Retinoblastoma: Evaluation and Diagnosis

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Contents

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1.1 Historical Background

In 1809, a Scottish surgeon named James Wardrop wrote a monograph where he described a subset of fungus haematodes cases distinguishing them from other cases of "soft cancer," medullary sarcoma, or inflammation. He was the first to recognize retinoblastoma (RB) as a discrete tumor arising primarily from the retina [1]. Virchow in 1864 used the name of glioma retinae because of retinoblastoma's similarity to intracranial glial tumors. Verhoeff, in 1922, observed the retinal origin and the presence of immature, embryonic cells that formed the tumor and coined the term retinoblastoma. In 1926, the American Ophthalmological Society accepted the term retinoblastoma and the older terms, such as glioma retinae and fungus haematodes, were abandoned [2]. In 1809, it was the astute clinical observations and descriptions of the disease that made the diagnosis of what we now know as retinoblastoma.

1.2 Clinical Presentation

The symptoms of retinoblastoma are most often first detected by a parent or family member directly or occasionally from an abnormal light reflex in a photograph. To a lesser extent sporadic cases of retinoblastoma are first discovered by a routine pediatric exam or screening, less commonly by pediatric ophthalmologists

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Table 1.1 Presenting features of retinoblastoma (United States)

Leukocoria or cat's eye reflex	45 %
Strabismus	25 %
Inflammatory symptoms (preseptal cellulitis)	10 %
Poor vision	10 %
Screening due to family history	5 %
Incidental detection	5 %

Modified from Abramson et al. [13]

and rarely incidentally on imaging for other conditions. In the United States and other developed nations, the most common presenting findings in intraocular retinoblastoma are leukocoria or cat's eye reflex (45 %) (Chap. 2), strabismus (25 %), inflammatory symptoms (pseudo-preseptal cellulitis) (10 %), and poor vision (10 %) (Table 1.1) [3].

For several reasons discussed elsewhere in developing nations, retinoblastoma tends to be more advanced at presentation with extraocular disease (Chap. 5). One of the major limitations to prompt treatment of retinoblastoma worldwide is access to health care. As retinoblastoma care providers, it is important for us to increase accessibility for our patients into a system that is equipped to treat this condition adequately. Community education and awareness and training of ancillary staff that are able to triage and arrange prioritized evaluations are some of the important components of this approach (Chap. 5).

1.3 Misdiagnosis

Histopathological studies of enucleated eyes report misdiagnosis rates from 11 to 40 %, and clinical studies of referral patterns report misdiagnosis rates from 16 to 53 % [3]. This may be attributed to many factors including rare incidence of retinoblastoma, multiple conditions that simulate retinoblastoma, the unfamiliarity of the primary health care providers, the age of presentation, and the difficulty in examining children (Chap. 2). Consequently, a thorough and detailed assessment should be done on patients suspected of having retinoblastoma.

1.4 Stepwise Evaluation for Retinoblastoma

A practical stepwise approach specifically to evaluate a child suspected to have retinoblastoma includes detailed history taking, initial office examination, and focused ophthalmic ultrasonography, followed by examination under anesthesia and neuroimaging if necessary (Fig. 1.1). This approach is merely a guide that can be modified as needed based upon clinical setting.

1.4.1 History

For a child suspected of having retinoblastoma, it is important to examine the patient and family promptly upon referral, and the initial consultation may be performed in an office setting (Table 1.2, Box 1.1). The story of how and over what time course the condition was noted, the health care professionals that saw the patient, and what was done to the child before they arrived must be recorded. A birth history including the pre- and perinatal history is important. Typically the gestational age at birth, type of delivery, birth weight, and any delivery or pregnancy complications, including infections or medications taken during the pregnancy, are noted. It is also important to inquire if any abnormalities were noted on the eye screening exam after birth or if there were any unusual birthmarks or malformations. The current history should include the child's health, any medical conditions, and environment including pets, recent trauma, or illness. For retinoblastoma suspects, the family history should include number of siblings, their health and ocular history, and any family medical disorders. It should be noted if there was any poor vision, blindness, or loss of an eye in the family. Both parents should be questioned about their ocular health and examined if no recent dilated exam has been preformed. A small subset of parents of children with RB will have evidence of retinoma/retinocytoma and even unknown treated retinoblastoma (Chap. 7) [4].

