Retinoblastoma occurs in about 1 in 20,000 live births, and between 50–60 cases are diagnosed each year in the UK (MacCarthy et al, 2009). Onset generally occurs between the third month post-conception and four years of age (Balmer et al, 2006). There is no gender or race predisposition. One or more tumours may be present in one (unilateral retinoblastoma) or both eyes (bilateral retinoblastoma). Tumours grow in the developing retina, which is the light-sensitive lining of the eye. Some children are born with retinoblastoma tumours; for others, retinoblastoma can develop in the first few years of life.

There are two forms of retinoblastoma: non-heritable (somatic) and heritable (germline). Patients with bilateral disease or multiple tumours in one eye have heritable retinoblastoma, with a change in the Rb gene. This accounts for 45% of cases (Draper et al, 1992). The gene change can occur as a new event in the patient (sporadic) or may have been inherited from a parent who is affected or a carrier. A child who inherits the altered Rb gene has a 90% chance of developing retinoblastoma, so screening from birth at a retinoblastoma specialist centre is vital for suspected infants. Adults who had retinoblastoma who wish to have children should be offered genetic counselling and testing (Dommering et al, 2012).

Most unilateral cases are sporadic and non-heriteditary, but about 15% of cases occur in individuals who have germline mutations (Abramson and Scheffler, 2004). It is therefore important to counsel such cases appropriately.

How does retinoblastoma develop?

The retinoblastoma gene (RB1 gene) is found on chromosome 13 and there are two copies of it. In the first few years of life, the retina grows very quickly and at this fast pace, mutations are more likely to occur as genes are copied. As a result of these mutations, a retinoblastoma can occur; this can happen in several different ways, as discussed below.

One possibility is that a child carries a faulty copy of the Rb gene (germline), inherited from a parent; thus, every retinal cell in that individual carries one faulty gene. One or more of these cells can lose the other normal copy and develop into tumours (if the other copy remains normal, that cell will not develop into a tumour). This is the familial form of retinoblastoma as it has been inherited from the family.

Another possibility is that the Rb gene becomes faulty during the process of fusion of sperm and ovum. In such cases, the change has occurred in that child only, and is not inherited from the parents. The gene can, however, be passed on to the offspring of that child and is therefore heritable, but as it occurred as a new event, it is sporadic rather than familial. Here too, every retinal cell in that individual carries one faulty gene. One or more of these cells can lose the other normal copy and develop into tumours. About 90% of people who inherit a mutated RB1 gene from a parent will develop retinoblastoma: most will have bilateral disease; a few will have multifocal disease (more than one tumour in an eye); and a few will have unilateral disease with only one tumour. About 10% will not develop a tumour at all (Corson and Gallie, 2007). In heritable retinoblastoma all the cells in the body, including the blood cells, will contain the altered copy.

The two scenarios above account for 45% of all cases of retinoblastoma. Of this, 10% are familial and 90% are sporadic (Corson and Gallie, 2007).

A third possibility is that the child has inherited one normal copy of the Rb gene from each parent. As a random event during retinal development, one cell loses both copies of the RB1 gene and develops a tumour. This is an isolated event and, as a rule, such cases are unilateral and unifocal. This is the non-heritable form of retinoblastoma and accounts for 55% of all cases (Corson and Gallie, 2007).
Signs and symptoms
There are several signs that could indicate retinoblastoma but it is important to remember that a child with retinoblastoma may appear systemically well. The initial signs are confined to the eye and are most commonly detected by parents (Wallach et al, 2006). Unfortunately, many patients face a delay in diagnosis and treatment owing to a lack of awareness of the significance of the signs described by parents or observed by primary health professionals (Goddard et al, 1999).

If a child presents with one of the following, a red reflex test must be performed with a direct ophthalmoscope (Childhood Eye Cancer Trust, 2013):

- Leukocoria (intermittent) or white pupillary reflex noticed in dim lighting or a photo. This can be difficult for parents to describe
- Strabismus (squint)—Retinoblastoma must be ruled out for all cases of squint in babies and children using a red reflex test
- A change in the colour of the iris or part of the iris
- Inflammation, redness or increased pressure in or around the eye without an infection
- Absence of red reflex when doing a red reflex test
- Deterioration of vision in one or both eyes
- Nystagmus
- Parental history of retinoblastoma—The condition is heritable so children of an affected parent with retinoblastoma must be screened from birth
- Parental concern over vision or eye appearance.

