease, Optic nerve meningioma and retrolental fibroplasia(RLF).

One more variant of retinoblastoma reported in child of 4 years, male child presented with leucokoria, fundus revealed part of the fundus is white in colour and inferior part of the fundus showed red glow, B Scan showed multiple membranous configuration with different reflective densities and multiple cyst with in membranes noted, provisionally diagnosed as PHPV, CT Scan orbit was advised to exclude multi branching configuration type of retinoblastoma.

One male baby of age 3 years presented with retro lental white lesion with part of the fundus visible as red glow with no proper details, on B Scan closed funnel retinal detachment seen with low dense echoes in vitreous cavity, CT scan orbit reveal.

Ultrasound and CT scans should be the first line of investigations. Ultrasonography cannot help to distinguish retinoblastoma from Coats' disease which presents as massive sub retinal exudation from leaking telangiectatic retinal blood vessels.[12]

Various imaging modalities are available today for diagnosis but still histopathology is gold standard method where final confirmation of diagnosis will be possible, patients with coats disease, PHPV and other masquerades need to be evaluated properly to plan the management.

Localised ocular inflammation in older children should always suspect retinoblastoma, it is typically unilateral and sporadic, it occurs in a single somatic cell which becomes malignant. Karciogluetal found both clinical and histopathologic features were atypical in older children which showed Flexner winter Steiner differentiation albeit fewer than would in younger patients.[13]

5. Conclusion

All children when present with signs of inflammation, meticulous workup is required to exclude retinoblastoma, children above five years show rare presentation of retinoblastoma with atypical manifestations, these children should be followed frequently, every visit thorough proper ocular examination helps in early diagnosis and management. Coats like response is common presentation in most of the cases, this will cause confusion and diagnosis becomes difficult. Children with no view of the posterior pole due to hyphaema in cases of trauma may have occult retinoblastoma which can be missed.[14] Retinoblastoma must be considered in the differential diagnosis for any intraocular disease in all age group of children for early diagnosis and management.[15] Atypical presentation usually associated with advanced disease.

Though we have many imaging modalities today in this era, still diagnosis of retinoblastoma is not simple. Every child requires proper and detailed evaluation to reduce the risk of morbidity and mortality.

6. Abbreviation

RB: Retinoblastoma, PHPV: Persistent Hyperplastic Primary Vitreous, RLF: Retrolental Fibroplasia.

7. Ethical Approval

The study received ethical clearance from the Osmania Medical College ethics committee /Sarojini Devi Eye Hospital, Hyderabad, Telangana State.

8. Source of Funding

None.

9. Conflict of Interest

The authors declare that they have no conflict of interest.

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