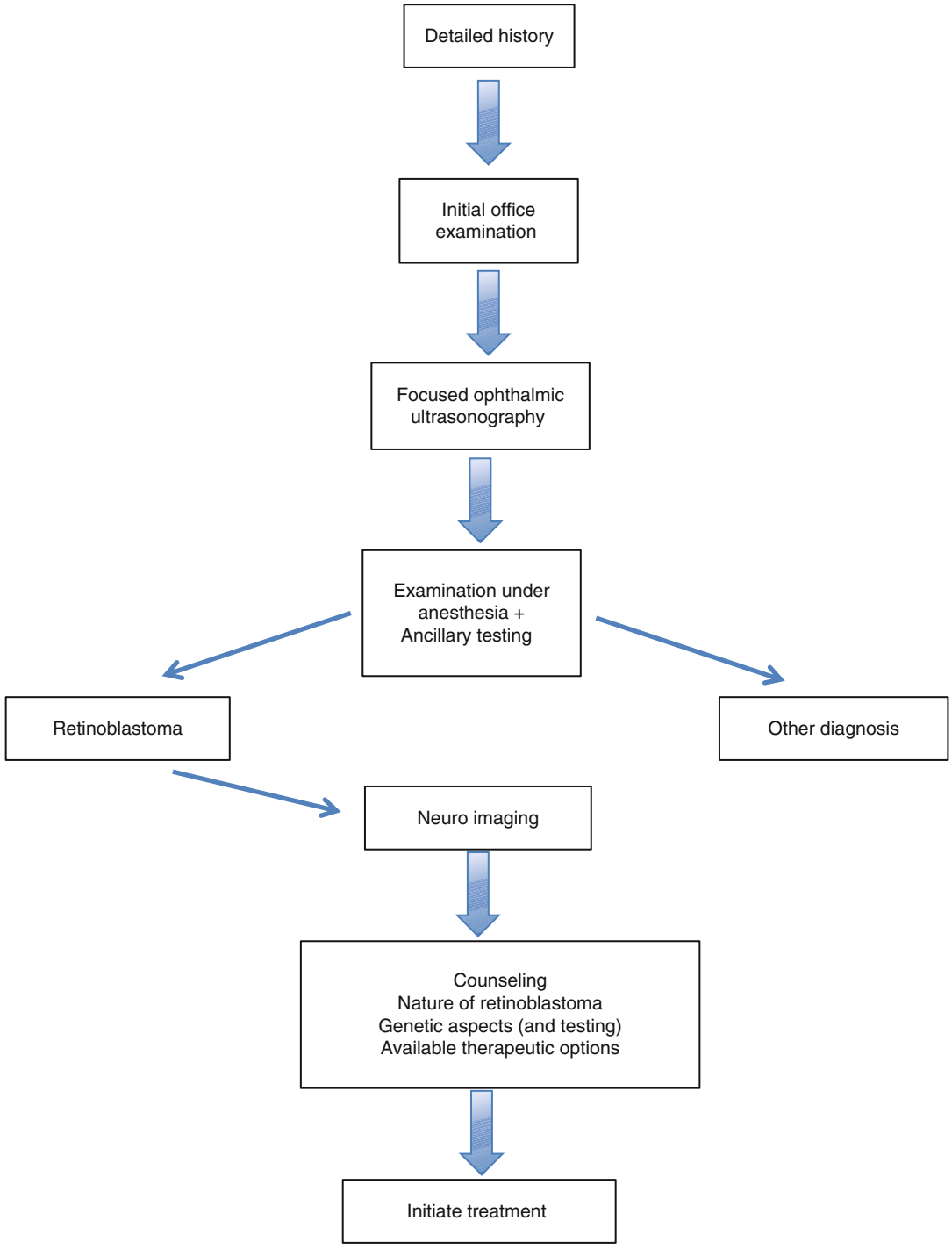

Fig. 1.1 Stepwise evaluation for retinoblastoma. This approach is merely a guide that can be modified as needed based upon clinical setting

Table 1.2 Elements of medical history in a child suspected of having retinoblastoma