In the UK, all suspected cases or cases where retinoblastoma cannot be ruled out by a red reflex test must be referred urgently to a local ophthalmology department according to National Institute of Health and Care Excellence (2005) guidelines.

Presentation
Children present with suspected retinoblastoma at different ages depending on the type of retinoblastoma. A child with the heritable form is usually diagnosed within the first year of life, with the average age at diagnosis being nine months (Wallach et al, 2006). Cases of non-heritable unilateral retinoblastoma usually present much later and the average age at diagnosis is 24 months (Wallach et al, 2006).

Investigations
If an infant or child presents to the GP with a sign or indication of retinoblastoma, a red reflex test must be performed. When retinoblastoma is suspected or if the test shows anything unusual, urgent referral needs to be made to a local ophthalmology department, stating the cause for concern. In the UK, if the local ophthalmology department identifies or suspects retinoblastoma, an urgent referral is made to one of two retinoblastoma hospitals in the UK—the Birmingham Children’s Hospital or the Royal London Hospital—for diagnosis and treatment.

The speed of referral is vitally important as a swift referral can reduce the long-term impact of the disease and treatment on the baby or child. Although this cancer has a very high survival rate in the UK, many children live with the consequences of a delayed diagnosis. Late diagnosis for a child with retinoblastoma can mean the loss of one or both eyes, life with an artificial eye, a visual impairment or, in some cases, complete blindness. In unilateral cases, 70% of children will need their eye removed to save their life (Rodriguez-Galindo et al, 2008).

Differential diagnosis
Although retinoblastoma is one of the most common causes of leukocoria, it is important to be aware of the possible differential diagnoses. Although on rare occasions leukocoria may be diagnosed from an observation of the normal optic disc, a pathological cause should always be actively ruled out. Some possible differential diagnoses of leukocoria include: congenital cataract; Coats’ disease; retinopathy of prematurity; coloboma of the optic nerve; myelinated retinal nerve fibres; toxocariasis, and; persistent fetal vasculature (Lahrouchi et al, 2014).

Staging
The International Classification for Intraocular Retinoblastoma divides intraocular retinoblastomas into five groups, labelled A through E, based on the chances that the eye can be saved using current treatment options (Linn Murphree, 2005) (Table 1).
The first principle of treating a patient with retinoblastoma is to save the patient’s life, and then to save their vision. Each eye is assessed individually. The type of treatment used is determined by:

- The size and location of the tumour(s)
- Risk of metastasis or a second tumour
- Systemic status
- The patient’s age.

Treatment options include cryotherapy, laser therapy, plaque therapy, chemotherapy and, to a lesser extent intra-arterial chemotherapy, intravitreal chemotherapy or radiotherapy.

In the UK, treatment is carried out at one of two designated national treatment centres—the Birmingham Children’s Hospital or the Royal London Hospital. Regular follow-up of the affected child is required at the specialist centre during and for a period after active treatment. Longer term follow-up can be at centres closer to the family home (Batra et al, 2014).

Prognosis

In the UK, about 98% of children survive their retinoblastoma; this is true for both unilateral (one eye affected) and bilateral disease (both eyes affected) (MacCarthy et al, 2009). For patients with the heritable (germline) form of retinoblastoma, there is an increased risk that another type of tumour will develop in later life. Retinoblastoma has one of the best cure rates of all childhood cancers in the developed world (Leal-Leal et al, 2006).

Genetic testing

Retinoblastoma can be inherited, so adults who have had retinoblastoma and wish to have children should be offered genetic counselling and testing (Dommering et al, 2012). Information on the genetics of retinoblastoma was scarce 20 years ago and therefore many patients who carry the altered gene may not be aware of the risks associated with this. Patients planning a family should be referred to a geneticist who can offer genetic counselling. The patient may wish to consider testing to identify the gene change so that the risk to offspring can be assessed. If the gene change is found, other techniques include:

- Pre-implantation genetic diagnosis
- Chorionic villus sampling at 11 weeks of pregnancy or an amniocentesis at 16 weeks of pregnancy.

Anyone considering having testing in pregnancy should be seen by a geneticist before they plan a pregnancy so that the necessary background work can be done. (Gallie, 2009; Parulekar, 2010; Dimaras et al, 2012).

