Clinical Ophthalmic Oncology

Retinoblastoma

Jesse L. Berry
Jonathan W. Kim
Bertil E. Damato
Arun D. Singh
Editors

Third Edition

Springer

Clinical Ophthalmic Oncology

Jesse L. Berry • Jonathan W. Kim
Bertil E. Damato • Arun D. Singh
Editors

Clinical Ophthalmic Oncology

Retinoblastoma

Third Edition

Springer

Editors
Jesse L. Berry
Associate Professor of Ophthalmology
Children's Hospital Los Angeles
The USC Roski Eye Institute
Keck School of Medicine
Los Angeles, CA
USA

Bertil E. Damato
University of Oxford
Nuffield Department of Clinical
Neurosciences
John Radcliffe Hospital
Oxford
UK

Jonathan W. Kim
Children's Hospital Los Angeles
The USC Roski Eye Institute
Keck School of Medicine
Los Angeles, CA
USA

Arun D. Singh
Department of Ophthalmic Oncology
Cole Eye Institute, Cleveland Clinic
Cleveland, OH
USA

ISBN 978-3-030-11122-9 ISBN 978-3-030-11123-6 (eBook)
https://doi.org/10.1007/978-3-030-11123-6

Library of Congress Control Number: 2019934958

This Springer imprint is published by the registered company Springer Nature Switzerland AG.
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Ophthalmic tumors are rare and diverse, so their diagnosis can be quite complex. Treatment usually requires special expertise and equipment and, in many instances, is controversial. The field is advancing rapidly, because of accelerating progress in tumor biology, pharmacology, and instrumentation. Increasingly, the care of patients with an ocular or adnexal tumor is provided by a multidisciplinary team, consisting of ocular oncologists, general oncologists, radiotherapists, pathologists, psychologists, and other specialists.

For all these reasons, we felt that there was a need for the new edition of the textbook providing a balanced view of current clinical practice. Although each section of *Clinical Ophthalmic Oncology* now represents a standalone volume, each chapter has a similar layout with boxes that highlight the key features, tables that provide comparison, and flow diagrams that outline therapeutic approaches.

The enormous task of editing a multi-author, multivolume textbook could not have been possible without the support and guidance by the staff at Springer: Caitlin Prim, Melanie Zerah, ArulRonika Pathinathan, and Karthik Rajasekar. Michael D. Sova kept the pressure on to meet the production deadlines.

It is our sincere hope that our efforts will meet the high expectation of the readers.

Los Angeles, CA, USA — Jesse L. Berry
Los Angeles, CA, USA — Jonathan W. Kim
Oxford, UK — Bertil E. Damato
Cleveland, OH, USA — Arun D. Singh

Acknowledgments

I want to acknowledge my friend and mentor, Linn Murphree; my grandmother, Jeannette, for always believing in me; my husband, Paul, and our growing family. (JB)

I want to acknowledge and thank my teachers, A. Linn Murphree, Bertil Damato, and David Abramson, for their wonderful mentorship over the years. I would also like to thank my parents, Heja and Jinku, for inspiring a young boy to become a physician. To Diana and Devin, I dedicate all of my work here and forever to both of you. (JWK)

To my family, Frankanne, Erika, Stephen, and Anna. (BED)

To my parents who educated me beyond their means, my wife Annapurna, and my children, Nakul and Rahul, who make all my efforts worthwhile. (ADS)

A. Linn Murphree, MD, Professor of Ophthalmology and Pediatrics at the Keck School of Medicine, University of Southern California (USC), and former Director of the USC Ocular Oncology Service and the Children's Hospital Los Angeles (CHLA) Retinoblastoma Program

Following his training as a Fulbright Fellow in Human Genetics at the University of Copenhagen, Dr. Murphree began his medical training at Baylor College of Medicine with an interest in human genetics. He discovered a passion for both ophthalmology and pediatrics in medical school and subsequently combined those three interests by focusing his career on ophthalmic genetic diseases including retinoblastoma.

Dr. Murphree assumed the position of Division Head, Pediatric Ophthalmology, at CHLA upon completion of his fellowship in pediatric ophthalmology at Johns Hopkins Hospital. With his first NIH grant, he was one of the pioneers in discovering the location of the retinoblastoma gene on chromosome 13 by performing detailed deletion mapping. Subsequently, he developed a clinical referral practice focused on ocular oncology and developed the largest retinoblastoma referral center in the western USA.

In addition to the discovery of the retinoblastoma gene, Dr. Murphree's contributions to the field of pediatric ocular oncology are numerous and groundbreaking. In his clinical practice, Dr. Murphree recognized an unmet need for a wide-field retinal camera to document the intraocular findings associated with retinoblastoma. He recruited a team of engineers and collaborated with optical engineers in private industry to develop the RetCam, which is the most widely used retinal camera in the world to document pediatric retinal abnormalities. Dr. Murphree's work on systemic chemotherapy in the 1990s caused a paradigm shift in the treatment of intraocular retinoblastoma away from enucleation and external beam radiation. Dr. Murphree also created the International Classification system for retinoblastoma, which is still the most popular method for diagnosing retinoblastoma for clinicians worldwide. He is the author or coauthor of more than 70 major papers on retinoblastoma genetics and treatment. Dr. Murphree's work over four decades revolutionized the field of retinoblastoma and improved the lives of countless children afflicted with retinoblastoma.

Dr. Murphree was the former editor of the *Retinoblastoma* volume of *Clinical Ophthalmic Oncology*, and we are indebted to him for his mentorship during the writing of this current edition. He is universally respected in the field of ocular oncology for his ingenuity, expertise, kindness, and generous spirit. As the current editors of the *Retinoblastoma* sections, we honor his legacy and thank him for all of his previous and current contributions.

Jesse L. Berry
Jonathan W. Kim
Bertil E. Damato
Arun D. Singh

Contents

Contributors

Jesse L. Berry, MD Department of Ophthalmology, USC Roski Eye Institute, Keck School of Medicine of USC, Children's Hospital Los Angeles, Los Angeles, CA, USA

Silvia Bhatt-Carreño, MPH Department of Epidemiology, Mailman School of Public Health, Columbia University Medical Center, New York, NY, USA

Randy C. Bowen, MD Department of Ophthalmology, University of Wisconsin, Madison, WI, USA

Rachel C. Brennan, MD Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA

Guillermo L. Chantada, MD Hemato-oncology Department, Hospital JP Garrahan, Buenos Aires, Argentina

Bhavna Chawla, MBBS, MS (Ophthalmology) Ocular Oncology Service Dr. Rajendra Prasad Centre for Ophthalmic Sciences, New Delhi, India

Patricia Chévez-Barrios, MD Departments of Pathology and Genomic Medicine and Ophthalmology, Weill Cornell Medical College, New York, NY, USA

Murali Chintagumpala, MD Texas Children's Cancer Center at Baylor College, Houston, TX, USA

Bertil E. Damato, MD, PhD, FRCOphth University of Oxford, Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford, UK

Anthony B. Daniels, MD, MSc Department of Ophthalmology and Visual Sciences, Vanderbilt Eye Institute, Nashville, TN, USA

Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA

Meghan J. DeBenedictis, MS, LCGC, MEd Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA

Helen Dimaras, PhD Department of Ophthalmic Oncology, The Hospital for Sick Children; The University of Toronto, Toronto, ON, Canada

Ira J. Dunkel, MD Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Michael A. Dyer, PhD Department of Developmental Neurobiology, St. Jude Children's Research Hospital, Memphis, TN, USA

Ralph C. Eagle, MD Department of Pathology, Wills Eye Hospital Thomas Jefferson University, Philadelphia, PA, USA

Jose J. Echegaray, MD Departments of Vitreoretinal Surgery and Ocular Oncology, Bascom Palmer Eye Institute, University of Miami, Miami, FL, USA

