PEDIATRICS CME

Leukocoria in Children: Findings on CT and MRI of the Principal Causes

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ABSTRACT

Leukocoria is the result of an alteration in the normal red reflex of the ocular fundus, secondary to an obstruction of the normal passage of light to the fundus of the eye that produces a white light reflex. There are many ocular pathologies that can present as leukocoria, among which retinoblastoma is the most frequent. Other causes include cataracts, Coats disease, persistent fetal vasculature, coloboma, retinopathy of prematurity, vitreous hemorrhage, astrocytic hamartoma, and ocular toxocariasis. Although in many situations the diagnosis of these pathologies is clinical or possible with the use of ocular sonography, in certain circumstances, CT or MR imaging may play a very important role in the differential diagnosis. In this review article, we propose that findings such as ocular size, the presence of calcifications, intravenous contrast enhancement, MR imaging signal intensity, CT density, and other pathology-specific findings, along with some clinical data, will guide us to the cause of leukocoria. Knowledge of the most prevalent ages of presentation of these pathologies assists with establishing the final diagnosis.

Learning Objectives: To understand why leukocoria occurs, to list the major causes of leukocoria in children, and to recognize the imaging findings of the most frequent causes of leukocoria and apply them in the differential diagnosis

INTRODUCTION

Leukocoria, from the Greek *"leukos"* (white) and *"kore"* (pupil), literally means "white pupil" and is the absence of the normal deep orange-red pupillary reflex of the eye, which, in the case of leukocoria, is replaced by a whitish color.[1] This abnormal reflex can be seen using an ophthalmoscope or, in many cases, is found incidentally on flash photography. The normal red reflex occurs when light enters the eyeball, passes through normal translucent structures, and reflects the highly vascularized choroid. When the normal passage of light to the ocular fundus is interrupted at any level within the eyeball, leukocoria occurs (Fig 1).[1,2]

The most frequent cause of leukocoria is retinoblastoma, which accounts for 60% of cases of leukocoria in children.[3] Other common causes are cataracts, Coats disease, persistent fetal vasculature, coloboma, vitreous hemorrhage, ocular toxocariasis, and astrocytic retinal hamartoma, among others.[3–5] The objective of this article is to review the MR imaging and CT characteristics of the most prevalent causes of leukocoria, focusing on features that allow differentiation among them.

ABBREVIATION KEY

PFV = persistent fetal vasculature
ROP = retinopathy of prematurity

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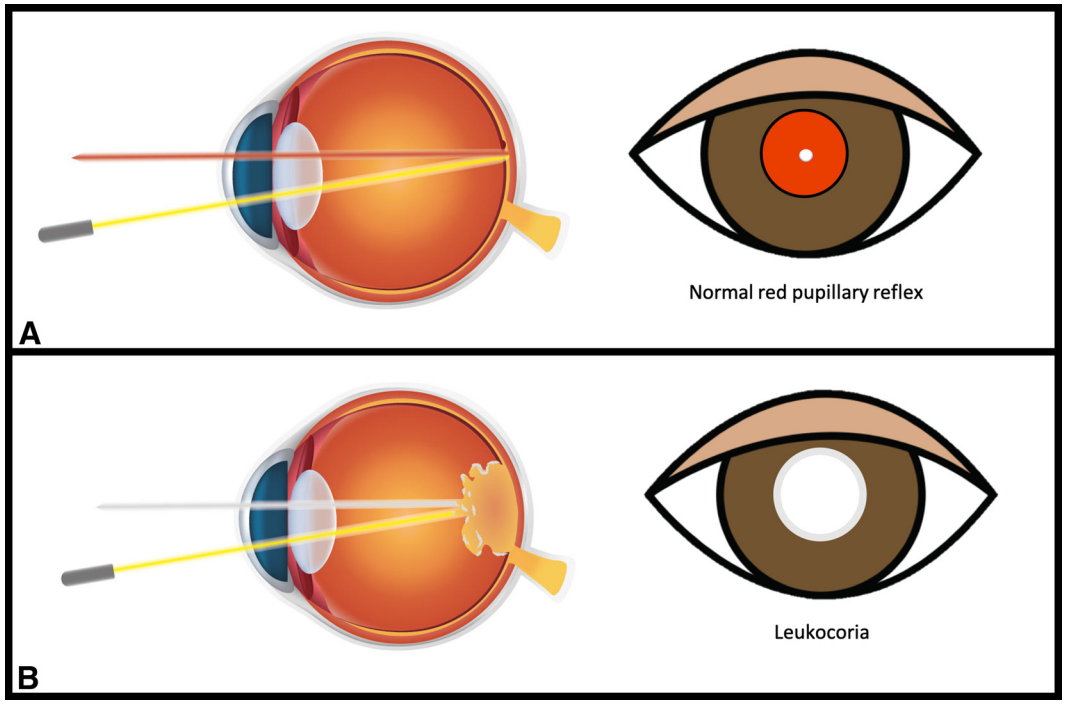

FIG 1. Schematic of a normal and abnormal pupillary red reflex. In a normal red reflex (*A*), light passes through the structures of the globe and reaches the posterior wall of the eyeball. The resulting reflection is red due to the vascularized choroid. In leukocoria (*B*), an obstructing structure such as retinoblastoma prevents light from reaching the posterior wall, producing a whitish reflection.

