Retinoblastoma – to expand awareness

We need to be more aware of retinoblastoma.

ROSALIND D WAINWRIGHT, *FCP (Paeds)*
Registered Paediatric Oncologist, Head of Paediatric Haematology / Oncology, Chris Hani Baragwanath Hospital, University of the Witwatersrand, Johannesburg

Rosalind Wainwright has a special interest in Fanconi's anaemia and retinoblastoma and, with Professor M Kruger, has been attempting to establish a national retinoblastoma protocol.

Correspondence to: Rosalind Wainwright (rosalind.wainwright@wits.ac.za or sjaspan@iafrica.com)

Retinoblastoma is the most common eye cancer that occurs in the retina of infants or young children. It occurs in 1:20 000 births and can be unilateral in 60% or bilateral in 40% of cases. The clinical signs can sometimes be subtle and are often missed, which could lead to delay in diagnosis, possibly loss of vision or even loss of life. Both the public and health professionals in South Africa need education to expand awareness of retinoblastoma.

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Genetics

The genetics involve the Rb gene situated on chromosome 13, which is large, with 27 different sections. The molecular genetics is very complicated as it is a very big gene, and changes/mutations may occur in any part of it. Clinical observation revealed the role of tumour suppressor genes – as explained by Knudson's 'two hit model' of cancer induction – and retinoblastoma was thought to display this perfectly. The most significant recent findings in the molecular biology of retinoblastoma include evidence for aneuploidy and genomic instability as causes for cancer, rather than Knudson's two hit hypothesis.[1] The latest evidence suggests that the loss of both RB1 tumour suppressor gene alleles affects quiescent RB1 retinomas. These lesions have low-level genomic instability and high expression of senescence-associated protein.[2] Retinomas can remain unchanged throughout life, but with the loss of the tumour suppressor genes proliferative retinoblastomas commonly emerge. These retinoblastomas show altered gene copy number, expression of oncogenes, and reduced expression of the senescence proteins. RB1 inactivation in developing retina induces genomic instability, but senescence can block transformation at the stage of the retinoma. However, stable retinoma is rarely clinically observed because of progressive genetic instability.[3]

Clinical

Most babies/children present with a 'white' reflex, cat's eye, or leukocoria as the light reflects off the tumour. This sign is best seen in low artificial lighting or in a flash photo, and it is the commonest presentation of retinoblastoma (Fig. 1). It is the best sign to target for awareness, as it is easily observed. Strabismus is occasionally noted, a red irritated eye, decreasing visual acuity, or pain being more unusual. Rarely a presentation due to a trilateral retinoblastoma with a pineal or suprasellar mass, causing pituitary dysfunction, hypothalamic overgrowth syndrome and central blindness, can be encountered.[4] In the case of a very late presentation, an enlarging eye, proptosis, secondary glaucoma, orbital cellulitis, unilateral pupil dilatation, heterochromic iridis, spontaneous hyphaema, pseudohypopyon or blindness can be present.[5] Once there are signs of metastatic spread – subcutaneous lumps, lymphadenopathy, bone tenderness, organomegaly, anaemia and bleeding from bone marrow involvement, central nervous system signs from lesions in the brain and/or meninges – the child's prognosis is very poor. Staging[6] of the tumour includes a bone marrow aspiration and trephine, cerebrospinal fluid (CSF) for cytology, computed tomography (CT) of the brain and orbits (or magnetic resonance imaging (MRI)), a bone scan, and a blood work-up – full blood count, lactate dehydrogenase (LDH) and liver function tests. The diagnosis of retinoblastoma is a clinical one but all cases are always assessed by an ophthalmologist, who will perform a Bscan (sonar) and an examination under anaesthesia, in which the number, size and location of every tumour is documented either with a retinal drawing or, if a Retcam is available, with a retinal photograph. The ophthalmologist also does a local staging (group[7]) of each eye into 5 groups, which helps to prognosticate how a child is likely to respond. Good eye salvage (80 - 90%) is obtained in the lower groups, dropping to 30% in group 5 (Appendix I).

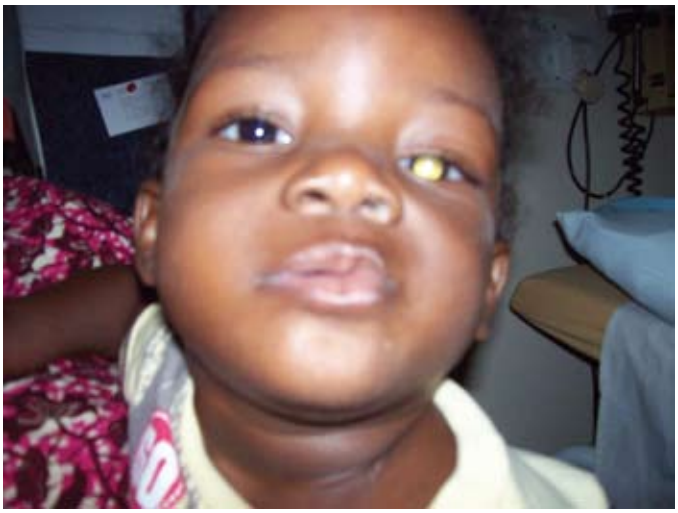

Fig. 1. Child with retinoblastoma.

