Retinoblastoma

Key facts

- Retinoblastoma (RB) is an intraocular embryonal tumour, typically occurring during early childhood.
- The condition is the most common eye cancer in children, affecting approximately 1 in 20,000 individuals.
- 40% of cases are bilateral and 60% of cases are unilateral.
- 10% of cases have an identifiable family history. In these situations, the condition is inherited in an autosomal dominant manner.
- All identified cases of retinoblastoma should have appropriate molecular genetic management with either germline or tumour studies.
- All pregnancies identified as being at increased risk of retinoblastoma should have appropriate antenatal or perinatal molecular investigations, and ocular surveillance should be instigated in the neonatal period where the child is shown to have a high probability of developing retinoblastoma, or if the risk cannot be excluded.

Clinical features

- Retinoblastoma is an intraocular tumour, typically diagnosed before the age of five.
- Early identification and treatment while the tumour is confined to the eye has a very high cure rate (approximately 99%).
- Individuals and families with an inherited susceptibility have an increased probability of second primary tumours, including sarcomas. In adulthood, there is an increased probability of epithelial and sarcomatous tumours, in particular melanoma, lung, bladder, endometrial and breast. Therefore, it is vital to stress the importance of avoidance of overexposure to ionising radiation, UV light and cigarette smoke.

Diagnosis

- The diagnosis should always be considered where the normal red reflex of the eye has been replaced by a white reflex.
- Other indications include loss of vision, a painful swollen eye or strabismus in the first few years of life.
- The diagnosis should always be considered if there is a family history of retinoblastoma, until this risk is excluded with molecular investigations.

Genetic basis and genetic testing

- Almost all cases of retinoblastoma occur due to variants in the retinoblastoma gene (*RB1*).
- A very small proportion (less than 1%) of unilateral cases may be due to N-myc amplification.
- 10% of children with retinoblastoma will have an identifiable family history, typically bilateral disease, but occasionally unilateral or low-penetrant disease.
- Most cases of unilateral retinoblastoma are associated with genetic variants in both copies of the *RB1* gene in the retina (somatic variants). These variants are present in the retinoblastoma tumour tissue, but are not usually present in the DNA extracted from blood.

- Of the 40% of tumours that are bilateral, there will be an identifiable germline variant in 95% or more of cases.
- Following the identification of retinoblastoma, genetic testing should follow a stepwise process to try and identify the underlying molecular cause:
  - » Unilateral cases, where enucleation is undertaken, should have tumour studies followed by germline studies to exclude a heritable cause of retinoblastoma. In the small proportion of cases where genetic testing is not informative, further studies, such as linkage exclusion analysis, may be undertaken to exclude risk in first- and second-degree relatives where feasible.
  - » In unilateral cases not requiring enucleation, germline mutation studies should be attempted. These will be negative in 85% of cases. Additional studies, such as linkage exclusion, should be considered in the management of the extended family.
  - » Preliminary research on cell-free DNA analysis from aqueous humour suggests this may be an important diagnostic approach in non-enucleated non-germline cases, if validated in ongoing studies.
  - » Germline cases should have genetic testing of blood sample (and, if necessary, RNA studies).
- All pregnancies identified as being at increased risk of retinoblastoma (due to an affected parent or sibling) should have antenatal or perinatal molecular investigations. Early studies of non-invasive prenatal diagnosis utilising cell-free fetal DNA (cffDNA) have provided informative results, and in future may enable pre-delivery surveillance decisions.

Clinical management

- In the UK, all individuals with retinoblastoma should have their care led by one of two national services, based in London and Birmingham. In some instances, shared care between national and local services is appropriate, under the guidance of the units above.
- Clinical genetic input can be provided by local genetic services, although this is often included in the care pathway at the national services, as the information may be necessary for the primary management, as well as to provide screening advice for the extended family.
- Enucleation is required in up to 50% of new cases identified, but would be required much less frequently in known families where gene carriers, or at risk individuals, are followed up from the neonatal period. All children known to be at risk of retinoblastoma should have a follow-up surveillance plan in place by two weeks of age.
- Local treatment of the eye would involve laser therapy or cryotherapy, following ongoing assessment by national services.
- In some instances, chemotherapy is required. Traditionally, this has been systemic (into the venous system) but more recently, chemotherapy delivered locally (intra-arterial into the ophthalmic artery behind the eye or intra-vitreal into the eye) has been used where appropriate.
- Transition care should, in all instances, include a clinical genetic review to ensure individuals are aware of the underlying genetic mechanism for their retinoblastoma, as well as the reproductive options available.

Direction to further reading, guidelines and patient groups

- Childhood Eye Cancer Trust

This information is intended for educational use and was current in June 2020. For clinical management, it is recommended that local guidelines and protocols are used.

Produced in collaboration with Birmingham Women's and Children's NHS Foundation Trust's Clinical Genetics department.