Retinoblastoma

Retinoblastoma is the most common cause of leukocoria. While rare, representing only 1% of pediatric malignancies, it is the most common malignant intraocular tumor in childhood,[3] with a prevalence of 1 in 18,000 children younger than 5 years of age in the United States.[6] The average age of presentation of retinoblastoma is between 18 and 24 months,[7,8] and almost all patients (95%) are diagnosed before 5 years of age.[6]

Retinoblastoma is a type of primitive neuroectodermal tumor that originates from immature neuroectodermal cells destined to form receptors in the retina.[3] Retinoblastoma is associated with the presence of a mutation located on the 13q14 locus, which inactivates the retinoblastoma tumor-suppressor gene (*Rb 1*).[6] There are 2 types of retinoblastomas: sporadic (55%–60%) and hereditary (40%–45%), both associated with the mutation described, though in the latter type, the mutation is inherited.[6] The mean age of presentation of the hereditary type is 12 months, with the sporadic type appearing at a later age (range, 18–24 months).[3,6] Approximately 60%–70% of retinoblastomas are unilateral; of these, 85% are sporadic and 15% are hereditary.[7,8] The remaining 30%–40% are bilateral and are almost always hereditary.[8] Among cases of bilateral retinoblastoma, approximately 5%–7% are associated with neuroectodermal tumors in the pineal or suprasellar region, which usually manifest later than the primary tumors that arise in the globe.[6] Involvement of these locations is termed "trilateral retinoblastoma" when referring to 3 involved sites (globes and midline tumor) or "quadrilateral retinoblastoma" when 4 sites are compromised (globes and 2 midline tumors).[6,9] Only a very small number of cases report retinoblastoma with single eyeball involvement and the presence of a midline neuroectodermal tumor.[10]

For tumors of the globe, there are 3 growth patterns of retinoblastomas: the endophytic pattern, in which the tumor grows toward the vitreous and can be associated with vitreous seeding, wherein clusters of cells detach from the tumor and float in the vitreous; the exophytic pattern, in which growth is directed outward toward the subretinal space and can be associated with retinal detachment or choroidal or scleral invasion; and the mixed pattern, which is the most frequent.[6,8,11]

There are different patterns of invasion and metastasis in retinoblastoma, (1) direct dissemination to the orbit and adjacent structures, (2) dissemination through the optic nerve to the brain and subarachnoid space, generating leptomeningeal metastasis, (3) hematogenous spread, mainly to the bone, lungs and liver, and (4) infrequently dissemination to regional lymph nodes.[12]

The first imaging study performed is usually sonography, due to its diagnostic capacity and wide availability. Orbital sonography can be performed without sedation and can be repeated multiple times without exposing the child to ionizing radiation. Retinoblastomas appear as echogenic soft-tissue masses with variable shadowing due to calcifications and heterogeneity due to necrosis and hemorrhage.[8] The vitreous body may show "floating" debris, which may represent vitreous seeding, necrotic debris, or hemorrhage.[8]

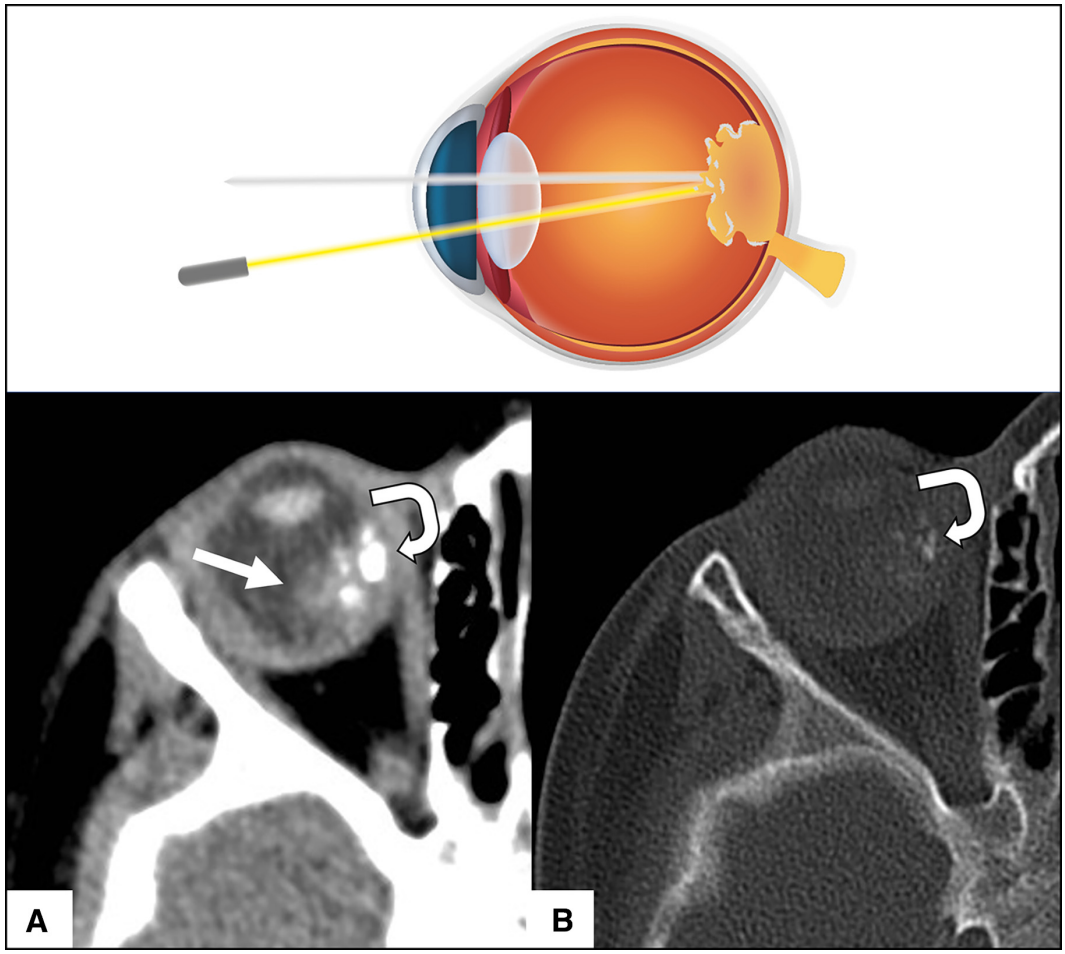

FIG 2. Retinoblastoma of the right eye. Axial images from a noncontrast CT in a soft-tissue kernel (*A*) and bone kernel (*B*) show a hyperdense intraocular mass (*white arrow*) with calcifications (*curved arrows*), compatible with retinoblastoma.