Debra Friedman, MD Division of Hematology-Oncology, Vanderbilt University School of Medicine, Nashville, TN, USA

Dan S. Gombos, MD FACS MD Anderson Cancer Center, The Retinoblastoma Center of Houston (MD Anderson/Texas Children's/Baylor/Methodist Hospital), Section of Ophthalmology-Department of Head and Neck Surgery, Houston, TX, USA

Maya Hada, MD Department of Ophthalmology, SMS Medical College & Hospital, Jaipur, Rajasthan, India

Rima Fuad Jubran, MD, MPH, MA, CM Division of Hematology, Oncology and Blood and Marrow Transplantation, Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, Los Angeles, CA, USA

Department of Pediatrics, Keck School of Medicine, University of Southern California, Children's Hospital Los Angeles, Los Angeles, CA, USA

Jonathan W. Kim, MD Department of Ophthalmology, USC Roski Eye Institute, Keck School of Medicine of USC, Children's Hospital Los Angeles, Los Angeles, CA, USA

Benjamin C. King, MD Hamilton Eye Institute, Department of Ophthalmology, University of Tennessee Health Sciences Center, Memphis, TN, USA

Carlos A. Leal, MD Department of Oncology, Instituto Nacional de Pediatria, Mexico City, Mexico

Eduardo F. Marback, MD Department of Ophthalmology, Federal University of Bahia, Rio Vermelho, Salvador, Bahia, Brazil

Brian Marr, MD Department of Ophthalmology, Columbia University Medical Center, New York, NY, USA

Anna T. Meadows, MD The Children's Hospital of Philadelphia, Philadelphia, PA, USA

Thomas A. Mendel, MD, PhD Department of Ophthalmology and Visual Sciences, Vanderbilt Eye Institute, Nashville, TN, USA

Francis L. Munier, MD Department of Ophthalmology, Jules-Gonin Eye Hospital, University of Lausanne, Lausanne, Vaud, Switzerland

A. Linn Murphree, MD Department of Ophthalmology, Children's Hospital Los Angeles, University of Southern California, Los Angeles, CA, USA

USC Roski Eye Institute, Department of Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Manuela Orjuela-Grimm, MD, ScM Department of Epidemiology, Mailman School of Public Health, Columbia University Medical Center, New York, NY, USA

Rachana Shah, MD, MS Division of Hematology, Oncology and Blood and Marrow Transplantation, Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, Los Angeles, CA, USA

Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Arun D. Singh, MD Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA

Nakul Singh, MS School of Medicine, Case Western University, Cleveland, OH, USA

Alison H. Skalet, MD, PhD Casey Eye Institute, Department of Ophthalmology, Oregon Health and Science University, Portland, OR, USA

Department of Radiation Medicine, Oregon Health and Science University, Portland, OR, USA

Christina Stathopoulos, MD Department of Ophthalmology, Jules-Gonin Eye Hospital, University of Lausanne, Lausanne, Vaud, Switzerland

Julie Ann Stoner, PhD University of Nebraska Medical Center, Nebraska Medical Center, Omaha, NE, USA

Brian C. Tse, MD Department of Ophthalmology, University of Miami Bascom Palmer Eye Institute, Miami, FL, USA

Rajkumar Venkatramani, MD, MS Texas Children's Cancer Center, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA

Judith Grob Villablanca, MD Children's Hospital of Los Angeles, Los Angeles, CA, USA

Matthew W. Wilson, MD, FACS Hamilton Eye Institute, Department of Ophthalmology, University of Tennessee Health Sciences Center, Memphis, TN, USA

Kenneth K. Wong, MD Department of Ophthalmology, USC Roski Eye Institute, Keck School of Medicine of USC, Children's Hospital Los Angeles, Los Angeles, CA, USA

Honggai Yan, MD Department of Ophthalmology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

Junyang Zhao, MD Department of Ophthalmology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

Retinoblastoma: Evaluation and Diagnosis

1

Brian Marr and Arun D. Singh

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 "spongiod 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 the 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.

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 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 greater proportion of cases with extraocular disease (Chap. 5). One of the major limitations to prompt treatment of retinoblastoma worldwide

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%

Based on data from Abramson et al. [14]

B. Marr (✉)
Department of Ophthalmology, Columbia University Medical Center, New York, NY, USA
e-mail: bpm2133@cumc.columbia.edu

A. D. Singh
Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA

J. L. Berry et al. (eds.), *Clinical Ophthalmic Oncology*,
https://doi.org/10.1007/978-3-030-11123-6_1

is access and availability to healthcare. 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).

Misdiagnosis

Histopathological studies of eyes enucleated 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 healthcare 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.

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.

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). The story of how and over what time course the condition was noted, the healthcare 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 performed. A small subset of parents of children with RB will have evidence of retinoma/retinocytoma and even unknown treated retinoblastoma (Chap. 8) [4].

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.

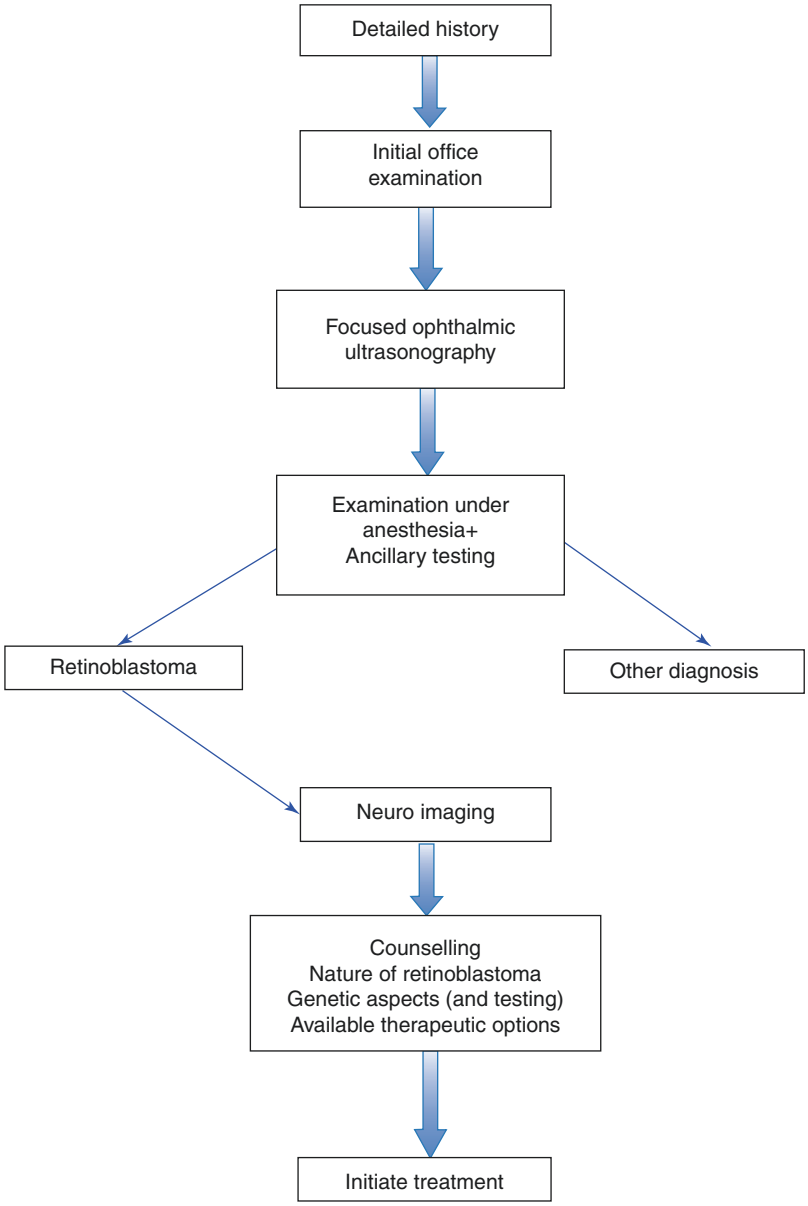

Fig. 1.1 Stepwise evaluation for retinoblastoma. This approach is merely a guide that can be modified as needed based upon clinical setting

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

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

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	

before placing the speculum. A detailed fundus examination with scleral depression may be performed with 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.