Clinical scenarios

Unilateral retinoblastoma

This type, which comprises two-thirds of retinoblastoma cases, often presents with an advanced stage of disease, a single tumour is

usually present, and the standard treatment is primary enucleation.[6] The mean age of presentation is around 24 months in developed countries, with an equal sex incidence. In developing countries the children present at an older age – 3 years or more. In the few cases that are diagnosed early, enucleation may be all the treatment that is required. At the time of enucleation a ball implant is inserted to maintain the orbital shape pending the histology result, which determines further management. The pathologist needs to comment on the depth and extent of choroidal or ciliary body involvement, the scleral or optic nerve involvement, and distance from the resection margin. Therapy is determined depending on this stage (Appendix II).[6] In the less advanced cases chemotherapy only (usually VEC – vincristine, etoposide, carboplatinum) is given, or combined with orbital radiotherapy. Intrathecal chemotherapy is sometimes used but the evidence supporting its use is weak. Orbital brachytherapy causes less severe side-effects than external beam radiotherapy but is not available in all the paediatric oncology units. Cosmesis is extremely important, as in younger children marked hypoplasia of the orbital bone can ensue after radiotherapy. Occasionally a patient with unilateral retinoblastoma may have the hereditary type – this could be suspected if the child is very young and out of the typical age range for the sporadic type of retinoblastoma.

Bilateral retinoblastomas

In these patients, who tend to be very young, with a mean age of 9 months, the primary concern is whether vision can be saved, as well as the child's life. As these patients all have hereditary disease there is also the concern of long-term effects from therapy, especially second malignancies, as there is an increased life-long risk for further malignancy (sarcoma, bone, melanomas).[5] External beam radiation should be avoided if possible, as osteosarcoma may develop in the radiation field. These patients need to be seen regularly for the first 6 years of life as new tumours may continue to appear in either eye, necessitating regular examinations under anaesthesia (EUAs). The type of focal therapy used depends on availability and the group[7] of each eye. Usually a combination of focal therapy with chemotherapy is given, with the response to therapy being assessed monthly or 6-weekly by EUAs. If there is a poor response or progressive disease then the whole eye will need brachytherapy, and this can be administered with 'claws',[8] either after chemotherapy or earlier if there is no response. Enucleation is performed if there is no vision, as saving the child's life remains paramount.

In bilateral disease 3 different types of focal therapy are currently used – diode laser (TTT), hyperthermia applied directly to the tumour (which is currently the top option), or cryotherapy – triple freeze thaw, or argon laser photocoagulation causing obliteration of the surrounding retinal blood supply. The type of local treatment selected depends on the size and location of the lesions and availability. A team approach to every retinoblastoma case is essential. The team should include an ophthalmologist, radiotherapist and paediatric oncologist to discuss the response and treatment options for each patient.

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New treatment options

Pilot studies of chemotherapy for intra-ocular retinoblastoma have been reported from several groups using different combinations, dosages, schedules and duration of carboplatin, etoposide or teniposide, with or without vincristine, and with or without cyclosporine to counteract multidrug resistance.[9] Chemotherapy alone reduces tumour size but does not cure retinoblastoma, so adjuvant therapy for consolidation is always required. Intra-arterial chemotherapy is in use for intraocular retinoblastoma and appears to be safe and effective – this therapy is only used in developed countries. Intra-ocular injection of carboplatin is used in some units to attempt to salvage an eye with advanced disease.[10]

Awareness programmes

As this is a rare condition, screening by ophthalmologists is not feasible or cost effective. Other approaches have been tried using different media – photos, radio,[11] television, film, contact made at vaccination schedules, as well as pamphlets offered with the Road-To-Health card at birth. Improving awareness is especially important in developing countries as the incidence is increased, and many babies/ children die undiagnosed or have advanced disease at presentation due to delay in referral to an oncology centre. At our unit a delay of 9 - 10 months occurs from the time the mother first seeks medical attention to arrival at the unit. Advanced disease leads to a poorer outcome with more severe after-effects due to intensified therapy. Awareness programmes need continuity owing to mobility of staff in the more remote areas.