CT is less frequently used due to its inferior resolution of the intraocular and orbital soft tissues, in addition to the necessity to avoid radiation exposure in patients with germline mutations due to the increased risk of secondary malignancies in this group.[13] On CT, retinoblastoma appears as a hyperdense mass (due to its hypercellularity) compared with the vitreous body, with calcifications and moderate enhancement after intravenous contrast administration (Fig 2). CT detection of calcifications in retinoblastoma has a sensitivity of 81%–96% and even higher specificity.[13]

On MR imaging, retinoblastoma appears as a mass with slightly higher signal intensity than ocular fluid on T1-weighted images, low signal intensity on T2-weighted images, and decreased ADC values, findings indicative of high tumor cellularity.[6] After the administration of intravenous contrast, the tumor shows enhancement. This is homogeneous in small tumors, but as the tumor grows, it may show areas of necrosis that do not enhance (Fig 3). Susceptibility sequences can help detect calcifications; Rodjan et al[14] found that signal-intensity voids on in vivo T2*WI correlate well with calcifications on ex vivo CT in retinoblastoma, with an accuracy of about 93% on their sample. DWIs have proved useful in evaluating the response to treatment; treatment response has been shown to be associated with decreased diffusion restriction.[6,15]

MR imaging is useful in the diagnostic evaluation of retinoblastoma and ruling out the presence of possible alternative diagnoses, but its main role in retinoblastoma is the evaluation of infiltration of the optic nerve, intracranial leptomeningeal metastatic disease, and distant metastases (Fig 4).[13] The main predictors of local recurrence and distant metastases are tumor size, involvement of the optic nerve beyond the lamina cribrosa, compromise of the anterior segment of the eye, and infiltration of the choroid and sclera.[13,16] These findings can be very subtle, so it is important to perform a structured evaluation of the tumor on MR imaging. For better evaluation of the characteristics of the tumor, the involvement of the optic nerve, and choroidal or extraocular invasion, the use of surface coils has been recommended, which improves the sensitivity and specificity of these findings.[17]

Cataracts

Cataracts are defined as a clouding of the lens of the eye, which can cause partial or total blindness. In children, a third of cataracts are hereditary, while the remaining two-

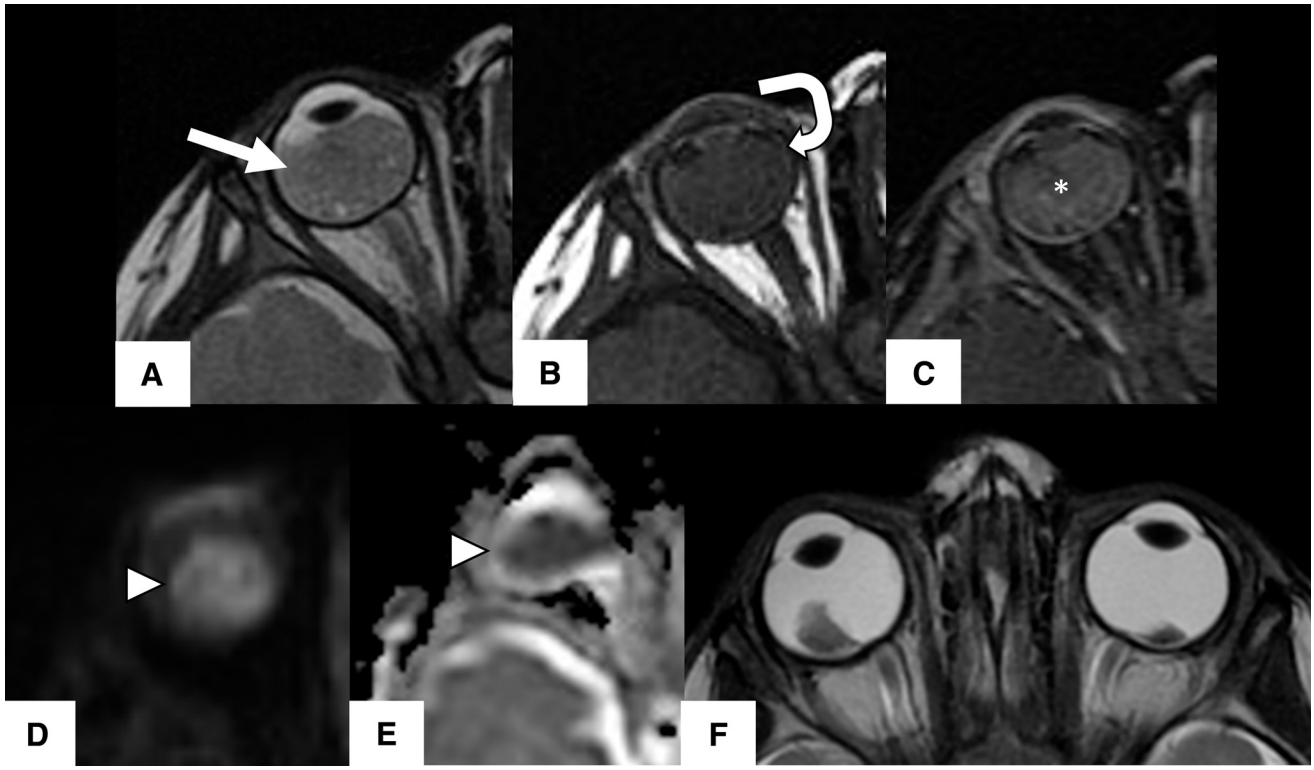

FIG 3. Retinoblastoma of the right eye. Orbital MR imaging. Axial T2-weighted (*A*), T1-weighted (*B*), postcontrast T1 (*C*), DWI (*D*), and an ADC map (*E*) show classic findings of retinoblastoma, including a T2-hypointense intraocular mass (*white arrow*) that is isointense on T1 (*curved arrow*) and shows contrast enhancement (*asterisk*) and diffusion restriction (*arrowheads*). An axial T2-weighted sequence (*F*) in a different patient shows bilateral retinoblastomas.

thirds are acquired. Common causes of acquired cataracts include ocular trauma, use of corticosteroids, and exposure to radiation.[18,19]

In general, ophthalmologic evaluation is sufficient for the diagnosis of cataracts. However, depending on the cause, we can identify varied findings on CT and MR imaging. In traumatic and hypermature cataracts, excess fluid is usually identified in the affected lens, which is represented on CT as hypodensity of the lens, generally 30 Hounsfield units less than in the normal lens (Fig 5). T2 hyperintensity of the affected lens is the homologous finding on MR imaging (Fig 6). In some cases, such as patients with type 2 neurofibromatosis, however, signal intensity may be normal.[20,21] In patients with microphthalmia and congenital cataracts, calcifications have been identified in the lens.[21] In cataracts, there are usually no alterations of the posterior segment of the globe.

