Retinoblastoma – to expand awareness

We need to be more aware of retinoblastoma.

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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. 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. 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.

Clinical

Most babies/children present with a ‘white’ reflex, cat’s eye, or leukokoria as the light reflects off the tumour. This sign is best seen in low artificial lightening 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. 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. 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 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) 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).

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

Fig. 1. Child with retinoblastoma.
Retinoblastoma

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. 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). In the less advanced cases chemotherapy only (usually VEC – vincristine, etoposide, carboplatinum) is given, or combined with orbital radiotherapy. Intraocular 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). External beam radiation should be avoided if possible, as osteosarcoma may develop from several groups using different media – photos, television, film, contact made at hospital, was conducted. One new case of retinoblastoma was detected by improving awareness of retinoblastoma in the hospital. This is in keeping with the ‘early warning signs of childhood cancer’ campaign. In 2002 a programme called St Siluan (“early warning signs of childhood cancer” 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. Leukocoria 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.

References

5. St Jude Retinoblastoma Conference, 25-26 January 2007 St Jude Children’s Research Hospital, USA.

**Appendix I. New group classification of intra-ocular retinoblastoma**

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Very low</td>
<td>Eyes with small discrete tumours away from critical structures.</td>
</tr>
<tr>
<td>B</td>
<td>Low</td>
<td>Eyes with no vitreous or subretinal seeding and discrete retinal tumour of any size or location.</td>
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<tr>
<td>C</td>
<td>Moderate</td>
<td>Eyes with only focal vitreous or subretinal seeding and discrete retinal tumours of any size and location.</td>
</tr>
<tr>
<td>D</td>
<td>High</td>
<td>Eyes with diffuse vitreous or subretinal seeding and/or massive, non-discrete endophytic or exophytic disease.</td>
</tr>
<tr>
<td>E</td>
<td>Very high</td>
<td>Eyes that have been destroyed anatomically or functionally by the tumour.</td>
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**Appendix II. International classification of retinoblastoma**

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