RETINOBLASTOMA

Joanna KOBYLARZ, Bożena ROMANOWSKA-DIXON

Introduction

Retinoblastoma, even though it accounts for only ca. 3% of neoplasms recognized in patients below the age of 15 years, is the most common primary malignant ocular tumor in children. According to published data, each year around 7,000–8,000 children are born with a retinoblastoma, and ca. 3,000–3,500 die because of this tumor. Prognosis depends on the standard of, and access to medical care, which is why mortality rates are much lower in developed countries, relative to underdeveloped countries. In developed countries, the tumor is usually recognized in 7–10% at neonatal age, that is in the first 4 weeks of life in full-term children, and before week 44 of gestational age in preterm children [11–13].

The clinical manifestation and the course of the disease varies; retinoblastoma may be familial or sporadic, solitary or multiple, occur unilaterally or bilaterally and develop synchronically, or metachronically. In advanced stages, retinoblastoma may extend to the orbit, and metastasize to the CNS and other remote organs. Based on this criterion, there are two types of retinoblastoma: intraocular and extraocular. Extraocular retinoblastoma is associated with a higher mortality rate relative to the intraocular type. Retinoblastoma of the CNS (so-called trilateral retinoblastoma) usually occurs in the pineal gland and is associated with a particularly poor prognosis – most children die because of the disease or its complications. The chief reason for extraocular extension of retinoblastoma is late presentation to the ophthalmologist, and thus late initiation of treatment. The sooner retinoblastoma is recognized and treated, the greater the chances for not only the child's survival but also for salvaging the eye or even useful vision [13, 14].

Pathogenesis

Retinoblastoma is a neuroectodermal tumor, which develops from the primitive cells of the retina. Well-differentiated tumors are characterized by the presence of Flexner–Wintersteiner rosettes and fleurettes with small necrotic areas and few mitotic figures. Poorly-differentiated retinoblastomas do not show these features, have a very high mitotic index, and may demonstrate anaplastic cellular features (fig. 8.42).

Retinoblastoma is a genetic anomaly. It develops as a result of a genetic defect – a mutation of the oncogene *RB1*, one of the tumor suppressor genes on chromosome 13 in locus 13q14. For retinoblastoma to arise, both alleles of *RB1* gene need to be affected by mutation, which was described by Knudson in his theory. New research also demonstrates alterations in the expression of other oncogenes and suppressor genes. Retinoblastoma shows an autosomal dominant pattern of inheritance with a 90–95% penetration. Familial cases in which a single allele is inherited represent 40% of retinoblastomas. The remaining 60% are sporadic cases in which both alleles are mutated at the time of individual development. Patients with the inherited type are at a risk of developing retinoblastoma at a third site (tumors in both eyes and the third tumor in the pineal gland region or in the parasellar region), 13q syndrome (multifocal retinoblastoma and multiple phenotype abnormalities) and other primary neoplasms (sarcoma, urothelial tumors, lung carcinoma, leukemia, melanoma and breast carcinoma) [13–15].

Symptoms

Symptoms related to retinoblastoma depend on the size and location of the tumor(s) at the time of diagnosis. In the initial stage, small tumor(s), particularly those located at the retinal periphery can be asymptomatic. A symptom which is most often reported by children presenting for treatment is a white pupil ('leukocoria' or cat eye). It is a white reflex from the ocular fundus caused by the tumor showing through the pupil (fig. 8.43), which can be seen in slit lamp photographs (photoleukocoria) or even in family photographs when a flash is used. Leukocoria can be observed when the disease is advanced and the tumor(s) occupies/occupy a significant portion of the eye ball [13, 14, 16, 17].

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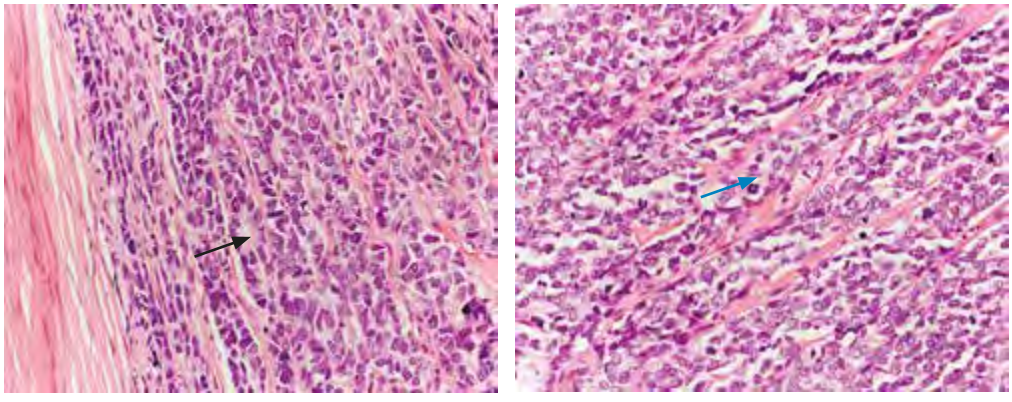