Time since onset	Duration
Prior evaluation	Prior diagnosis Prior treatment Prior surgical procedure Prior biopsy
Perinatal history	Pregnancy complications Prematurity Birth weight Type of delivery Use of oxygen
Personal history	Malformations Exposure to pets Recent trauma Systemic illness
Family history	Genetic disease Blindness Enucleation Amblyopia Retinoblastoma

Box 1.1 Elements of fundus examination in a child with retinoblastoma

Tumor size		
Tumor location		
Associated features	Subretinal fluid	Localized, diffuse
	Subretinal seeds	Localized, diffuse
	Vitreous seeds	Localized, diffuse

Table 1.3 Elements of initial examination (office) in a child suspected of having retinoblastoma

External examination	Facial abnormalities (13q deletion syndrome) Strabismus Periorbital swelling Presence of heterochromia	
Visual acuity		
Pupillary response		
Pupillary light reflex	Normal	
	Abnormal	Leukocoria absent Leukocoria present
Anterior segment examination	May be limited	
Indirect ophthalmoscopy	May be limited	
Ultrasonography	Mass Calcification Retinal detachment Other abnormalities	

1.4.2 Initial Examination

The initial examination of the child can be started in the office while taking the history, by observing the comfort and behavior of the child, and noting any size, proportion, or facial abnormalities (Table 1.3). It may be possible to observe leukocoria, strabismus, or periorbital swelling and visual behavior before initiating the formal examination. Assessing the vision is dependent on the age of the patient and the amount of cooperation; however, the condition of each eye should be assessed and recorded along with the pupillary response and the presence or absence of heterochromia of the irises. A brief observation of the periorbital tissues, cornea, conjunctiva, and sclera should be performed before administrating dilation drops. Using a direct ophthalmoscope, the pupillary light reflex can be noted in both eyes.

Upon completion of this portion of the examination, drops for pupillary dilation can then be administered (tropicamide 0.5 % and ophthalmic phenylephrine 2.5 %). It is worth emphasizing that both eyes should be examined in equal detail. The examination of the posterior pole is best done with an indirect ophthalmoscope. Depending on the age, the child may cooperate or parents may be needed to help secure the patient while lying supine on a table or chair (Fig. 1.2). Younger children can be swaddled with a blanket or sheet. The goal of the indirect examination at this point is to confirm the suspicion of retinoblastoma and determine whether further evaluation is necessary with an exam under anesthesia (EUA). It may be necessary to place an eyelid speculum in for proper visualization of the posterior pole; appropriate topical anesthesia such as ophthalmic proparacaine 0.5 % solution should be administered before placing the speculum. A detailed fundus examination with scleral depression may be performed with an anesthetic, eyelid speculum, and restraint; however, this is fairly traumatic for both the child and the family and is generally unnecessary if a planned exam under anesthesia is possible.

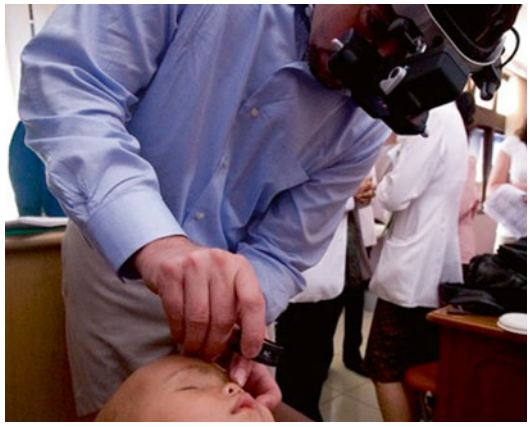

Fig. 1.2 An indirect ophthalmoscopic examination being performed in an office setting with the mother helping to hold the child

1.4.3 Ophthalmic Ultrasonography

A limited ophthalmic ultrasonography can be done in A/B scan mode using a 10 MHz transducer to visualize the presence of a mass, calcification, retinal detachment, or abnormalities of the posterior pole. Intraocular calcification can be highlighted during the ultrasound in B scan mode by turning down the gain of the unit.

If retinoblastoma is recognized and further examination is necessary, ideally the child is scheduled for an EUA, and neuroimaging is ordered (MRI of the brain and orbit with and without contrast) to visualize the orbit and posterior portion of the optic nerve and assess for pinealoblastoma (Chap. 19).