Coats Disease

Coats disease, considered a type of exudative retinopathy, represents the third most frequent cause of leukocoria in children (16%).[3] Coats disease is a rare, congenital idiopathic disease that affects the vascular development of the retina. A defect occurs at the level of the endothelial cells of the blood-retinal barrier; causing weakness of the vessel walls, with formation of telangiectasias, aneurysms, and progressive retinal and subretinal fluid leakage, consequently leading to accumulation of fluid at the subretinal level, generating secondary retinal detachment.[6,22]

Coats disease is unilateral in 80%–90% of patients.[6,22] It occurs predominantly in children, with the appearance of symptoms in the first decade of life, generally between 3 and 9 years of age, and peaking between the ages of 6 and 8.[6,22] This disease has been described in adults but is usually less severe. There is a striking male predominance, with males accounting for 69%–85% of cases.[22]

It is very important to differentiate Coats disease from retinoblastoma, and imaging can play a critical role. Findings will depend on the stage of the disease. In the early stages, the examination findings can be normal or discrete retinal thickening may be identified on MR imaging.[22] In advanced stages, the subretinal exudate is identified, which, due to its high protein content, is hyperdense on CT, and on MR imaging, it is slightly hyperintense on T1WI and hypointense in T2WI compared with the normal signal intensity of the globe. As the exudate accumulates, retinal detachment progresses and begins to obliterate the vitreous space.[22] With contrast administration, peripheral linear enhancement is identified on MR imaging, corresponding to the detached retina.[22,23] The affected eye in Coats disease is usually smaller than the contralateral one (if the other eye is normal in size), Galluzzi et al[22] proposed a significant volume difference that is not present on retinoblastomas. The lack of

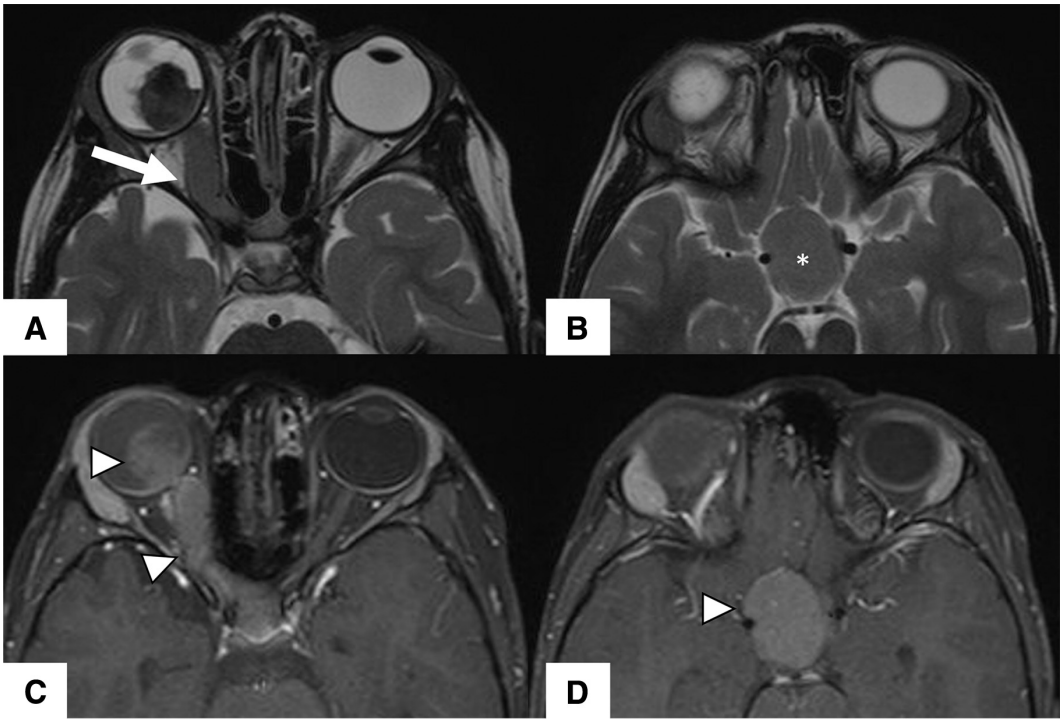

FIG 4. Retinoblastoma in the right eye with optic nerve invasion. Axial T2-weighted (*A* and *B*) and T1-weighted postcontrast (*C* and *D*) sequences show a retinoblastoma associated with thickening of the ipsilateral optic nerve (*white arrow*) and optic chiasm (*asterisk*). After the administration of intravenous contrast, there is enhancement of the retinoblastoma, the right optic nerve, and the optic chiasm (*arrowheads*).

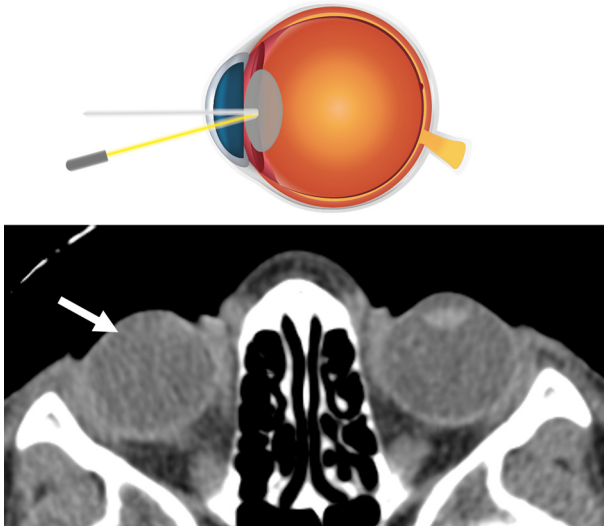

FIG 5. Non-contrast-enhanced CT of the orbit shows hypodensity of the right lens (*arrow*), compatible with a cataract.