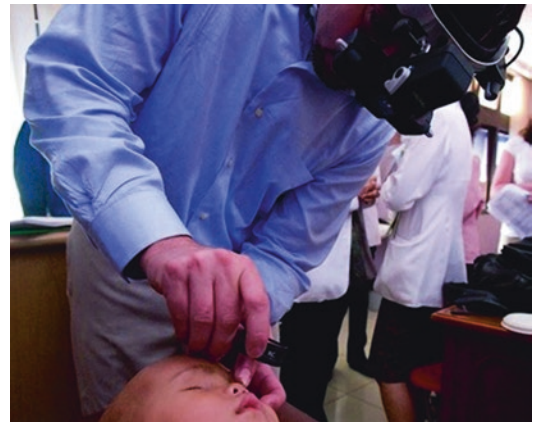

Fig. 1.2 An indirect ophthalmoscopic examination being performed in an office setting with the mother helping to hold the child

Ophthalmic Ultrasonography

A limited ophthalmic ultrasonography can be done in A/B scan mode using a 10 Hz transducer to visualize the presence of a mass, calcification, retinal detachment, or abnormalities of the posterior pole.

If retinoblastoma is recognized and further examination is necessary, ideally the child is scheduled for a 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. 22).

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 hours prior to the exam. Breast milk is allowed up to 4 hours before the exam and clear liquids up to 2 hours 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	Prior to dilation	
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	

External Examination

The overall appearance of the patient should be assessed by looking at the face 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, a flat nasal bridge, small mouth and nose, high arched or cleft pallet, micrognathia, and/or microcephaly which may be noted during this part of the examination (Chap. 9).

Anterior Segment Examination

Intraocular pressure should be measured using a Schiotz tonometer, tonopen, 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 the eyes (Fig. 1.3), and the 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

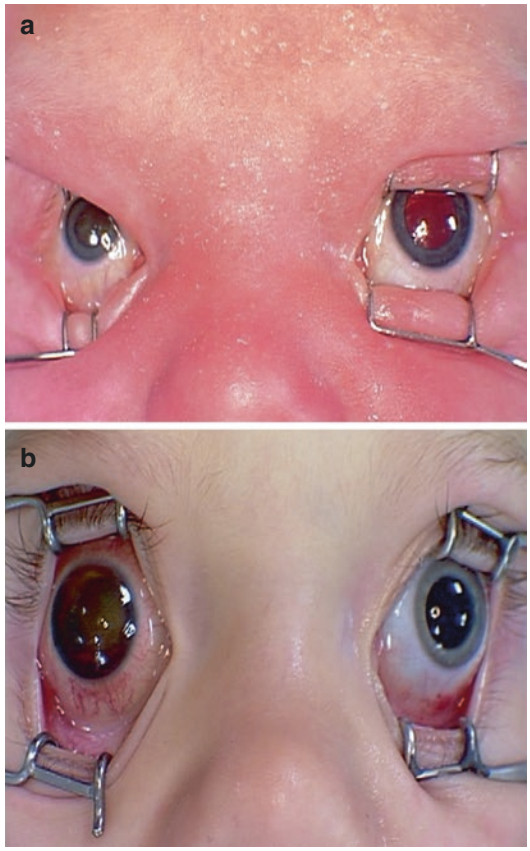

Fig. 1.3 (**a**) A patient with persistent fetal vasculature showing the discrepancy between the corneal diameters. (**b**) A patient with advanced retinoblastoma showing increased corneal diameter and heterochromia from iris neovascularization

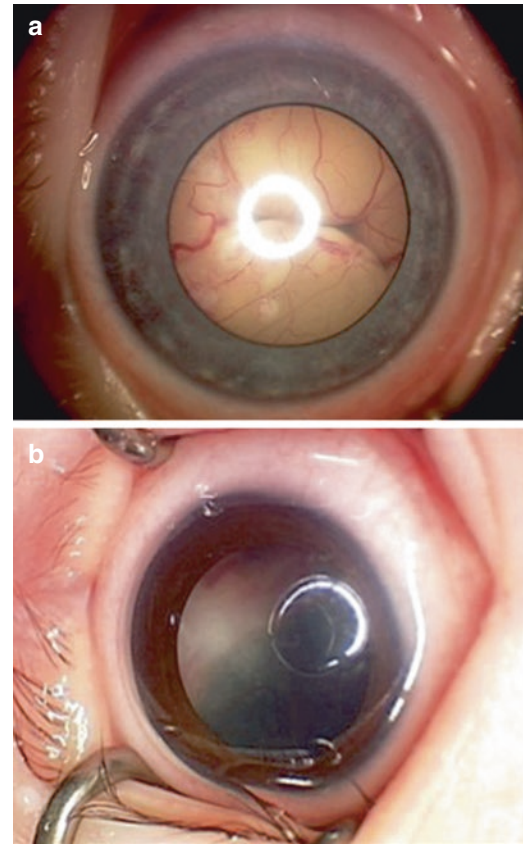

Fig. 1.4 Anterior segment photograph of a patient with advanced retinoblastoma (**a**). Note the branching patterns of the retinal blood vessels toward the periphery of the lens. Anterior segment photograph of the patient with persistent fetal vasculature (**b**). Note the retrolental vascular mass

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).

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 pars plana.

One eye at a time, 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 degrees 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 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).

Ancillary Testing

Photography

It is useful to document both the anterior segment and 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 to treatments. Care should be taken to standardize the orientation and position of the photographs to help with future comparisons.

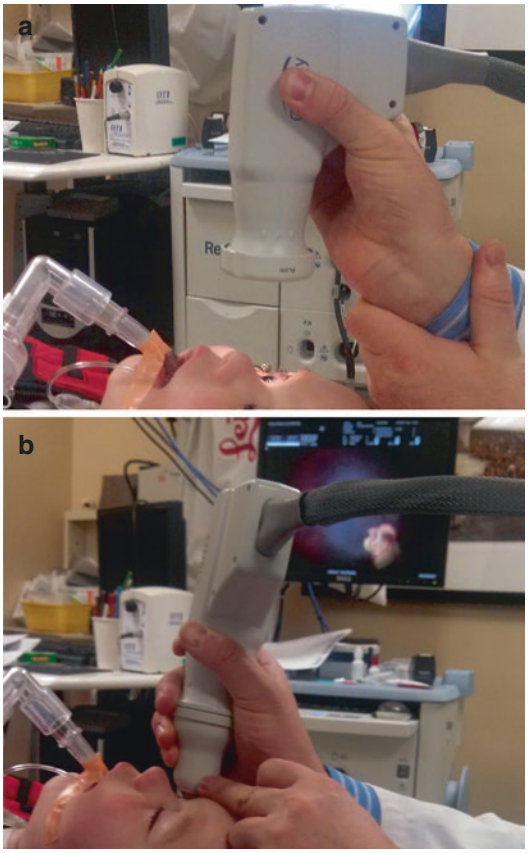

Fig. 1.5 Photography of a patient during an examination under anesthesia. The external lens used to photograph the anterior segment (**a**). The wide-angle fundus lens is used to take photographs of the posterior pole (**b**)

Fluorescein Angiography

Fluorescein angiography (FA) can be a useful tool during a 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 hypo-fluorescent tumor mass that stains and leaks depending on its size. FA is especially useful in differentiating RB from advanced Coats' disease. In contrast to RB, Coats' disease has large dilated telangiectatic vessels that remain in the plane of the retina and have marked areas of peripheral capillary nonperfusion (Fig. 1.6).