1.5 Examination Under Anesthesia

The type and method of general anesthesia vary depending on institution and availability. Safe anesthesia methods can range from mask anesthesia or laryngeal mask airway (LMA) using inhaled anesthetics, with or without intravenous anesthesia to using intravenous anesthetics alone [5]. As with all anesthesia, children must limit intake of food and liquids before the procedure. Guidelines suggest all food, milk, or formula be discontinued 8 h prior to the exam. Breast milk is allowed up to 4 h before the exam and clear liquids up to 2 h before; however, requirements vary by institution and are determined by the anesthesiologist and type of anesthesia used. Some younger infants require extended observation after anesthesia to be monitored for apnea. Current recommendations are that preterm infants less than 36 weeks must be at least 55 weeks post conceptual age to go home after anesthesia without extended monitoring, otherwise an overnight stay is recommended. Full-term infants must be 50 weeks post conceptual age to go directly home, and full-term infants between 40 and 50 weeks post conceptual age require 6 hours of observation before discharge. Family members should be made aware of these recommendations so they can make arrangements for the examination.

Once the patient is asleep, a full ophthalmic examination that includes all components of the initial office examination repeated in greater detail of both eyes is performed (Table 1.4).

Table 1.4 Elements of initial examination (office) in a child suspected of having retinoblastoma

External examination	Facial abnormalities (13q deletion syndrome) Strabismus Periorbital swelling Presence of heterochromia	
Intraocular pressure		
Corneal diameter		
Pupillary response		
Pupillary light reflex	Normal	
	Abnormal	Leukocoria absent
		Leukocoria present
Anterior segment examination	Conjunctiva/sclera Cornea Anterior chamber Iris Lens Retrolental (anterior) vitreous	
Indirect ophthalmoscopy	Vitreous Optic disk Macula Peripheral retina Pars plana	
Ultrasonography	Mass Calcification Retinal detachment Other abnormalities	

1.5.1 External Examination

The overall appearance of the patient should be assessed by looking at the face, ears and hands for any abnormalities that may aid in diagnosis or that are associated with retinoblastoma such as 13q deletion syndrome. As an example, a patient with 13q deletion syndrome may have hypertelorism, flat nasal bridge, small mouth and nose, high arched or cleft palate, micrognathia, and/or microcephaly which may be noted during this part of the examination (Chap. 8).

1.5.2 Anterior Segment Examination

Intraocular pressure should be measured using a Schiotz tonometer, Tono-Pen, Perkins tonometer, or pneumotonometer. Substantially elevated intraocular pressure in retinoblastoma patients due to iris neovascularization or angle closure has been associated with higher risk of optic nerve involvement and metastatic disease [6].

Next, using a caliper, the horizontal and vertical corneal diameters (CD) are measured. Simulating conditions such as persistent fetal vasculature (PFV) can have significant discrepancies between eyes (Fig. 1.3), and eyes with chronically elevated intraocular pressure can have increased corneal diameters.

A handheld slit lamp or illuminated magnification system should be used to assess the anterior segment. Care should be taken to look for any shallowing of the anterior chamber, neovascularization of the iris, iris atrophy, cataract, retinoblastoma seeding of anterior segment, or hyphema. It is important to evaluate the conjunctiva and sclera as well as the anterior vitreous and posterior portion of the lens. It may be possible to see the underlying retina or tumor against the posterior portion of the lens or a retrolental mass or persistent tunica vasculosa lentis in simulating conditions. As an example, observation of the blood vessel branching patterns behind the lens can give a clue to their origin and help differentiate certain entities. Retinal vessels will have a branching pattern opening toward the periphery of the lens whereas persistent tunica vasculosa lentis in PFV will have a branching pattern toward the center of the lens or a retrolental mass will have disorganized vessels (Fig. 1.4).