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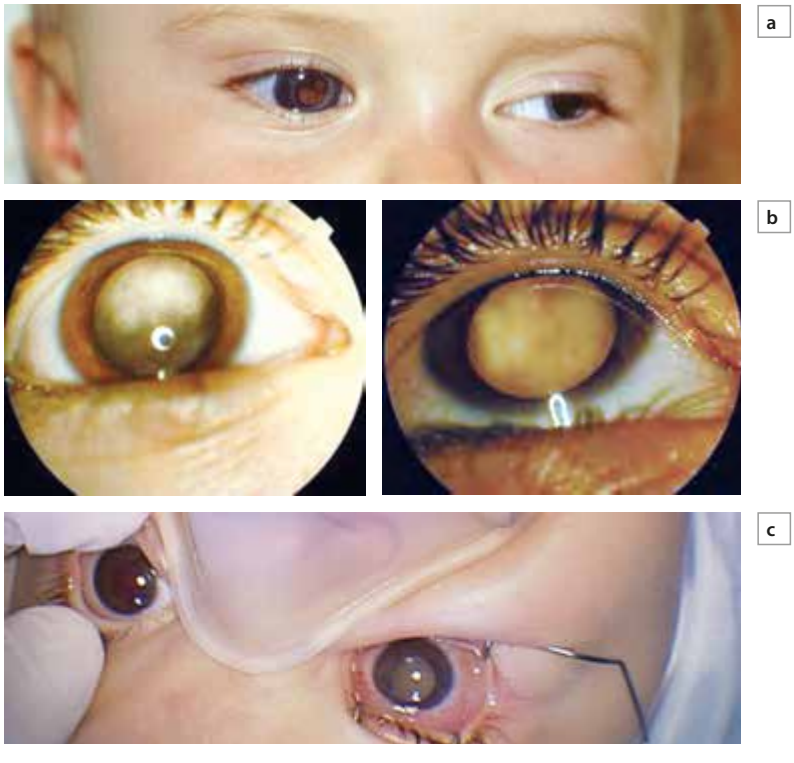

Figure 8.42. Retinoblastoma – histopathological examination: **a** – Flexner Wintersteiner rosette (black arrow); **b** – mitosis (blue arrow).

Figure 8.43 a–c. Leucocoria – white or creamy reflex from the pupil.

Retinoblastoma **must** be excluded in every child presenting with leukocoria. In the differential diagnosis of retinoblastoma, one should take into account other possible reasons underlying leukocoria, of which the most common are: primary persistent hyperplastic vitreous body, Coats' disease, ocular toxocariasis, retinopathy of prematurity, retinal hamartoma, choroidal coloboma, vitreous hemorrhage, astrocytoma, familial exudative vitreoretinopathy, retinal hypoplasia, rhegmatogenous retinal detachment, juvenile retinal dysplasia, medulloepithelioma and congenital cataract [18, 19].

Strabismus is another frequent symptom related to retinoblastoma, usually caused by tumor invasion of the macular region and damage to central vision. In a paper discussing the outcomes of retinoblastoma treatment at our Clinic in 1996–2004, a thorough medical history provided by patients helped to establish that strabismus was the first symptom in 37.5% children presenting with leukocoria [20]. Therefore, **every squinting child**, regardless of age, should be evaluated by an ophthalmologist to exclude out or confirm retinoblastoma. Other, less common symptoms included: ocular redness and pain mostly caused by a secondary glaucoma, pseudouveitis, nystagmus, unilateral pupil dilation, iris heterochromia, blood or pseudohypopyon in the anterior chamber, and preseptal orbital cellulitis. Exophthalmos secondary to orbital infiltration is the second feature related to advanced retinoblastoma after leukocoria in reports from developing countries. Retinoblastoma may also be discovered by accident, at a routine ophthalmologist examination (e.g. ophthalmic screening in pre-term children and children following obstetric trauma). According to our retrospective studies published in 2009, both eyes were salvaged in all children whose retinoblastoma was detected by accident in the first month after birth [17]. Unfortunately, incidental discovery of retinoblastoma still represents a small proportion of diagnoses.