Ophthalmic Ultrasonography

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

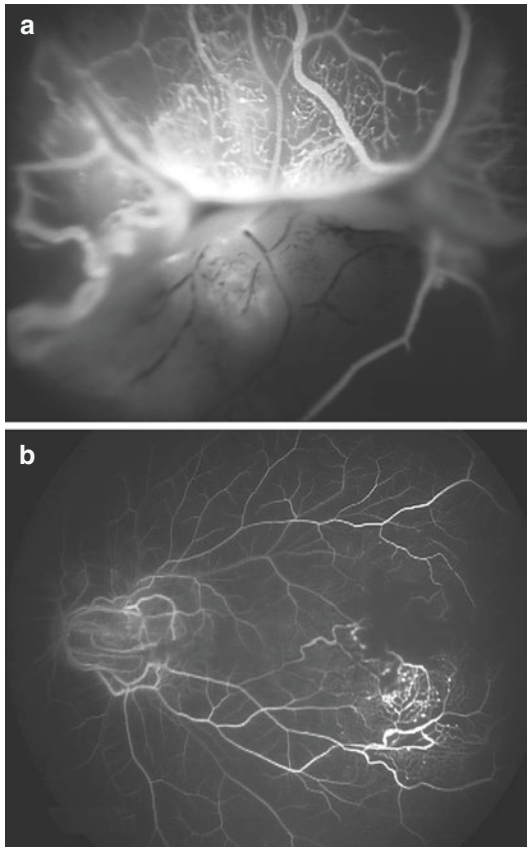

Fig. 1.6 Fluorescein angiograms taken during an exam under anesthesia. A fluorescein angiogram of a patient with retinoblastoma demonstrating irregular vessels within the retina and slower filling vessels within the tumor inferiorly (**a**). Fluorescein angiogram of a patient with Coats' disease demonstrating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

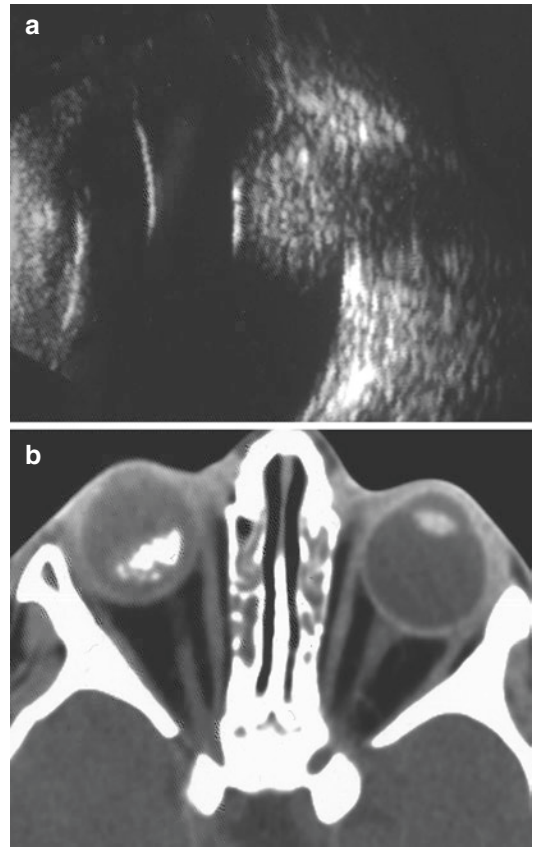

Fig. 1.7 Calcification within retinoblastoma. Ultrasonography of an eye with retinoblastoma in B scan mode showing a hyperreflective mass and acoustic shadowing (**a**). A CT scan of a patient with retinoblastoma demonstrating the intraocular calcification seen within the tumor in the right eye (**b**)

multiple areas of hyper-reflectivity with acoustic shadowing (Fig. 1.7a).

Ultrasound Biomicroscopy

Ultrasound biomicroscopy (UBM) also can be performed during a 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 that are being considered for intravitreal chemotherapy injection (Chap. 15).

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. 14). 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].

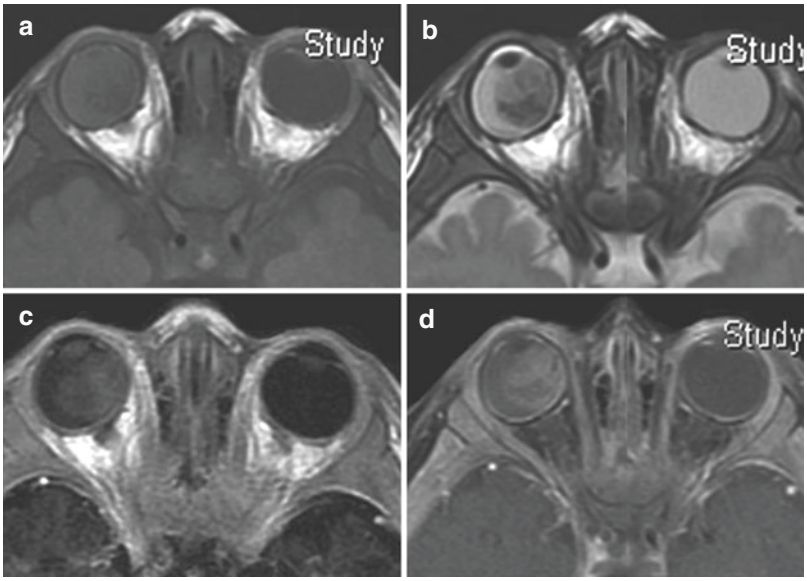

Fig. 1.8 Magnetic resonance imaging (MRI) of a patient with retinoblastoma. A T1-weighted image demonstrating an intraocular mass in the right eye (**a**). On T2-weighted image, the tumor is darker than the adjacent vitreous (**b**). A T1-weighted image following administration of contrast demonstrating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

Neuroimaging

Neuroimaging is ordered on all patients diagnosed with retinoblastoma at time of diagnosis to assess the orbits and optic nerves and to screen for pinealoblastoma. Repeat imaging may be performed every 6 months basis for all germline cases up to the age of 6 (+/−1) years for pineal screening (Chap. 23) [11]. Computed tomography (CT) scans 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).

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), the need for screening of family members and relatives (Chap. 9), and of the available therapeutic options (Chap. 10) can be held with the family and patient so as to devise and initiate a treatment plan [13].

References

1. Kivelä T. 200 years of success initiated by James Wardrop's 1809 monograph on retinoblastoma. Acta Ophthalmol. 2009;87:810–2.
2. Dunphy EB. The story of retinoblastoma. Am J Ophthalmol. 1964;58:539–52.
3. Maki JL, Marr BP, Abramson DH. Diagnosis of retinoblastoma: how good are referring physicians? Ophthalmic Genet. 2009;30:199–205.
4. Shields CL, Shields JA, Baez K, et al. Optic nerve invasion of retinoblastoma. Metastatic potential and clinical risk factors. Cancer. 1994;73:692–8.
5. Gallie BL, Ellsworth RM, Abramson DH, et al. Retinoma: spontaneous regression of retinoblastoma or benign manifestation of the mutation? Br J Cancer. 1982;45:513–21.
6. Lin BA, Messieha ZS, Hoffman WE. Safety and efficacy of pediatric general anesthesia by Laryngeal Mask Airway without Intravenous Access. Int J Clin Med. 2011;2:328–31.
7. Sterns GK, Coleman DJ, Ellsworth RM. Characterization and evaluation of retinoblastoma by ultrasonography. Bibl Ophthalmol. 1975;83:125–9.
8. Abramson DH, Ellsworth RM. Ancillary tests for the diagnosis of retinoblastoma. Bull N Y Acad Med. 1980;56:221–31.