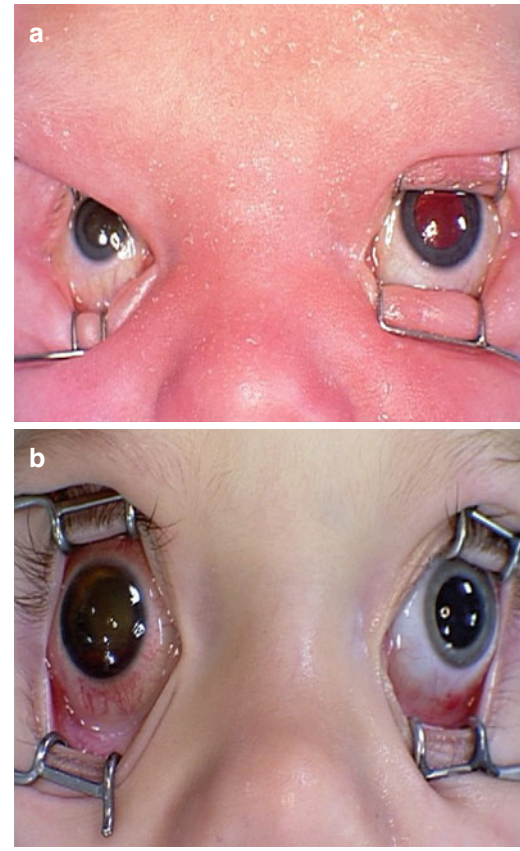

Fig. 1.3 (**a**) A patient with persistent fetal vasculature showing the discrepancy between the corneal diameters. (**b**) A patient with advanced retinoblastoma showing increased corneal diameter and heterochromia from iris neovascularization

1.5.3 Posterior Segment Examination

Indirect ophthalmoscopy is used to evaluate the fundus. An organized systematic approach to thoroughly assess the posterior pole is recommended to prevent overlooking important findings. This examination can be broken down into four parts to evaluate the vitreous, optic disk, macula, and peripheral retina including the pars plana.

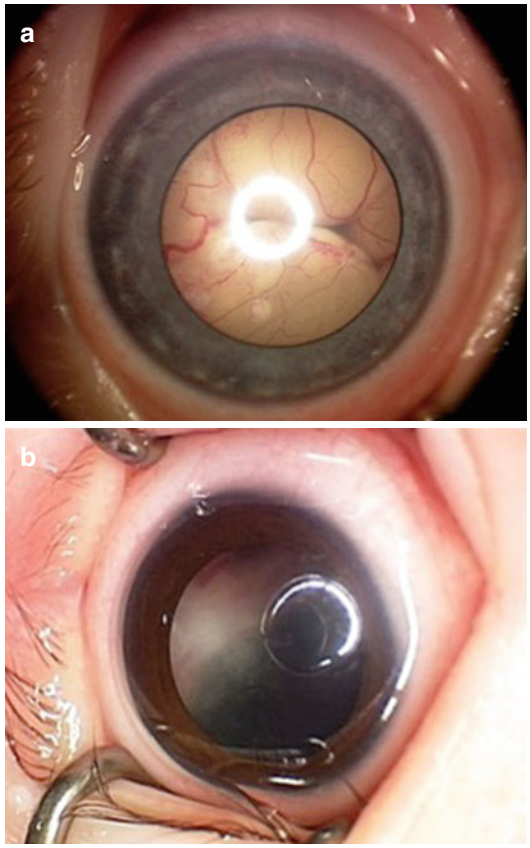

Fig. 1.4 Anterior segment photograph of a patient with advanced retinoblastoma (**a**). Note the branching patterns of the retinal blood vessels toward the periphery of the lens. Anterior segment photograph of the patient with persistent fetal vasculature (**b**). Note the retrolental vascular mass

The vitreous should be examined for the presence or absence of retinoblastoma seeding, hemorrhage, presence of abnormal vessels, fibrous membranes, inflammatory cells, or other abnormalities. If the optic disk and macula are visible, the size and presence of any abnormalities should be noted. Continued examination of the periphery can be done by working in a clockwise fashion and scleral depressing the ora serrata and then looking along that longitudinal segment to the posterior pole until the whole 360° of the eye is covered.

The appearance of retinoblastoma lesions can vary depending upon the size and location of the tumor; smaller tumors are round glazed elevations of the retina; as they grow they acquire large feeder vessels and have a gray-white hew and develop surrounding serous retinal detachments. The larger tumors develop intrinsic calcification and a whiter color with seeding into the subretinal and or the vitreous space. Specifically for retinoblastoma, the size and number of all tumors should be documented noting any associated retinal detachment or subretinal fluid; the presence of subretinal seeds and vitreous seeds and their location and pattern of distribution should be incorporated into a detailed fundus drawing (Table 1.4). This information should be used to make group and stage the eyes according to the classification systems (Chap. 3).