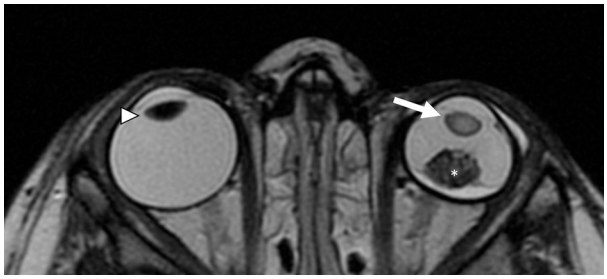

FIG 6. Axial T2-weighted image from orbital MR imaging shows hyperintensity of the left lens (*arrow*) compatible with a cataract. This patient was treated with radiation therapy for retinoblastoma (*asterisk*). A normal lens in the right eye (*arrowhead*) shows normal T2 hypointense signal.

calcifications, absence of a contrast-enhancing "mass," and smaller volume of the affected eye are, imaging findings that allow differentiation between Coats disease and retinoblastoma (Figs 7 and 8).

Persistent Fetal Vasculature

Persistent fetal vasculature (PFV), formerly called persistent hyperplastic primary vitreous, is a rare congenital malformation. It is produced by an inadequate development of the embryonic primary vitreous, the tissue that occupies the vitreous chamber during the embryonic stage. Under normal conditions, the primary vitreous is formed during the seventh week of gestation, its involution begins in the 20th week, and it has practically disappeared at the time of birth. The persistence and proliferation of the primary vitreous lead to the development of fibrovascular tissue located posterior to the lens, which extends through the hyaloid canal posteriorly.[3,6]

Clinically, it presents from birth or in the first days of life as leukocoria and microphthalmia.[3,6] This entity is generally unilateral, but it can be bilateral when associated with other conditions such as Norrie disease, Warburg syndrome, or retinal dysplasia.[24]

On imaging, retrolental fibrous tissue that extends posteriorly through the hyaloid canal is seen. This tissue is usually of triangular morphology, resembling a "martini glass," but it can have different shapes and may even be seen as only an irregular mass. This tissue is slightly dense on CT, hypointense on T2, and isointense on T1 on MR imaging. After IV contrast administration, there is homogeneous enhancement (Fig 9). Microphthalmia is considered typical of PFV; however, this description is not true in all cases because differences may be subtle or nonexistent in cases with buphthalmos associated with patients with glaucoma or myopia.[25] Other important associated findings include intraocular hemorrhage and retinal detachment. Ocular calcifications are not identified in this pathology.[3,6,8]

Coloboma

Coloboma is a congenital defect characterized by the failure of closure of the choroidal fissure, producing an interruption of the choroidal layer located between the retina and the sclera.[6,26] The most common site of coloboma is in the anterior segment involving the iris. Although less common, coloboma of the posterior segment (where it frequently involves the optic disc) is the type of coloboma that can produce leukocoria.[6,26]

Coloboma can be unilateral or bilateral and produce leukocoria due to the interruption of the choroidal layer, exposing the sclera, which becomes visible during assessment for pupillary red reflex.[6] It can occur as a stand-alone defect or can be associated with multiple syndromes, like Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth and/or development, Genital and/or urinary abnormalities, and Ear abnormalities and deafness (CHARGE) syndrome, Jacobsen syndrome, and Aicardi syndrome, among others. The mean age at diagnosis of the posterior coloboma is 9 months (ranging from 1.5 months to 19 years).[26]

On imaging, a smaller eyeball can be observed in association with a defect in the wall, with vitreous herniation through the defect. In some cases, a retrobulbar cyst is identified.[6] When the coloboma involves the optic disc, a fluid-containing space is seen that projects into the proximal aspect of the optic nerve (Fig 10).

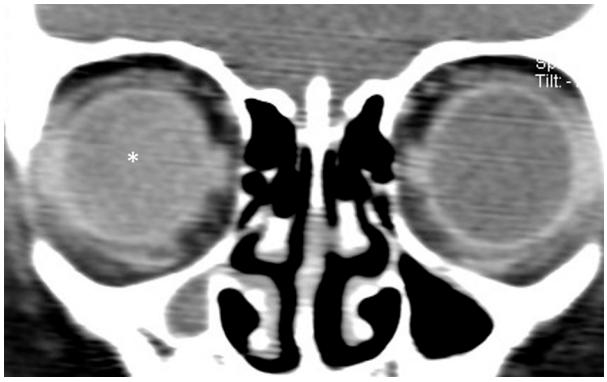

FIG 7. Coats disease in the right eye. Coronal reformatted CT. Hyperdensity of the right eyeball (*asterisk*). No calcifications are present.

Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is an alteration of vascular proliferative development that occurs in the partially vascularized retina of preterm infants. This can lead to retinal detachment and blindness. It generally develops in premature infants of low weight and low gestational age who have received prolonged ventilatory support.[3,23]