9. Liu CY, Jonna G, Francis JH, et al. Non-selectivity of ERG reductions in eyes treated for retinoblastoma. Doc Ophthalmol. 2014;128:13–23.
10. Francis JH, Abramson DH, Marr BP, et al. Ocular manipulation reduces both ipsilateral and contralateral electroretinograms. Doc Ophthalmol. 2013;127:113–22.
11. Albert DM. Trilateral retinoblastoma: insights into histogenesis and management. Surv Ophthalmol. 1998;43:59–70.
12. de Graaf P, Göricke S, Rodjan F, et al. European Retinoblastoma Imaging Collaboration (ERIC). Guidelines for imaging retinoblastoma: imaging principles and MRI standardization. Pediatr Radiol. 2012;42:2–14.
13. Skalet AH, Gombos DS, Gallie BL, et al. Screening children at risk for retinoblastoma: consensus report from the American Association of Ophthalmic Oncologists and Pathologists. Ophthalmology. 2018;125:453–8.
14. Abramson DH, Frank CM, Susman M, et al. Presenting signs of retinoblastoma. J Pediatr. 1998;132(3 Pt 1): 505–8.

2 Differential Diagnosis of Leukocoria

Jonathan W. Kim and Arun D. Singh

Introduction

Leukocoria is the most common presenting sign of intraocular retinoblastoma in developed countries [1]. The asymmetric white pupil light reflex may be noted on photographs, in dimly lit environments by the family, or by a general pediatrician at a well-child visit [2]. An abnormal pupil reflex is also frequently observed in several pediatric ocular conditions including cataract (Fig. 2.1), and it is important to clinically differentiate retinoblastoma from simulating diagnoses (Table 2.1). Directed by the available demographic and historical data, a comprehensive clinical and ultrasound examination in the office is usually sufficient to make the correct diagnosis. Occasionally, an examination under anesthesia may be necessary to distinguish retinoblastoma from simulating conditions, such as Coats' disease, persistent hyperplastic primary vitreous (PHPV), retinal dysplasia, or astrocytic hamartoma. Clinical findings associated with the commonly diagnosed conditions are summarized in the following section (Table 2.2) [3–5].

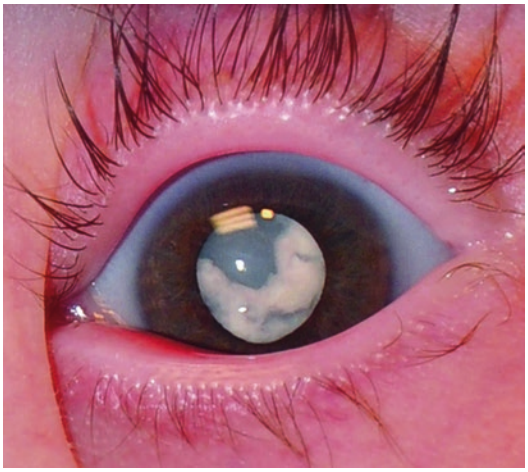

Fig. 2.1 Leukocoria due to cataract induced by a chronic retinal detachment

It is important to carefully and urgently evaluate any child with leukocoria for the possibility of retinoblastoma, although fortunately many children referred for this complaint will have a normal examination (i.e., pseudo-leukocoria). Commonly, it is the parents who first notice the abnormal or asymmetric pupil reflex in a photograph. The flash from a camera typically causes the eye to appear red, since the pupil does not have time to contract and the camera captures a red reflection from the normal retina. Any condition that blocks the camera's flash from reaching the retina may produce a unilateral whitish pupil reflex (i.e., photoleukocoria) [2]. However, it

J. W. Kim (✉)
Department of Ophthalmology, USC Roski Eye Institute, Keck School of Medicine of USC, Children's Hospital Los Angeles, Los Angeles, CA, USA
e-mail: jonkim@chla.usc.edu

A. D. Singh
Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA

J. L. Berry et al. (eds.), *Clinical Ophthalmic Oncology*,
https://doi.org/10.1007/978-3-030-11123-6_2

Table 2.1 Differential diagnosis of childhood leukocoria

1. Tumors
Retinoblastoma
Medulloepithelioma
Leukemia
Combined retinal hamartoma
Astrocytic hamartoma (Bourneville's tuberous sclerosis)
2. Congenital malformations
Persistent fetal vasculature (PFV)
Posterior coloboma
Retinal fold
Myelinated nerve fibers
Morning glory syndrome
Retinal dysplasia
Norrie's disease
Incontinentia pigmenti
Cataract
3. Vascular diseases
Retinopathy of prematurity (ROP)
Coats' disease
Familial exudative vitreoretinopathy (FEVR)
4. Inflammatory diseases
Ocular toxocariasis
Congenital toxoplasmosis
Congenital cytomegalovirus retinitis
Herpes simplex retinitis
Other types of fetal iridochoroiditis
Endophthalmitis
5. Trauma
Intraocular foreign body
Vitreous hemorrhage
Retinal detachment

should be kept in mind that photoleukocoria does not always indicate an underlying pathologic condition. There are case series of patients with documented unilateral leukocoria on photographs who had normal ocular examinations [6]. This phenomenon has been termed pseudo-leukocoria since the examination did not reveal any pathology. In these cases, the child appears to be fixating 15° off axis (inward deviation), which likely resulted in an abnormal light reflex off the optic nerve in that eye (Fig. 2.2). Therefore, photoleu-

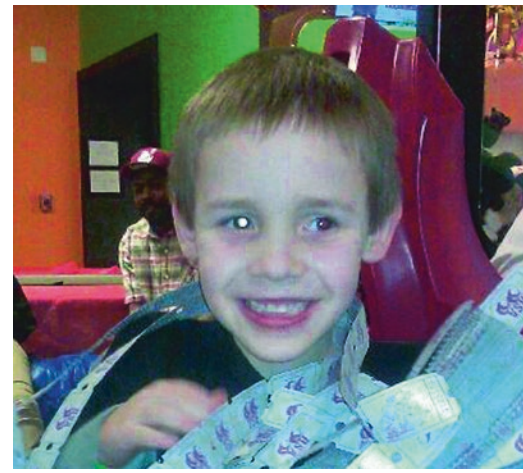

Fig. 2.2 Pseudo-leukocoria noticed on a photograph. Notice unilateral occurrence in the eye that appears to be fixating 15° off axis (inward deviation)

Table 2.2 Differential diagnosis of retinoblastoma: demographics and ultrasonographic features

Condition	Age of presentation	Risk factors	Laterality	Axial length	USG
Retinoblastoma	90% <3 years old	Family history	Unilateral or bilateral	Normal	Intraretinal/subretinal mass with calcification
Coats' disease	4–10 years of age	Male gender	Unilateral	Normal	Exudative RD
					Subretinal hyper-reflective particles
PFV	Days to weeks after birth		Unilateral	Short	Vitreous band from lens to optic nerve
Toxocariasis	Variable	Contact with dogs	Unilateral	Normal	Peripheral mass, vitreoretinal band, traction RD
ROP	Days to months after birth	Prematurity, oxygen supplementation	Bilateral	Short	RD with retinal bands

Reproduced with permission from Turell et al. [11]. With permission from Elsevier
USG ultrasonography, *ROP* retinopathy of prematurity, *RD* retinal detachment, *PFV* persistent fetal vasculature

kocoria is expected to be unilateral (i.e., one eye in a given photo). Alternating photoleukocoria may also occur. Simultaneous bilateral photoleukocoria indicates either true leukocoria or esotropia. However, it is critical that any child with possible leukocoria noted by the parents or any healthcare professional should have an urgent eye examination by an experienced pediatric ophthalmologist or ocular oncologist [7].