1.5.4 Ancillary Testing

1.5.4.1 Photography

It is useful to document both the anterior segment as well as the posterior segment findings with a photograph. A wide-angle handheld fundus camera is useful for taking photos of the front and back of the eye using different lenses (Fig. 1.5). Fundus photos should be taken at each EUA to aid in assessing the response. Care should be taken to standardize the orientation and position of the photographs to help with future comparisons.

1.5.4.2 Fluorescein Angiography

Fluorescein angiography (FA) can be a useful tool during an EUA to differentiate retinoblastoma from simulating lesions. The FA vascular pattern of retinoblastoma shows normal filling of enlarged dilated vessels diving in and through a hyper- and hypofluorescent tumor mass that stains and leaks depending on its size. FA is especially useful in differentiating RB from advanced Coats's disease. In contrast to RB, Coats's disease has large dilated telangiectatic vessels that remain in the plane of the retina and have marked areas of peripheral capillary non-perfusion (Fig. 1.6).

1.5.4.3 Ophthalmic Ultrasonography

During the EUA it is useful to obtain ultrasound imaging on both eyes to assess the orbit, measure

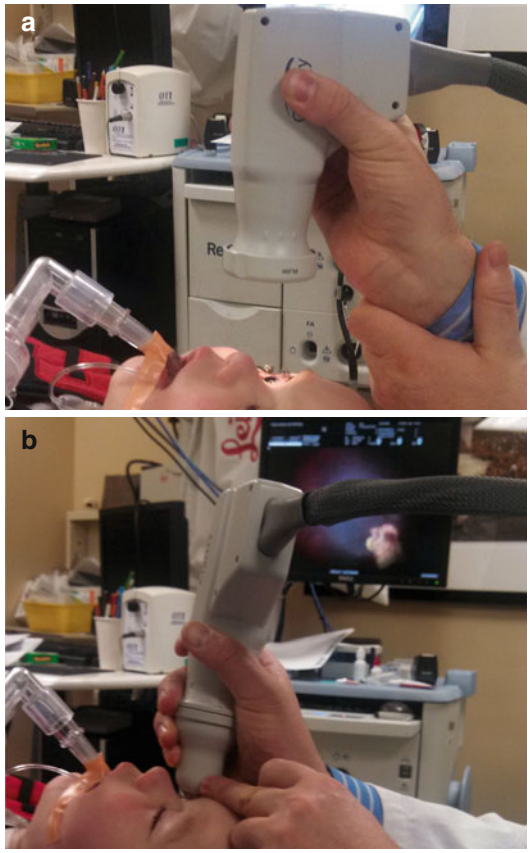

Fig. 1.5 Photography of a patient during an examination under anesthesia. The external lens used to photograph the anterior segment (**a**). The wide-angle fundus lens is used to take photographs of the posterior pole (**b**)