Teaching retinoblastoma awareness could be added to training programmes for undergraduates, and refresher courses/updates could be held for those who are currently working. Assistance from governmental departments with implementation would be vital for ongoing progress. Currently in South Africa the focus is on HIV and tuberculosis, and retinoblastoma has a low priority. Hopefully organisations like CHOC (a parent organisation) or CANSA (support for cancer) could fill the breach and assist with awareness programmes. To date our unit at Chris Hani Baragwanath Hospital has attempted two awareness programmes. In 2002 a programme called St Siluan 'early warning signs of childhood cancer'[12] was conducted over a 6-month period, with good success in terms of increased numbers of childhood cancer detected. In 2007 a retinoblastoma awareness month, with 'seered' posters distributed from three oncology units, and a neonatal arm with pamphlets distributed at delivery from our hospital, was conducted. One new case of retinoblastoma was detected from the campaign.

Conclusion

Improving awareness of retinoblastoma is a worthwhile goal, and any eye complaint merits careful attention from all nursing and medical personnel. Leucokoria is the easy clue to its presence. If there is any worrying sign, urgent referral to either a paediatric oncology unit or an ophthalmologist is imperative.

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Appendix I. New group classification of intra-ocular retinoblastoma[6,7]

Group A – very low risk	Eyes with small discrete tumours away from critical structures

All tumours are 3 mm or smaller, confined to the retina, and located at least 3 mm from the foveola and 11.5 mm from the optic nerve. No vitreous or subretinal seeding is allowed

Group B – low risk	Eyes with no vitreous or subretinal seeding and discrete retinal tumour of any size or location

Retinal tumours may be of any size or location not in Group A. No vitreous or subretinal seeding allowed; a small cuff of subretinal fluid extending no more than 5 mm from the base of the tumour is allowed

Group C – moderate risk	Eyes with only focal vitreous or subretinal seeding and discrete retinal tumours of any size and location

Any seeding must be local, fine, and limited so as to be theoretically treatable with a radioactive plaque. Retinal tumours are discrete and of any size and location. Up to one quadrant of subretinal fluid may be present

Group D – high risk	Eyes with diffuse vitreous or subretinal seeding and/or massive, non-discrete endophytic or exophytic disease

Eyes with more extensive seeding than Group C. Massive and/or diffuse intra-ocular disseminated disease may consist of fine or 'greasy' vitreous seeding or avascular masses. Subretinal seeding may be plaque-like. Includes exophytic disease and more than one quadrant of retinal detachment

Group E – very high risk	Eyes that have been destroyed anatomically or functionally by the tumour

Eyes with one or more of the following: irreversible neovascular glaucoma, massive intra-ocular haemorrhage, aseptic orbital cellulitis, tumour anterior to the anterior vitreous face, tumour touching the lens, diffuse infiltrating retinoblastoma, phthisis and pre-phthisis

Appendix II. International classification of retinoblastoma

Stage 0	Patients treated conservatively
Stage I	Eye enucleated, completely resected histologically
Stage II	Eye enucleated, microscopic residual tumour
Stage III	Regional extension
	a. Overt orbital disease
	b. Pre-auricular or cervical lymph node extension
Stage IV	Metastatic disease
	a. Haematogenous metastasis (without CNS involvement)
	1. Single lesion
	2. Multiple lesions
	b. CNS extension (with or without any other site of regional or metastatic disease)
	1. Prechiasmatic lesion
	2. CNS mass
	3. Leptomeningeal and CSF disease

In a nutshell

- Retinoblastoma is the most common eye cancer that occurs in the retina of infants or young children.
- The clinical signs can sometimes be subtle and are often missed, which could lead to delay in diagnosis, possibly loss of vision or even loss of life.
- The genetics involves the Rb gene situated on chromosome 13, which is large, with 27 different sections.
- Most babies/children present with a 'white' reflex, cat's eye, or leukocoria as the light reflects off the tumour.
- This sign is best seen in low artificial lighting or in a flash photo. It is the commonest presentation of retinoblastoma, and is the best sign to target for awareness, as it is easily observed.
- The diagnosis of retinoblastoma is a clinical one but all cases are assessed by an ophthalmologist, who will perform a Bscan (sonar) and an examination under anaesthesia, in which the number, size and location of every tumour is documented either with a retinal drawing or, if a Retcam is available, with a retinal photograph.
- Unilateral retinoblastoma comprises two-thirds of retinoblastoma cases, often presents with an advanced stage of disease, a single tumour is usually present, and the standard treatment is primary enucleation.
- The mean age of presentation is around 24 months in developed countries, with an equal sex incidence.
- In developing countries the children present at an older age – 3 years or more.
- In the few cases that are diagnosed early, enucleation may be all the treatment that is required.
- In patients with bilateral retinoblastma, who tend to be very young, with a mean age of 9 months, the primary concern is whether vision can be saved, as well as the child's life.
- These cases are all hereditary.
- Enucleation is performed if there is no vision, as saving the child's life remains paramount.
- Improving awareness is especially important in developing countries as the incidence is increased, and many babies/children die undiagnosed or have advanced disease at presentation due to delay in referral to an oncology centre.
- Advanced disease leads to a poorer outcome with more severe after-effects due to intensified therapy.