If any of the symptoms presented above occur (particularly the cat-eye white reflex or squinting), parents or foster parents should immediately bring the child to an ophthalmologist. An ophthalmologist who identifies or suspects a retinoblastoma should refer the affected child to a specialized ocular oncology center, which has all the necessary equipment and trained staff experienced with novel treatment modalities [13, 14].

Diagnosis

It is vitally important to obtain a detailed medical history from the parents or foster parents of children with retinoblastoma, in order to establish the occurrence of retinoblastoma in the family or rule out other diseases, which may give rise to similar symptoms. Fundoscopy is the most important evaluation in diagnosing a retinoblastoma. In order to accurately assess the number and location of tumor(s), it is recommended to examine a child with retinoblastoma under general anesthesia. After a thorough examination of the anterior segment of the eye and measurement of intraocular pressure, the ocular fundus must be evaluated with a maximum pupil dilation using Fison binocular ophthalmoscope with a scleral depressor to see the most peripheral sections of the retina up to the ora serrata. It is recommended to produce a photographic documentation of the ocular fundus. A- and B-scan US images of the globe and orbit aid accurate evaluation of the internal features of a tumor, such as calcifications and invasion of the optic nerve, choroid or orbit, and measure the tumor thickness and diameter at base. Computed tomography (CT) may show calcifications within a retinoblastoma. However, due to radiation exposure from CT, which increases the risk of other neoplasms developing at a later time, the use of this examination technique should be limited, particularly in children with retinoblastoma originating from germinal mutations. At present, MRI is the preferred imaging method as it is superior in showing soft tissue, safer and more useful, particularly in detecting extraocular extensions of the tumor, invasion of the optic nerve, and evaluation of the brain. Angiography, OCT, ultrabiomicroscopy (UBM) may be helpful in establishing the final diagnosis as part of a differential diagnosis process. Children with retinoblastoma suspected of developing metastases need to undergo bone marrow puncture, examination of the cerebrospinal fluid, bone scintigraphy and positron emission tomography (PET) scans [13, 14, 16].

It is hoped that fluid biopsy and genetic testing of eyes with retinoblastoma may prove useful in future, but further observations need to be made before their prognostic value is confirmed [13, 21, 22].

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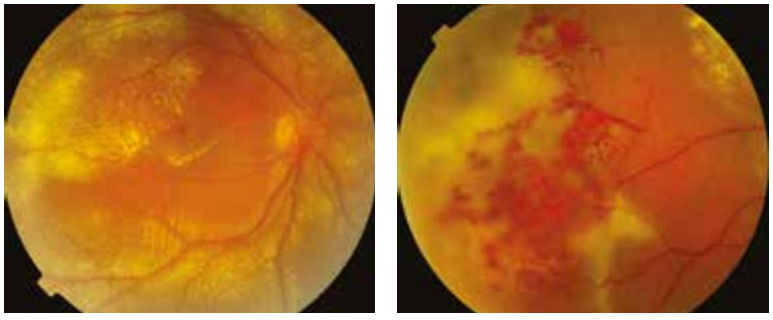

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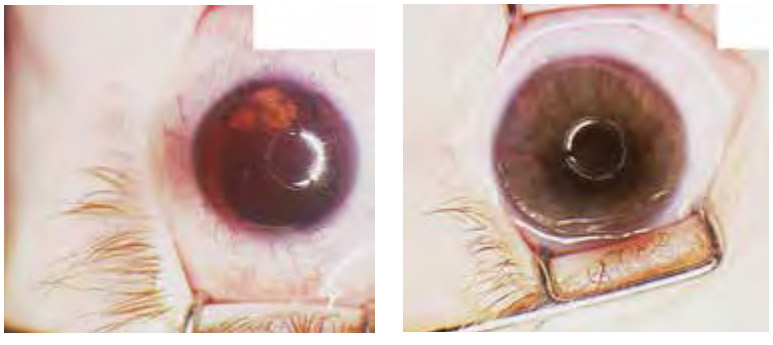

Figure 8.44. Differential diagnosis of retinoblastoma and Coats disease.

Figure 8.45. Retinoblastoma – tumor located in anterior chamber of the eye (**a**), iris neovascularization and secondary glaucoma (**b**).