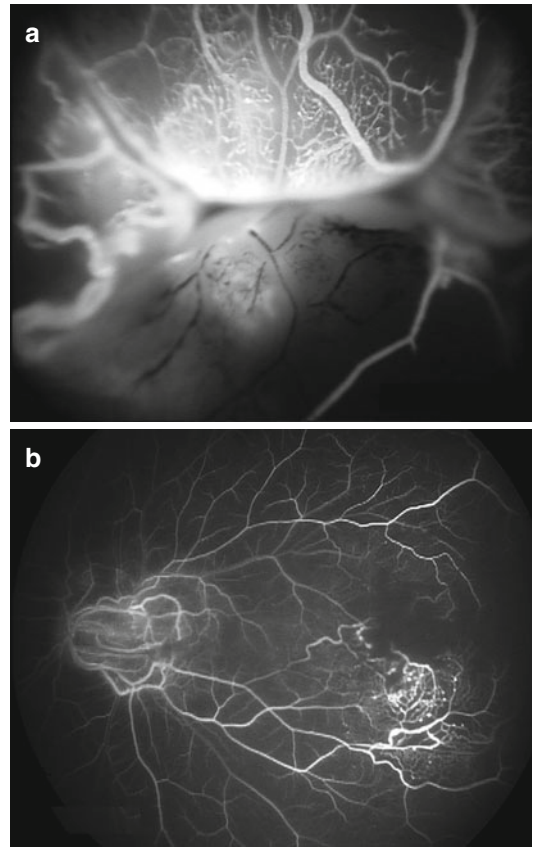

Fig. 1.6 Fluorescein angiograms taken during an exam under anesthesia. A fluorescein angiogram of a patient with retinoblastoma demonstrating irregular vessels within the retina and slower filling vessels within the tumor inferiorly (**a**). Fluorescein angiogram of a patient with Coats's disease demonstrating light bulb telangiectasia and peripheral non-perfusion (**b**)

the thickness of lesions, and obtain the axial lengths of the eyes. Historically ultrasound has been useful in the diagnosis and treatment of retinoblastoma by providing information of the size and extent of the disease as well as differentiating it from simulating lesions [7, 8]. Ultrasound can be done in A and/or B scan mode using a 10 MHz transducer to image the posterior pole and visualize the size and location of disease, the presence of a retinal detachment, or extraocular extension. Ultrasound is specifically useful for evaluating lesions inside the eye when there is a limited view with ophthalmoscopy. Larger retinoblastoma lesions have a characteristic appearance on ultrasound because they produce calcium that is easily detected by ultrasound showing multiple areas of hyperreflectivity with acoustic shadowing (Fig. 1.7a).

1.5.4.4 Ultrasound Biomicroscopy

Ultrasound biomicroscopy (UBM) also can be performed during an EUA and is useful in visualizing the pars plana, pars plicata, and ciliary body. In advanced cases, areas of anterior seeding can be detected using the UBM as well as extension of the tumor into the ciliary body or against the lens. This technique is important particularly for cases

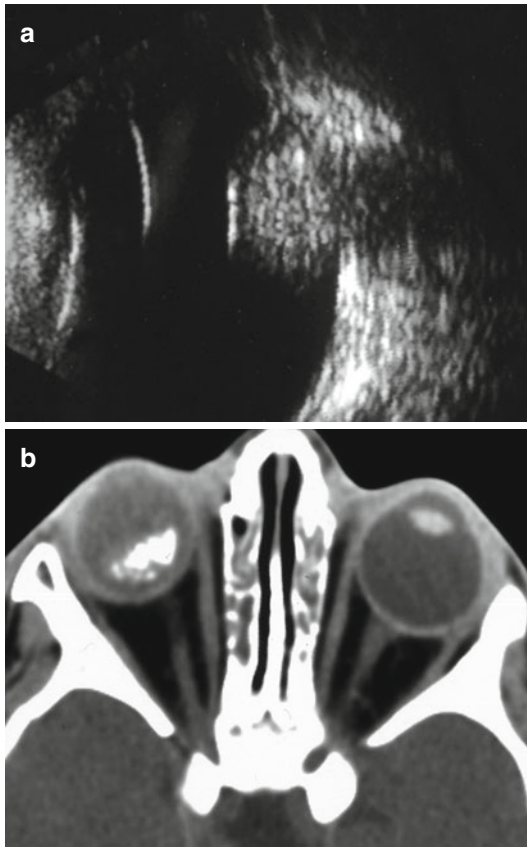

Fig. 1.7 Calcification within retinoblastoma. Ultrasonography of an eye with retinoblastoma in B scan mode showing a hyperreflective mass and acoustic shadowing (**a**). A CT scan of a patient with retinoblastoma demonstrating the intraocular calcification seen within the tumor in the right eye (**b**)

that are being considered for intravitreal chemotherapy injection (Chap. 13).

1.5.4.5 Electroretinogram

An electroretinogram (ERG) has been used to monitor retinal function prior to, during, and after treatment of retinoblastoma particularly with intra-arterial chemotherapy (Chap. 12). It is a useful surrogate for obtaining information about visual potential in preverbal children and the effect of treatment toxicity on retinal function. During the EUA a photopic 30 Hz flicker can be performed prior to the examination in the standard fashion [9]. It is preferable to perform the ERG before any physical manipulation, ophthalmoscopic examination, or photography is performed because such manipulations can affect the reliability of the readings [10].