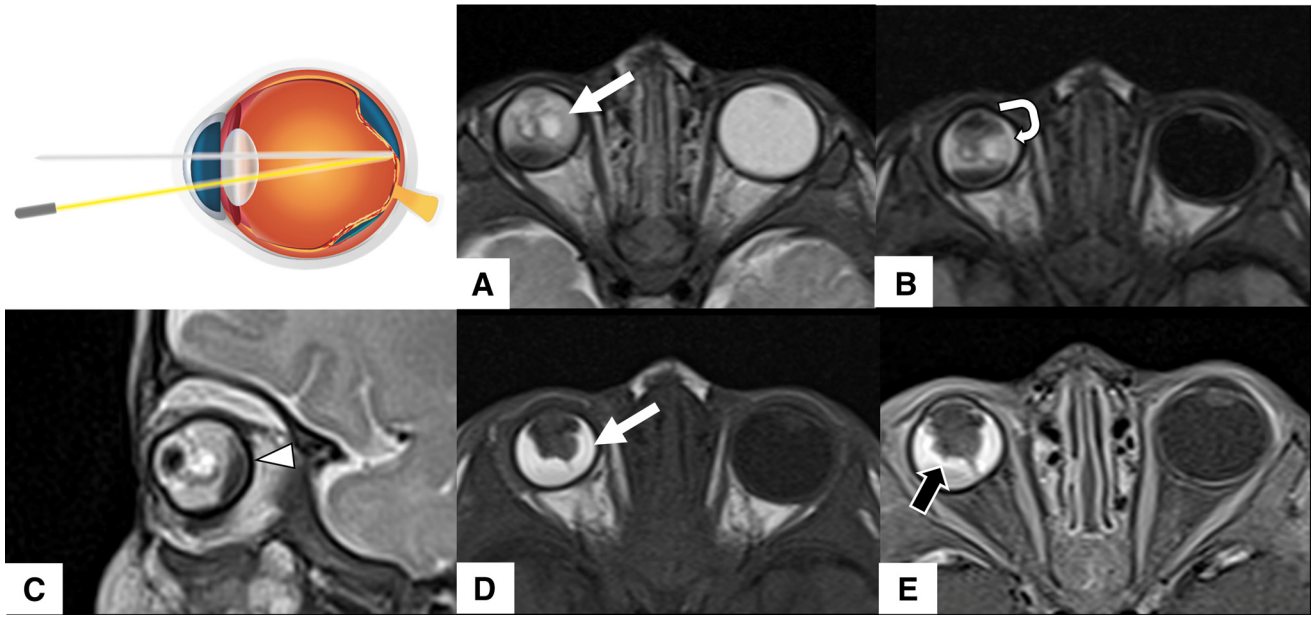

FIG 8. Coats disease of the right eye. Axial MR imaging sequences, T2 (*A*), FLAIR (*B*), sagittal T2 (*C*), T1 (*D*), and postcontrast T1 (*E*), show a subretinal exudate that is slightly hyperintense on T2 and T1 sequences (*white arrows*). This exudate remains hyperintense on FLAIR (*curved arrow*). After the administration of contrast, linear enhancement is identified in the periphery of the exudate, compatible with the enhancement of the detached retina (*black arrow*). A blood-fluid level is seen (*arrowhead*) on the sagittal image. On all sequences, the smaller size of the right eyeball can be appreciated.

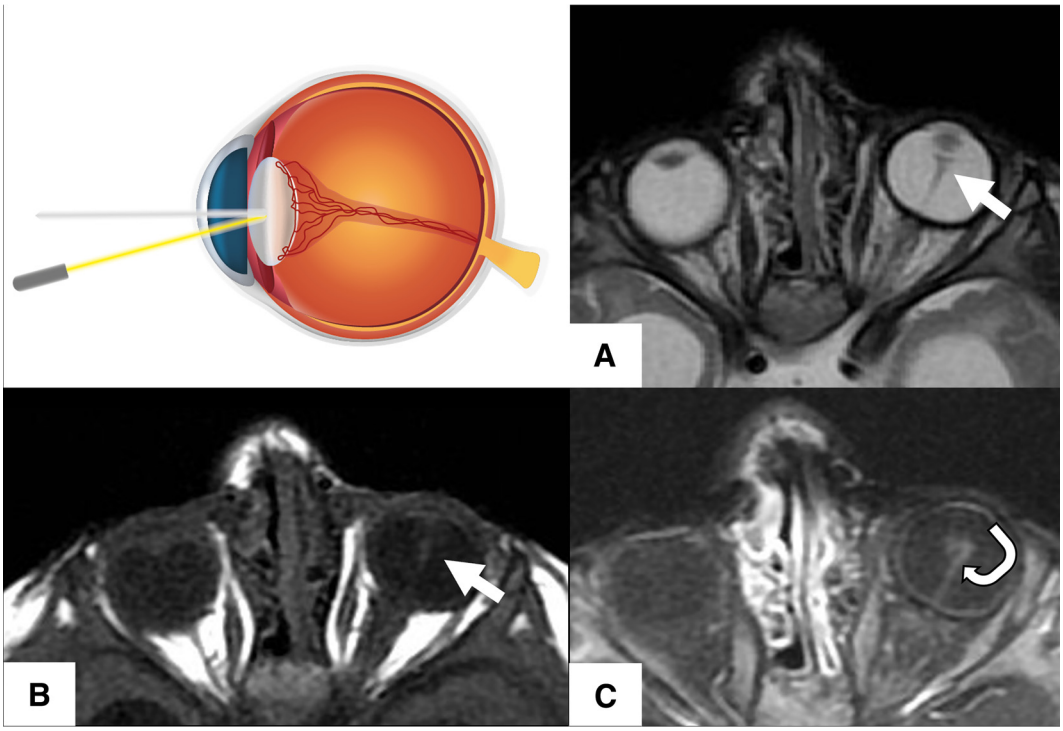

FIG 9. Persistent fetal vasculature of the left eye. Orbital MR imaging axial sequences, including T2-weighted (*A*), T1-weighted (*B*), and postcontrast T1-weighted (*C*), show left microphthalmia with the presence of retrolental fibrous tissue that extends posteriorly, which is hypointense on T2 and isointense on T1-weighted images (*arrows*). The fibrous tissue enhances following intravenous contrast administration (*curved arrow*).