Lifelong effects

Any individual who has had retinoblastoma should be monitored to detect and manage any long-term problems caused by the disease and treatment in order to ensure the best possible quality of life.

Effects of treatment

Late effects of chemotherapy for retinoblastoma can include hearing problems, kidney problems and second malignancies, while late effects of radiotherapy can include cataracts, dry eye, facial asymmetry and retinal detachment.

Artificial eyes and vision loss

Many patients with retinoblastoma have one or both eyes enucleated. People in the UK can visit the National Artificial Eye Service (NAES) and other NHS prosthetic services or a private oculist about their artificial eye. Fewer socket problems occur if the patient is under the care of a prosthetist. If problems persist, a referral to a local oculoplastic or orbital surgeon via the GP is important as reconstruction of the socket may be possible or necessary.

Some patients will suffer severe vision loss as a result of their retinoblastoma. This may be in one or both eyes.

Second cancers

There is an increased risk of second primary cancers developing in individuals with the heritable form of retinoblastoma (Halford et al, 2008). This patient...
Conclusions

Leukocoria or a recent onset squint (strabismus) are the most common signs of retinoblastoma and a red reflex test should be carried out in every case of parental concern regarding the eyes. If an abnormal red reflex is confirmed or if there is an inconclusive examination, an urgent referral is crucial to preserve the patient’s life, eyes and sight.

For referrals and information for UK patients, contact the retinoblastoma teams in London and Birmingham at:
- The Royal London Hospital
  Website: www.bartsandthelondon.nhs.uk
  Tel: 020 3594 1419
- Birmingham Children’s Hospital
  Website: www.bch.nhs.uk
  Tel: 0121 333 9475
- The Childhood Eye Cancer Trust
  Website: www.chect.org.uk
  Tel: 020 7377 5578

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A clinician’s perspective
Lesley Green
Support worker (London),
Childhood Eye Cancer Trust, UK

The Childhood Eye Cancer Trust (CHECT) has two part-time support workers present at retinoblastoma clinics in London and Birmingham. As a support worker, I am in the very privileged position of being able to offer support to families affected by retinoblastoma from the point of diagnosis (and sometimes before) for as long as they want. So I can be supporting adults who had treatment for retinoblastoma many years ago, tiny babies and their parents, and all ages in between. Ward support is just the tip of the iceberg of my role and, in this article, I describe what a fairly typical week at work is like.

Monday
Catching up on Facebook posts and messages from the weekend, I see how much peer support families are giving each other. I also find a message from a parent who is anxious about having seen something unusual in a photograph of her child. I message her back with some advice, letting her know she can call or email with any other questions.

On the ward last week, I met a family whose baby had just been diagnosed with retinoblastoma and wanted to link up with another family for support. I make a call to a family I think would be happy to be in contact with them and introduce the two families to each other over email.

During the outpatient clinic in the afternoon, I meet with six families—two families have questions about artificial eyes, another patient asks for information on driving, and one teenager offers to write about their experiences for the next issue of InFocus (CHECT’s newsletter). I also meet with another teenager, her family and the hospital visual impairment officer to offer help with benefits information, music lessons and educational support.

Tuesday
Working with other professionals and organisations is a big part of my job. Today, I will be speaking with: a visual impairment teacher who wants to coordinate support for a family with a very young child; two charities to discuss support for families we have referred to them, and; the hospital play specialist about half term activities for families.

Between appointments, I receive a call from an anxious parent. We speak for some time about the anxiety both mother and child feel about coming back for the next appointment and the uncertainty of not knowing what the outcome will be. I take another call from a mother concerned about employment issues for her son who has a visual impairment and email her some information. This led to a successful application for a place on a Prince’s Trust course.

Wednesday
This is usually a busy day on the hospital ward where I meet families when children are having their EUAs (examinations under anaesthetic). It is good to work closely with the retinoblastoma team and ward nurses. Today, I will be seeing 16 families.

The nurses introduce me to a family on their first visit. I explain what CHECT can offer, give them my contact details and sit and talk through how difficult this visit is for them. Four families need help accessing grants as the extra costs with hospital visits and treatment has had a huge impact on the family finances; four other families asked for information on any holidays available—it’s so good to be able to offer help with something for the whole family.

For some families, being able to sit and talk for a while helps to break up a long day. One family was waiting for their child to go to theatre for enucleation; I waited with dad while mum took their daughter to theatre. Mum said how good it was to look back and know that her husband wasn’t on his own. We spent time talking about all sorts of things, including how the siblings were coping—they had amazed their parents by talking about what a special eye would be like for their sister in a very matter-of-fact way.

