Retinoblastoma

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INTRODUCTION

Retinoblastoma is the commonest intraocular malignancy of infancy and childhood. It occurs most often before the age 3 years [1-3]. It is approximately 4% of all pediatric malignancies. It is estimated that 250 to 300 new cases of retinoblastoma are diagnosed in the United State each year, and 5,000 cases are diagnosed worldwide. The development of the ophthalmoscope, general anesthesia, and surgical enucleations has improved prognosis so that survival rates currently exceed 90% in most industrialized countries, as opposed to 50% survival in other parts of the world [4,5].

EPIDEMIOLOGY

There is no predisposition for retinoblastoma by race or gender. The right and left eye are affected equally. About two thirds of all cases are unilateral and one third are bilateral. The incidence of retinoblastoma worldwide ranges from 1 in 14,000 live births to 1 in 34,000[4]. There are no concrete records found for Africa and most especially Nigeria. A recent study in Ile-Ife gave a hospital incidence of 0.3%, Osahon and co 0.08% in Benin, [6] Kodinlinye in university college hospital (UCH) Ibadan as 0.5%.[7]

MOLECULAR/GENETIC BASIS

Retinoblastoma is a disease caused by the mutation of the gene known as the "RETINOBLASTOMA TUMOUR SUPPRESSOR GENE" (*RB1).* The retinoblastoma gene is located on the long arm of chromosome 13 (13q14), and it is the first human cancer suppressor gene to be completely characterized. Retinoblastoma tumour suppressor gene (*RB1*) is a tumour suppressor gene that regulates cell division. It is a large 4.73 kilobases message. An intact gene protects against expression of retinoblastoma. It is believed that the gene is a recessive suppressor gene and may play a role in cell growth and development. In order for retinoblastoma to develop, both copies of the gene at the 13q14 locus must be lost, deleted, mutated, or in activated. If either the maternal or paternal copy of the gene that is inherited by an individual is defective, then that individual is heterozygous for the mutant allele. In the two step inactivation mechanism (Knudson's hypothesis) [8,9], the first mutation, inherited via a germ cell, is present in all somatic cell and second mutation occur in the same somatic cell, leading to the disease; this form is hereditary. If both mutations occur in the same somatic cell the disease is non hereditary. Retinoblastoma gene inactivation is due to chromosomal deletion, single nucleotide alteration, micro deletion, loss of heterozygosity, or methylation of the promoter region. Usually allele with premature termination of coding sequence lead to complete penetrance and bilateral retinoblastoma, while missense alterations, substitution in the promoter region and some splice-site mutations cause incomplete penetrance and reduced expressivity. In bilateral retinoblastoma patients most of the mutations results in truncated gene product and such patients on an average have more than three tumours per eye.

There is an association of neuroblastic intracranial malignancy in patients with hereditary form of retinoblastoma, most often manifesting as pineoblastoma or other parasellar tumours [10]. The pineoblastoma is identical to retinoblastoma from an embryologic and pathologic standpoint [10-13]. This association of midline intracranial pineal tumours and suprasellar/parasellar neuroblastic tumours with bilateral retinoblastoma has b*l retino*[14]

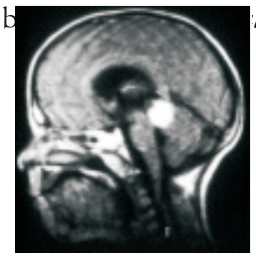

Fig.1: Aspect of trilateral Retinoblastoma (MRI)

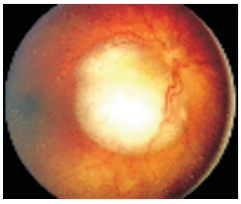

Fig. 2: Ocular fundus aspect of Retinoblastoma

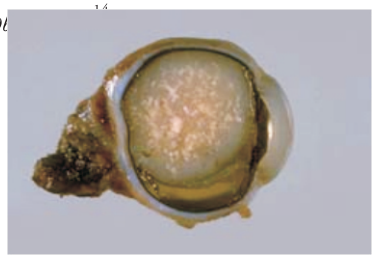

Fig3.: Gross sagittal section showing whitish Calcium flecks

Fig. 4: Leukoria

CLINICAL PRESENTATION

The clinical manifestation of retinoblastoma vary with the stage of the disease at the time of recognition.

- In its earliest clinical stage, a small retinoblastoma is less than 2mm in basal dimension appears ophthalmoscopically as a subtle, transparent or slightly translucent lesion in the sensory retina [1, 2].(figure 2)
- Slightly larger tumours lead to dilated retinal blood vessel that feed and drain the tumour.
- Some larger tumours show foci of chalk-like calcification that resemble cottage cheese. (figure 3)
- Leukoria is the commonest presentation in developed countries. Any retinoblastoma of any size can produce leukoria. This white pupillary reflex is a result of reflection of light from the white mass behind the lens.(figure 4)
- Strabismus; this is known as crossed eyes, may occur due to visual loss in the affected eye.
- Decreased vision.
- Spontaneous hyphema (blood in the anterior chamber of the eye) is found as a presentation in advanced tumours.
- Secondary glaucoma.
- Chronic inflammation.
- Proptosis and fungating orbito-ocular tumour is very common in developing countries like Nigeria- due to delayed presentation.