Retinoblastoma

Clinical Presentation

The most important clinical finding associated with retinoblastoma is the presence of a retinal-based intraocular mass, which is typically absent with the other conditions on the differential diagnosis. Dilated fundus examination in the office will reveal a whitish tumor often with prominent vascularity (Fig. 2.3). Endophytic tumors grow into vitreous and are typically whitish with associated seeding and without much vascularity. The identification of vitreous or subretinal seeding is therefore very suggestive of retinoblastoma (Fig. 2.4). Exophytic tumors grow in the subretinal space causing exudative retinal detachment and seeding under the retina (Fig. 2.5).

Subretinal lipid exudation can be rarely observed with exophytic tumors and should not be considered pathognomonic for Coats' disease [8]. Diffuse infiltrative growth pattern is rare and typically presents in older children but can be difficult to distinguish from endophthalmitis or uveitis (Fig. 2.6) [9]. Vitreous hemorrhage can be seen

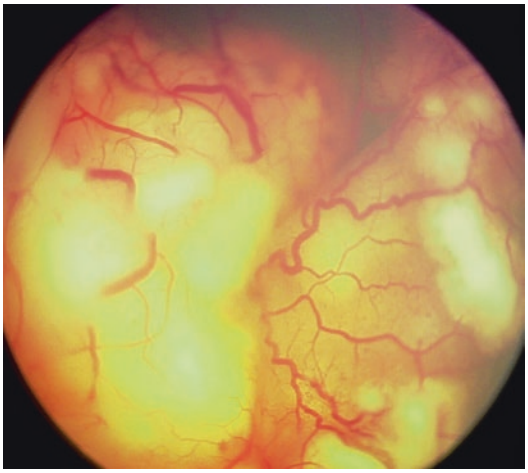

Fig. 2.3 Typical appearance of retinoblastoma. Note a whitish tumor with prominent retinal vascularity

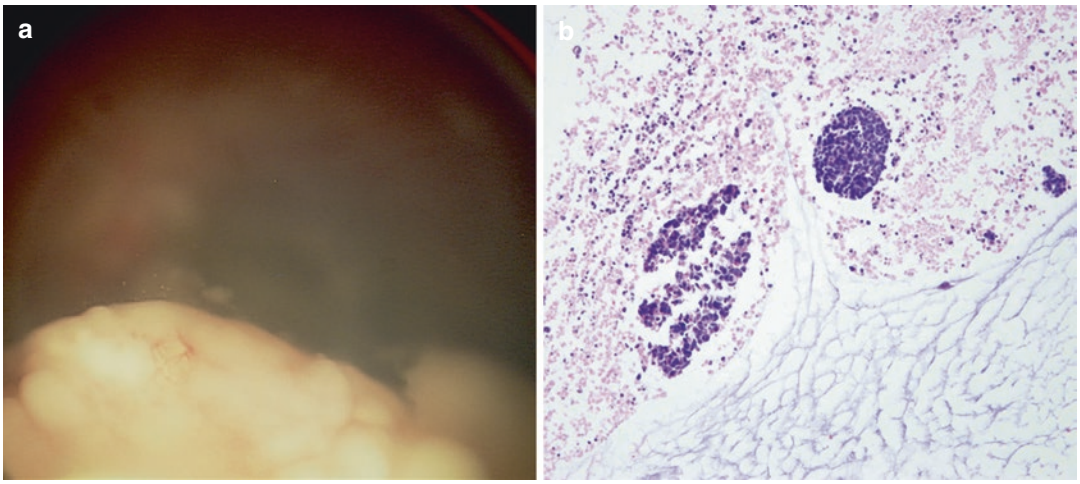

Fig. 2.4 Endophytic retinoblastoma. Prominent vitreous seeding without intrinsic vessels (**a**). Histopathology of vitreous seeding (**b**)

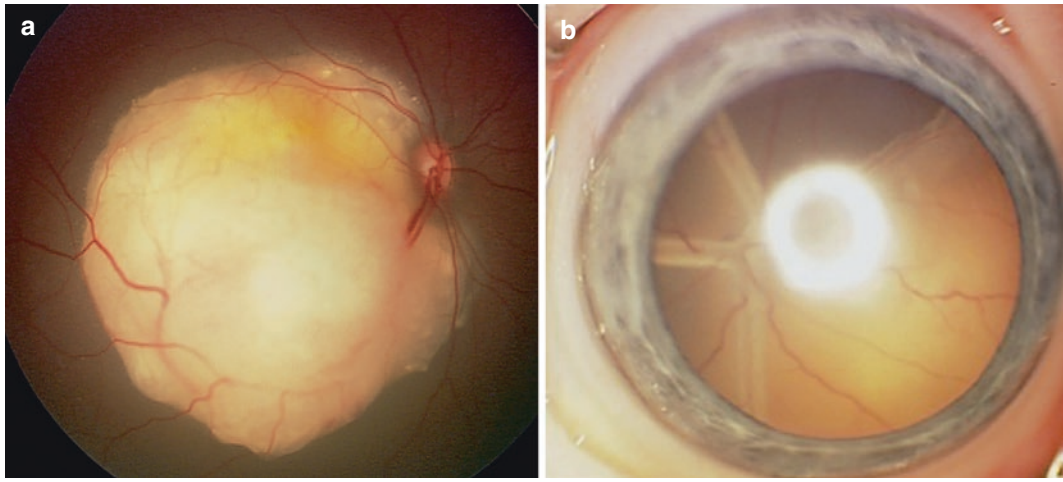

Fig. 2.5 Exophytic retinoblastoma grows in the subretinal space (**a**). When large, they can cause exudative retinal detachment (**b**)