Part of my role is getting to know the children and it gives me great pleasure to be led to the playroom by a small child. This can give parents time to think and talk—knowing that their child is happily occupied with someone they know—or to give a mum a toilet break by sitting with her child.

Friday
In the morning, I visit a new family during chemotherapy at the local hospital. We discuss linking, financial support and liaising with a CLIC Sargent social worker. I then take a call from a 38-year-old man who had bilateral retinoblastoma as a child and had very little information from his parents. I pass on information about our Beyond Rb group for adults, help him with a referral to an oncology clinic for check-ups and put him in contact with a geneticist as he wants to plan a family.

I make some calls to teenage members of the CHECT to discuss our exciting new JTV project—to produce a film channel for members to share video diaries as a way to support one another. It’s always so good to catch the energy of young people, especially at the end of a busy week.
Retinoblastoma: My story
Rob Hopson

Rob Hopson was diagnosed with bilateral retinoblastoma when he was 14 months old. His left eye was enucleated to save his life and he had subsequent chemotherapy and radiotherapy.

Looking back, Rob does not remember any problems growing up with an artificial eye. ‘I suppose I would get picked on from time to time, as can happen to anyone. I used to have to wear glasses with very thick lenses, which made me a bit of a target. However, I was well able to stand up for myself, and nine times out of ten the other boy would end up worse off! The majority of my mates were boys I had grown up with who knew the situation and they never mentioned it.

‘I also used to have fun with it when I was older. One time, a guy in a pub thought he was being clever and asked me to keep an eye on his pint. I took him at his word and dropped my artificial eye in his drink, which he admitted afterwards was fair play.’

One point of regret for Rob is driving. ‘I passed my test when I was 17, in 1989, and drove for 18 years. However, a few years ago, I couldn’t find my driving licence and had to apply for a new one. By this time, the Field of Vision test had come in. As I was applying for a new licence, I had to take the test. You need 120 ports of vision to pass and the highest I could get was 104, and so my licence was revoked. That really was a kick in the teeth, and I still miss driving now.’

Another regret is the reduced availability of the National Artificial Eye Service. ‘I always used to be able to go and see someone about my artificial eye on my doorstep, in Bristol. Now I have to travel to Bath. It’s not a huge distance, but it is another inconvenience if I need to see someone urgently about my eye.’

Knowing his was the heritable form of retinoblastoma, Rob and his wife, Kim, went for testing and counselling at the genetics department of Bristol Royal Infirmary when they decided they wanted to start a family. ‘We were warned it was a risk that any children we had would also have retinoblastoma,’ he says. Genetic testing of the parents can allow geneticists to offer an accurate test to a baby. This involves arranging for a blood sample to be taken from the umbilical cord when the baby is delivered. The testing can then be done quickly. Rob and Kim’s first child, Josh, now 12 years old, was diagnosed when he was six weeks old, while Jamie, now three years old, was diagnosed when he was just four days old.

‘It was one of those situations where we knew almost immediately, but a lot of families with retinoblastoma often only find out when it shows up in a photograph as white eye,’ Rob says.

Both boys have undergone treatment for their retinoblastoma at the Birmingham Children’s Hospital and at their local hospital in Bristol. Josh received chemotherapy, cryotherapy and laser therapy, and is now out of treatment and cancer free. Jamie first underwent chemotherapy at just eight days old and recently had to have laser treatment for a new tumour. Rob says: ‘In the first three years of Josh’s life, he could not go anywhere because of the treatment. The treatment had been working but then he relapsed, so he had to go back for more chemotherapy. Jamie had 18 months without treatment and 14 months of that was clear. But just over a year ago, at a regular check-up at Birmingham, they discovered he had relapsed. They found another tumour, which they are treating with a laser.

The treatments and, particularly, the genetic testing have developed so much since I was a baby—it is amazing. Hopefully it will get to the point where they will have some way of stopping retinoblastoma altogether,’ he adds.

As an adult retinoblastoma survivor, Rob also undergoes regular checks due to the risks associated with late effects of heritable retinoblastoma. He and Josh attend annual check-ups at an oncology clinic. In addition to this are Rob’s annual check-ups with the National Artificial Eye Service and annual reviews with his local optician.