Other features that can be related with retinoblastoma due to deletion of chromosome 13q include[13,14]; microcephaly, broad prominent nasal bridge, hypertelorism, microphthalmos, epicanthus, ptosis, protruding upper incisors, micrognathia, short neck with lateral folds. Large, low-set ears, facial asymmetry, imperforate anus, genital malformations, perineal fistula, hypoplastic or absent thumbs, toe abnormalities, and psychomotor and mental retardation. The midface of patients with 13q deletion is notable for prominent eyebrows, broad nasal bridge, large mouth, bulbous tipped nose, and thin lip[17, 18].

CLASSIFICATION

Retinoblastoma is generally classified in three different ways: familial or sporadic, bilateral or unilateral, and heritable or nonheritable [15]. Clinically, the first two classification schemes are mostly used[16]. Thus, a case may be classified as unilateral sporadic, bilateral sporadic, unilateral familial, or bilateral familial. About two thirds of all cases are unilateral and one third are bilateral.

Genetically, it is simpler to discuss with the latter classification of heritable or nonheritable. The three classification scheme, however, are interrelated. It is recognized that bilateral and familial retinoblastoma are caused by a germ line mutation and are thus a heritable tumour. Unilateral sporadic retinoblastoma is usually not heritable. However, it is estimated that approximately 10% to 15% of children with unilateral sporadic retinoblastoma have a germ line mutation[15].

DIAGNOSIS AND INVESTIGATION

- Accurate diagnosis in a child with suspected retinoblastoma is accomplished by taking a detailed history, physical evaluation, external ocular examination, slit lamp biomicroscopy, and binocular indirect ophthalmoscopy with scleral indentation. Examination under anesthesia of both eyes to investigate bilateral involvement may be performed in the office in older children to determine precisely the number and location of all tumours. The diagnosis is established by the classic appearance of the retinal tumours by an experienced examiner[19].
  - Needle biopsy confirmation is rarely, if ever, necessary.
  - Ancillary diagnostic studies can be helpful in confirming the diagnosis of retinoblastoma.
  - Fluorescein angiography shows early vascularity and late hyperfluorescence 0f the tumor.
  - Ultrasonography and computed tomography can demonstrate the intraocular tumour and detect calcium within the mass. Approximately 5% to 10% of retinoblastomas show no intrinsic calcification.
  - Magnetic resonance imaging does not usually detect calcium but may be of value in the assessment of the optic nerve, orbit, and brain. (figure 1)
  - Optic coherence tomography has been found useful in the detection of cystic retinoblastoma that might show less dramatic response to chemotherapy, and it is also helpful in the follow-up of patients to assess macular anatomy.
  - Genetic and DNA analysis.[19,20]

MANAGEMENT AND TREATMENT

The most important objective in the management of a child with retinoblastoma is survival of the patients, and the second most important goal is preservation of the globe. The focus on visual acuity comes later, after safety of the patient and globe is established. Therapy is tailored to each individual case and based on the overall situation,

include threat of metastatic disease, risk for second cancers, systemic status, laterality of the disease, size and location of the tumour(s), and estimated visual prognosis. The currently available treatment methods for retinoblastoma include;

- Intravenous chemoreduction (sometimes combined with subconjunctival chemoreduction).
- Thermotherapy.
- Cryotherapy.
- Laser photocoagulation.
- Plaque radiothaerapy.
- External beam radiotherapy.
- Enucleation.
- Orbital exenteration.
- And adjuvant systemic chemotherapy.[1,2,21]

In recent years, eyes with unilateral retinoblastoma are generally managed with enucleation, for bilateral retinoblastoma, chemoreduction is utilized in most cases unless there is extreme asymmetric involvement, with one eye having advanced disease necessitating enucleation while the other eye has minimal disease, treatable with focal methods. Most children with bilateral retinoblastoma are treated with chemoreduction for at least one of their two involved eyes. Chemoreduction with focal therapy has been very successful in terms of globe preservation and survival of the child in developed countries. However, enucleations, exenteration with chemotherapy and radiotherapy or palliation have remained the options of therapy for fungating orbito-ocular tumours in developing countries.

DIFFERENTIAL DIAGNOSIS

A number of ocular disorders in infants and children can clinically resemble retinoblastoma [22]. Despite the classic appearance of retinoblastoma, nearly 50% of patients diagnosed initially with possible retinoblastoma prove, on referral to ocular oncologist, to have simulating conditions and not retinoblastoma [20]. The most common pseudoretinoblastoma include, persistent hyperplastic primary vitreous, coats' disease, ocular toxocariasis and endophthalmitis. Therefore, it is important that the diagnosis of retinoblastoma be established without question prior to beginning treatment. Others would be retinopathy of prematurity, coloboma, combined hamartoma amongst others.

CONCLUSION

Since retinoblastoma proves to be a challenge both to diagnose and to treat, it is important for the clinician to take into consideration some important factors; first clearly establish the correct diagnosis before embarking on therapy. Some factors that need to be considered in management include; patient's age, tumour laterality, size, location, and extent, and anticipated visual prognosis visual prognosis. It is also good to note that methods of chemotherapy have changed the approach to retinoblastoma in recent years and have permitted many children to maintain their eye(s) and avoid external beam radiotherapy. Enucleation still proves to be useful for advanced tumor[19].

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