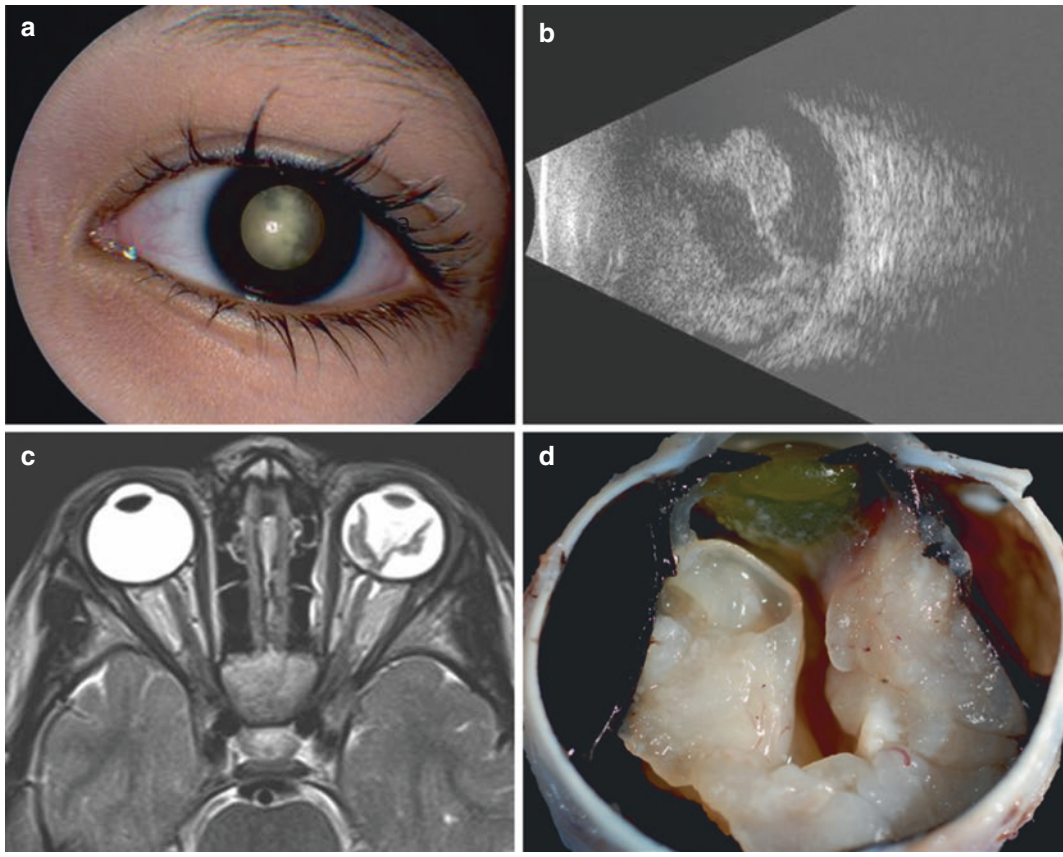

Fig. 2.6 Diffuse variant of retinoblastoma. External photograph demonstrating the appearance of diffuse retinoblastoma (**a**), B-scan ultrasonography revealed irregularly thickened retinal detachment with vitreous cells (**b**). Typical features of retinoblastoma including intraocular mass and intraocular calcification were not present. Magnetic resonance imaging confirmed enhancing thickened retina (**c**). Enucleated globe with diffuse infiltrating retinoblastoma (**d**). (Reprinted from Turell et al. [11]. With permission from Elsevier)

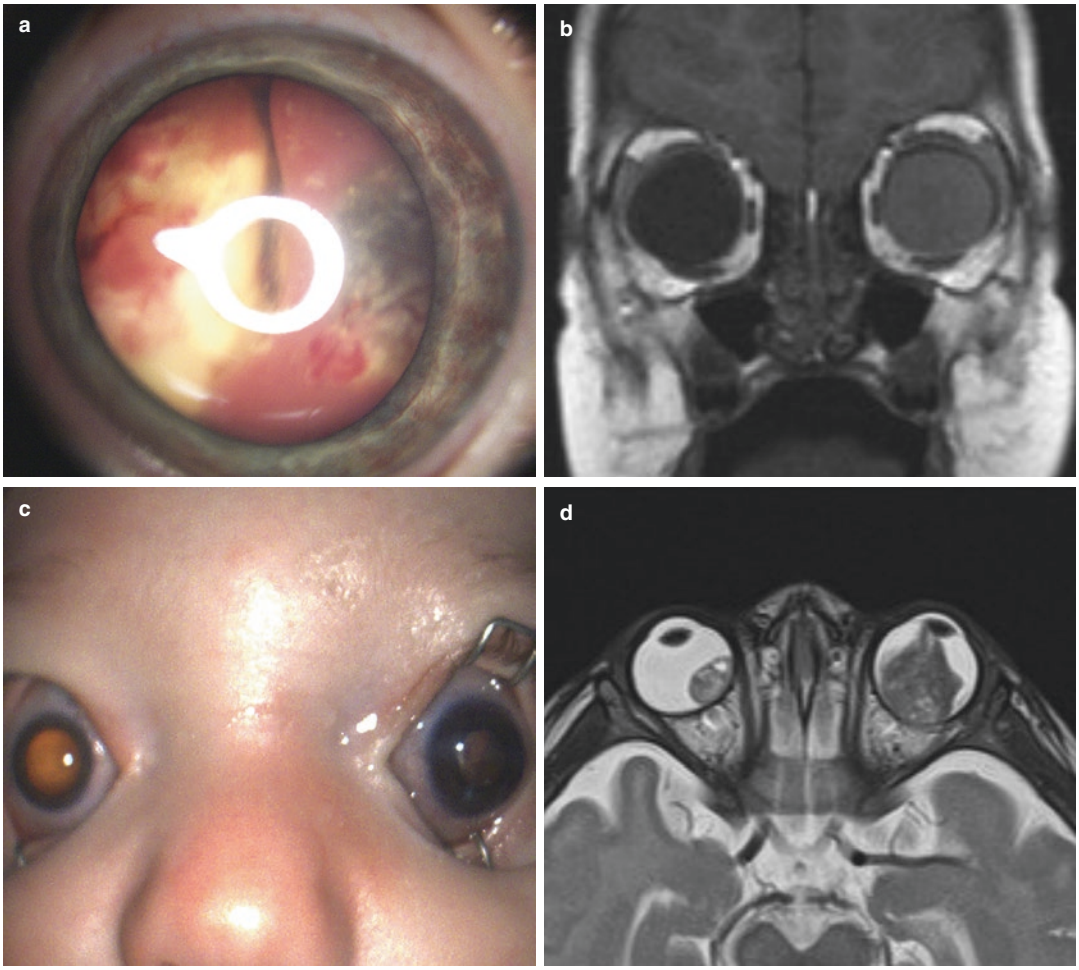

Fig. 2.7 Anterior segment involvement by retinoblastoma presenting as neovascular glaucoma (**a**) due to large tumor filling the entire globe on the MRI (**b**). Eventually due to raised intraocular pressure, buphthalmos can develop evident as asymmetric globes on external examination (**c**) and the MRI (**d**)

occasionally with very advanced tumors. As a general rule, retinal traction or cataracts are not seen with untreated retinoblastoma. Anterior segment involvement by retinoblastoma can cause pseudohypopyon or hyphema. In advanced cases, rubeosis iridis, neovascular glaucoma, buphthalmos (Fig. 2.7), and even orbital cellulitis and proptosis may be encountered (Fig. 2.8) (Chap. 20) [7].

Demographics/History

Approximately 90% of diagnosed cases of retinoblastoma cases are sporadic, while 10% have a positive family history. The average age of diagnosis is 18 months, but retinoblastoma may be present at birth or as old as 8 years. The majority of cases diagnosed below age 1 tend to have bilateral disease, while children older than 2 years typically have unilateral disease. Overall, retinoblastoma is unilateral in 70% and bilateral in 30% of cases. The incidence is equal in males and females, and there is no significant racial or ethnic predilection. There is a genetic association with 13q deletion syndrome, which also presents with other systemic anomalies including mental retardation.

Diagnosis

For most children referred for leukocoria, an unremarkable dilated fundus examination in the