1.6 Neuroimaging

Neuroimaging is ordered on all patients diagnosed with retinoblastoma at the time of diagnosis to assess the orbits and optic nerves and to screen for pinealoblastoma. Repeat imaging may be performed every 6 months for all germ-line cases up to the age of 6 (±1) years for pineal screening (Chap. 20) [11]. Computed tomography (CT) historically had been very useful in identifying intraocular calcified lesions of retinoblastoma; however, it is currently not recommended in children with retinoblastoma in order to limit their exposure to ionizing radiation (Fig. 1.7b) [12]. MRI of the brain and orbits with and without contrast is currently the preferred initial study. Intraocular retinoblastoma on T1-weighted images appears hyperechoic compared to vitreous and enhances with contrast. On T2-weighted images the RB lesions appear hypoechoic compared to vitreous. There should be no significant enhancement of the optic nerves post contrast (Fig. 1.8).

1.7 Counseling

After taking the detailed history, performing a thorough examination, and reviewing the ancillary studies, a detailed discussion regarding the nature of retinoblastoma, genetic aspects (and testing) (Chap. 8), and of the available therapeutic options (Chap. 9) can be held with the family and patient so as to devise and initiate a treatment plan.

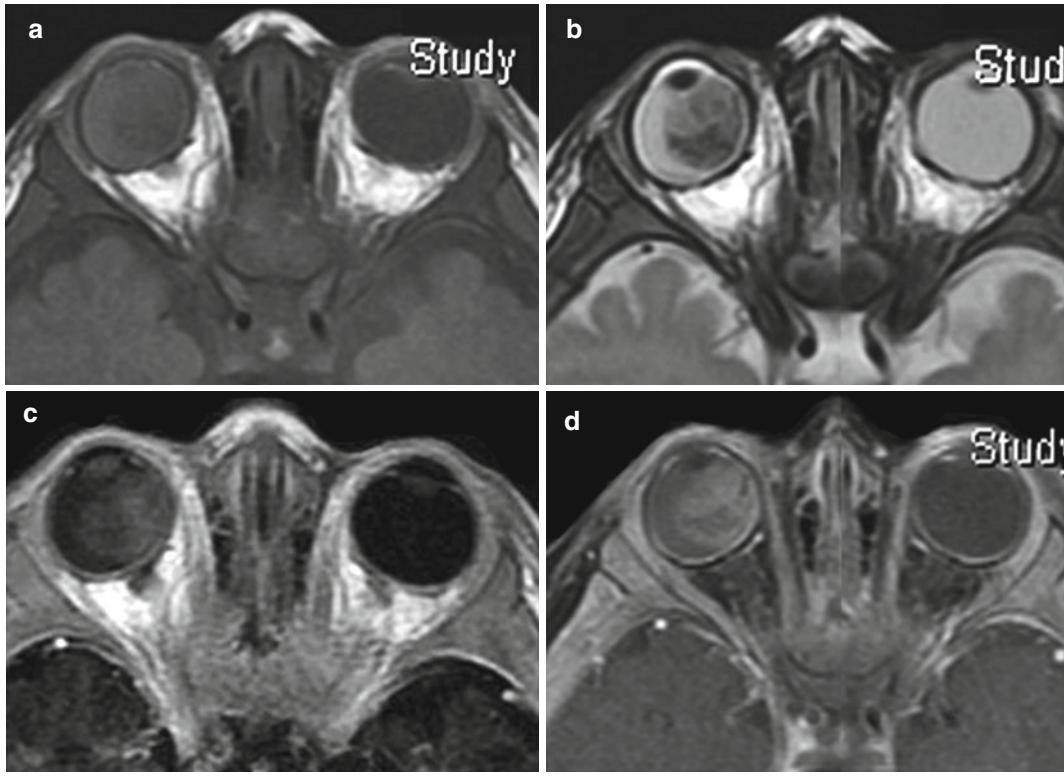

Fig. 1.8 Magnetic resonance imaging (MRI) of a patient with retinoblastoma. A T1-weighted image demonstrating an intraocular mass in the right eye (**a**). On T2-weighted image, the tumor is darker than the adjacent vitreous (**b**). A T1-weighted image following administration of contrast demonstrating enhancement of the tumor (**c**). With fat suppression, enhancement of the tumor is highlighted (**d**)

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