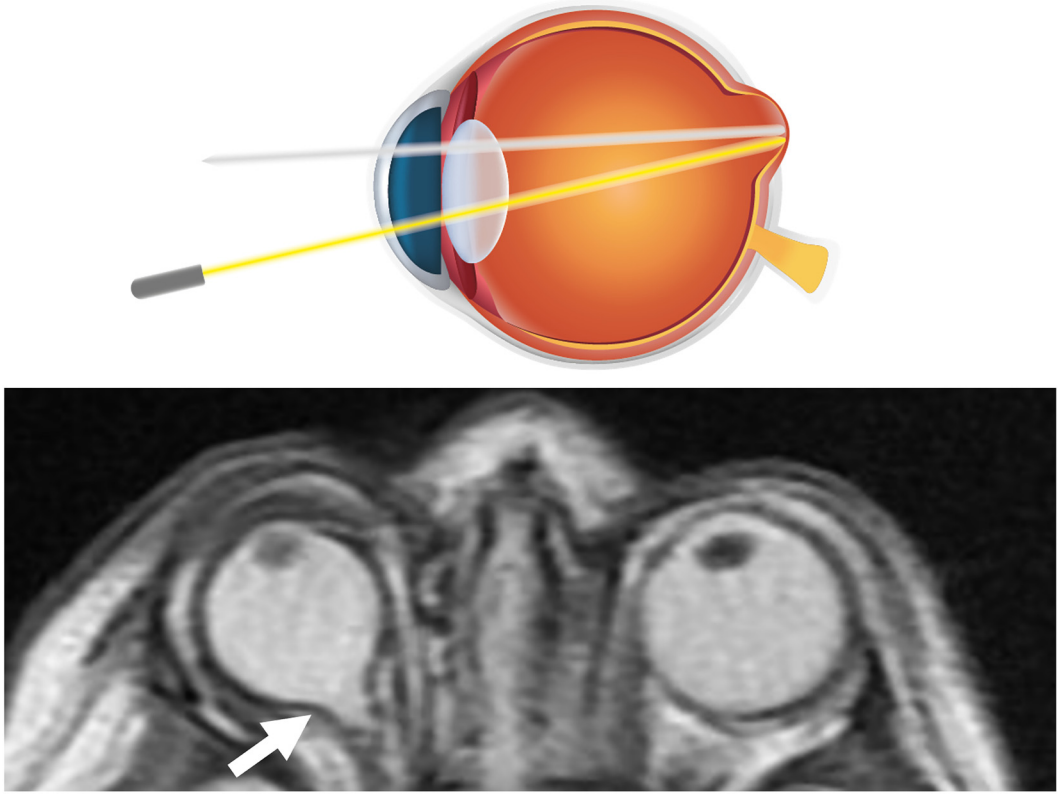

FIG 10. Coloboma. Axial T2-weighted sequence from orbital MR imaging shows microphthalmia of the right eye associated with a coloboma that involves the optic disc (*arrow*).

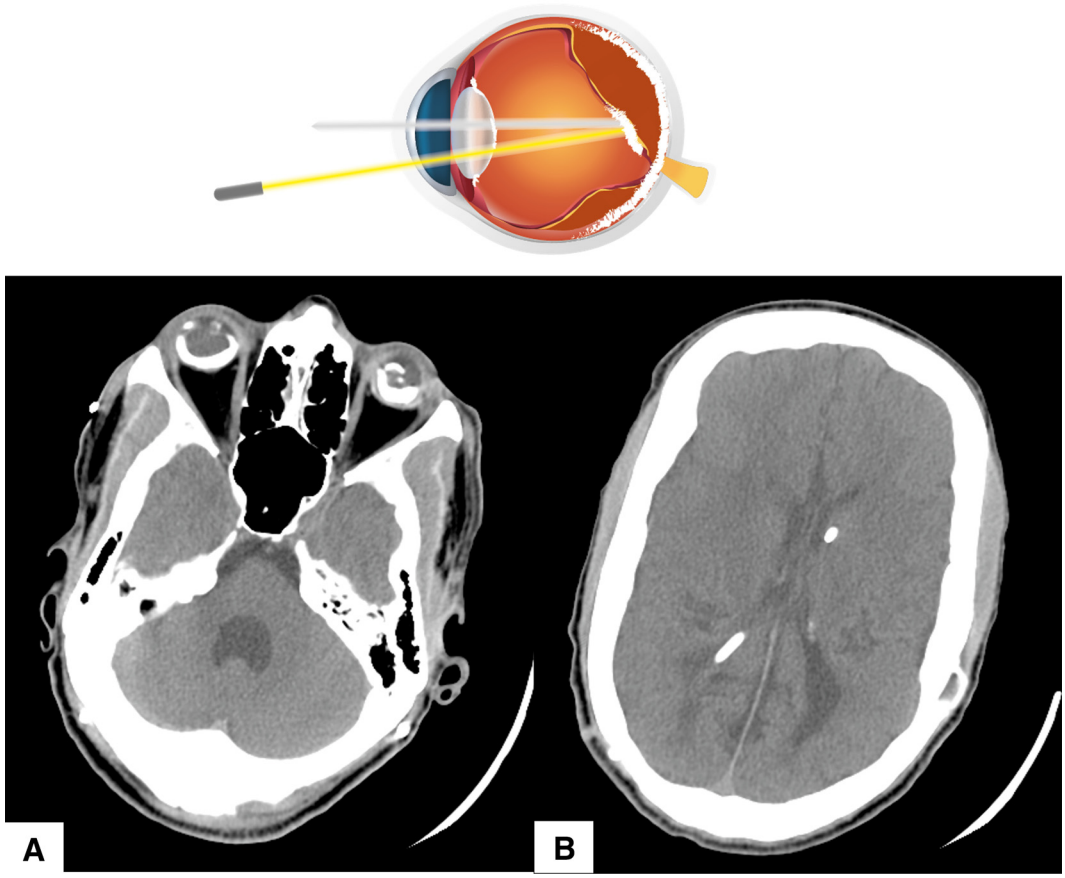

FIG 11. ROP. Axial image from a noncontrast CT of the brain shows the small size of both eyeballs and dense calcifications of retrolental tissue and choroid (*A*) due to late-stage changes of ROP. Periventricular leukomalacia is also present (*B*).

ROP is bilateral but frequently asymmetric. Leukocoria associated with ROP is secondary to retinal detachment, which is identified in advanced stages of the disease.[3]

On images, decreased size of both eyeballs is identified. On CT, there is hyperdensity of the entire eyeball secondary to neovascular growth. On MR imaging, T1WI and T2WI hyperintensity is observed due to chronic subretinal hemorrhage. A retrolental pseudomass can be seen, representing the apposition of the detached leaves of the retina.[3]

Calcifications are uncommon in the acute stage of the disease but can be seen in late stages involving the lens, choroid, and retrolental tissue (Fig 11).[3,23]

Vitreous Hemorrhage

Vitreous hemorrhage is defined as the presence of blood in the vitreous chamber. When this blood organizes and forms a clot, it can disrupt the red reflex and produce leukocoria.[27] The causes of vitreous hemorrhage in children are varied. The most frequent cause is trauma, including nonaccidental trauma.[27,28] Other causes include vitamin K–deficient bleeding of the neonate, advanced retinopathy of prematurity, persistent fetal vasculature, and leukemia or other blood dyscrasias.[27,28]

On CT, focal or diffuse hyperdensity of the vitreous chamber is identified.[29] On MR imaging, vitreous hemorrhage is variable in signal depending on the stage of the bleeding, but the normal vitreous humor signal is lost on T1- and T2-weighted imaging (Fig 12).[30,31] MR imaging and CT are useful to look for underlying causes, but CT is preferably avoided due to secondary radiation.