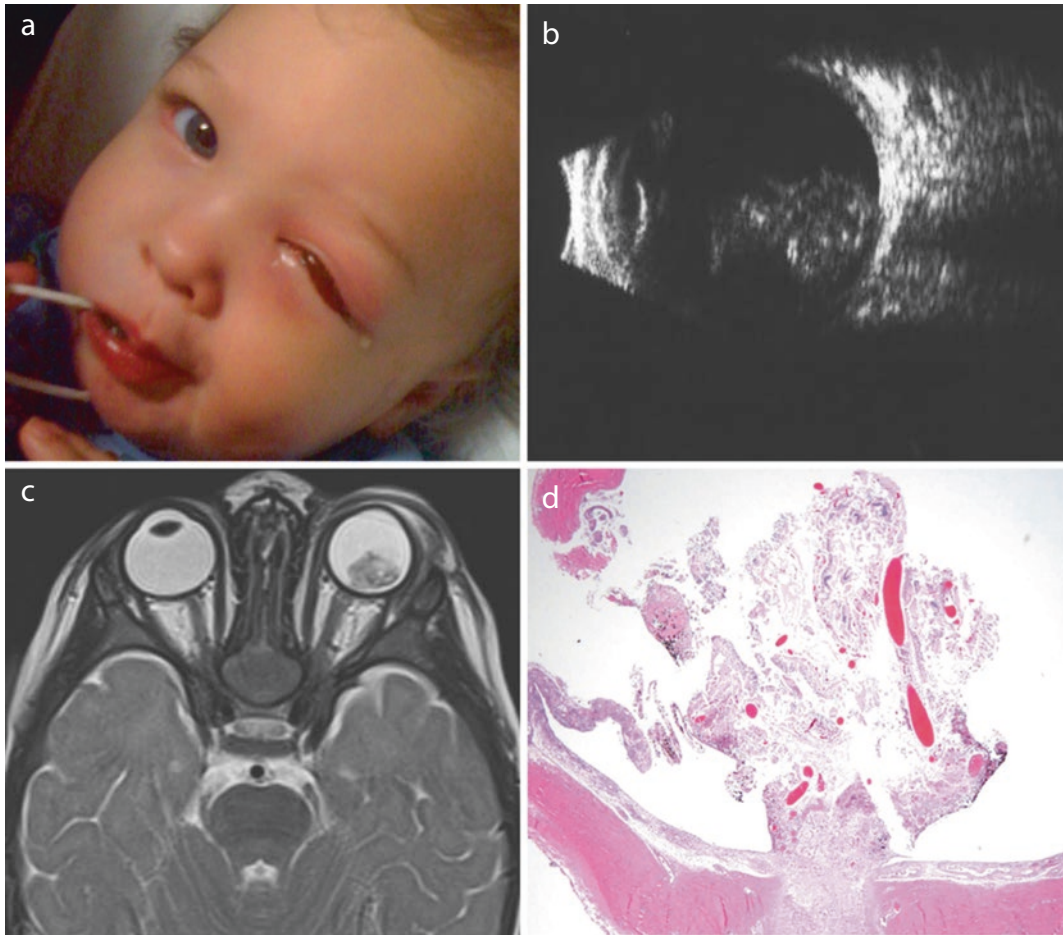

Fig. 2.8 Retinoblastoma presenting as orbital cellulitis. External appearance (**a**). B-scan ultrasonography reveals a large intraocular mass extending from the optic disk. Multiple hyperechogenic intensities are present throughout the mass consistent with calcium deposition (**b**). T2-weighted axial magnetic resonance image reveals an intraocular mass emanating from the optic nerve and retina of the left eye (**c**). Retrobulbar stranding and preseptal edema are evident as well. Histopathologic section (hematoxylin–eosin, original magnification ×40) of the enucleated globe consists of fibrin, detached and degenerating retina, inflammatory cells, prominent vascularity, a small amount of necrosis, and calcification (**d**). (Reprinted from Sachdeva et al. [12]. With permission from Elsevier)

office and normal B-scan ultrasound findings are sufficient to rule out the diagnosis (Chap. 1). If there is any suspicion for retinoblastoma after the office evaluation, both eyes should be examined very carefully under anesthesia to confirm the diagnosis and properly stage the patient. For bilateral patients, more characteristic findings in the contralateral, less advanced eye may be very helpful in making the diagnosis. It is important to emphasize that retinoblastoma is diagnosed clinically and intraocular biopsy is always contraindicated. On fundoscopy, the abnormal vessels associated with the tumor involve both the large and small retinal vasculature with dilation, tortuosity, and occasionally bizarre vascular patterns. There can be small vessel telangiectasias although not as large or as extensive as with Coats' disease. Ultrasound examination will show a dome or placoid-shaped intraocular mass, and larger tumors typically demonstrate intralesional calcification. Calcification within the mass may be demonstrated on CT scans, although clinicians should be aware of the risk of radiation in children with the RB1 mutation (Fig. 2.9). MRI is useful

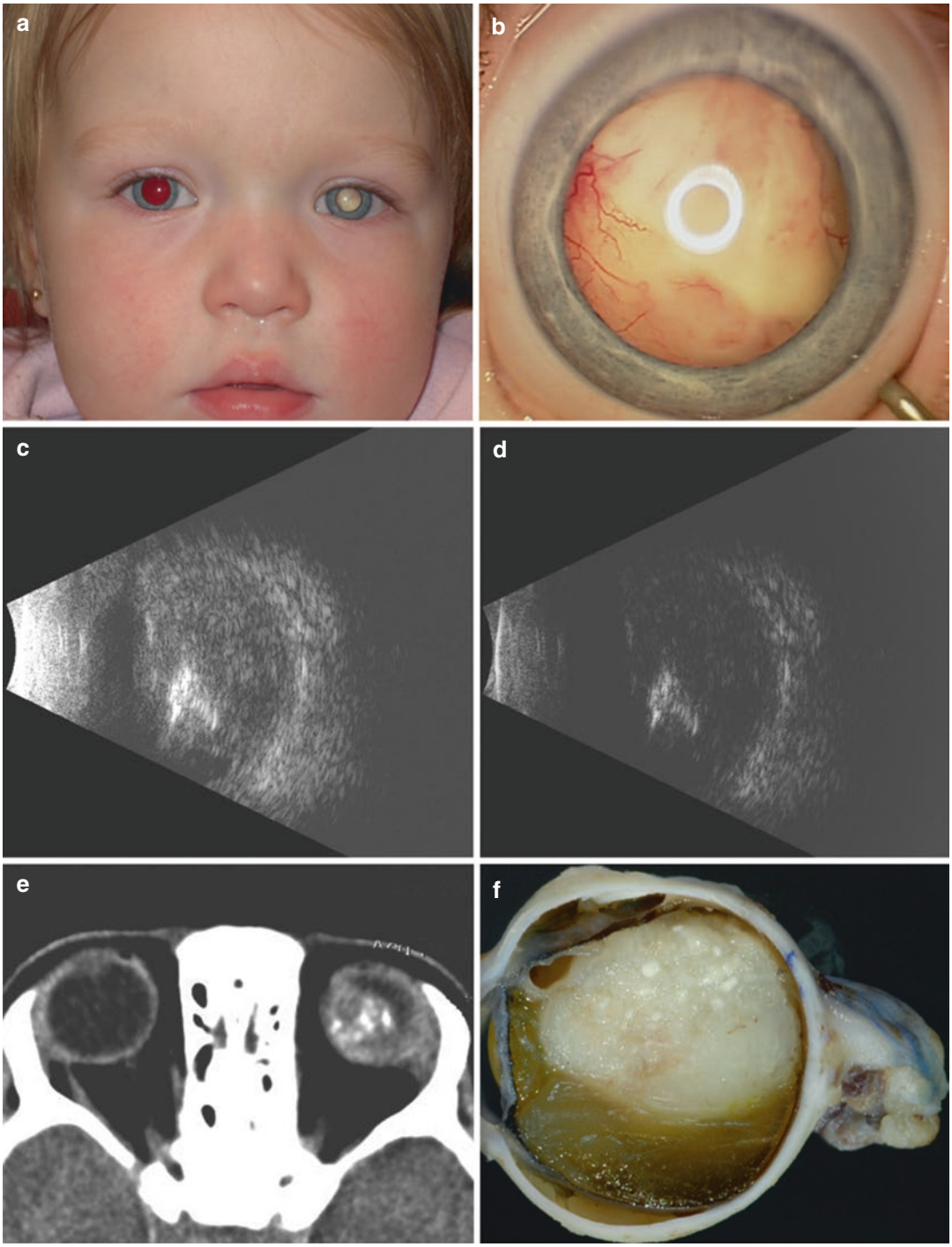

Fig. 2.9 Intrinsic calcification. A 2-year-old girl with left-sided leukocoria (**a**). Closer examination of the anterior segment reveals a quite eye with whitish-yellow pupillary mass with intrinsic vasculature (**b**). B-scan ultrasonography confirmed the mass with intrinsic calcification (**c**) which is evident when the gain is reduced (**d**) about 30 dB. Prior to referral CT scan had also revealed an intraocular mass with calcification (**e**). Enucleation was performed (**f**). The tumor was well differentiated (**g**) without optic nerve extension (**h**)