Retinal Astrocytic Hamartoma

Retinal astrocytic hamartoma is a benign malformation that originates from the nerve fiber layer of the retina and is histologically composed of fibrous spindle-shaped astrocytes with small, oval nuclei.[6] It is significantly associated with tuberous sclerosis, with up to 50% of patients with tuberous sclerosis developing astrocytic hamartomas. Of those patients who develop astrocytic hamartomas, 25% of the tumors are bilateral. Astrocytic hamartomas are also seen in patients with type 1 neurofibromatosis.[6] Extensive hamartomas may manifest as leukocoria on clinical examination.[6]

On imaging, one can see a single mass or multiple masses in the retina, which may be calcified, making it difficult to differentiate them from retinoblastomas; however, in general, retinal astrocytic hamartomas, due to the absence of necrosis and hemorrhage, do not grow significantly toward the vitreous humor, and this feature aids in the distinction from retinoblastomas.[3,32] Identification of classic features of tuberous sclerosis or type 1 neurofibromatosis in the brain is

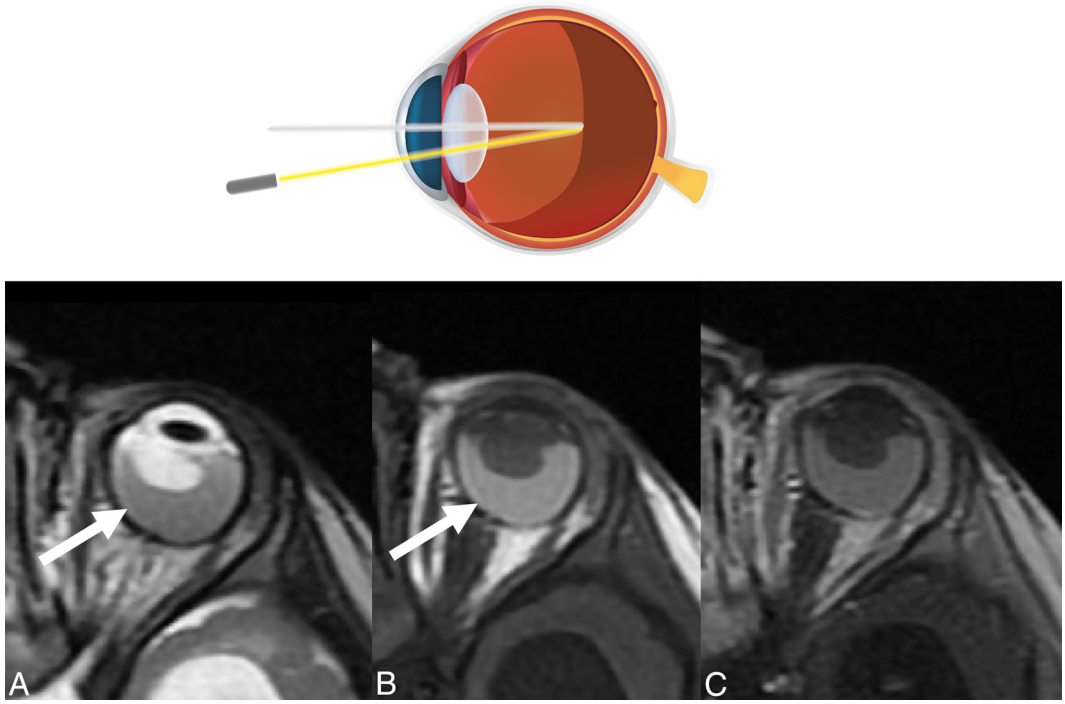

FIG 12. Left eye vitreous hemorrhage. Axial T2-weighted (*A*), T1-weighted (*B*), and postcontrast T1-weighted (*C*) images from orbital MR imaging show the presence of T2-hypointense and T1-hyperintense fluid in the vitreous chamber, compatible with vitreous hemorrhage (*arrows*). After contrast administration, no enhancement is identified.

important to guide the diagnosis.[3] Differentiating astrocytic hamartoma and retinoblastoma is very important because the former does not progress and does not require treatment, whereas retinoblastoma must be early and aggressively treated.[6]

Ocular Toxocariasis

Ocular toxocariasis, another known cause of leukocoria, is caused by an infection by the canine ascarid *Toxocara canis* or, less commonly, the feline ascarid *Toxocara cati*. *Toxocara* is a helminthic nematode that can invade deep tissues, causing migrating visceral larvae. In humans, *Toxocara* larvae are ingested and travel through the intestines and reach the liver, from which they can hematogenously migrate to the lungs or any other organ, including the eyes.[3] It occurs most commonly in older children and adolescents, unlike retinoblastoma, which occurs in younger children. The clinical presentation is also different because in addition to the unilateral leukocoria, it presents with red eye, orbital pain, photophobia, and systemic symptoms such as fever and hepatomegaly.[3]

On imaging, the globes are of normal size and without calcifications. On CT, focal uveoscleral thickening and an intravitreal mass may be seen, corresponding to the granulomatous reaction.[3] On MR imaging, the granuloma is identified as a mass, generally hyperintense on T2WI, though it may be hypointense, resembling a retinoblastoma. On T1WI, it is isointense and shows enhancement after IV gadolinium contrast administration. Intravitreal bands related to endophthalmitis can be identified. It is also common to observe associated retinal detachment with subretinal exudate, which can be hyperintense in T1 and T2.[3]

Diagnostic Imaging Approach to the Patient with Leukocoria

Leukocoria is a clinical diagnosis that, as we have already reviewed in this article, can be caused by multiple pathologic entities. Clinical characteristics are very important in the differential diagnosis, but some imaging findings such as ocular size, presence of calcifications, pattern of contrast enhancement, presence of hemorrhage and accompanying lesions can also be of use. Figure 13 presents a proposed flowchart to help guide the diagnosis. The most important entity in the differential diagnosis is retinoblastoma, both because it represents the most frequent cause and because of its poor visual prognosis and survival rate. Other important causes are cataracts, Coats disease, persistent fetal vasculature, vitreous hemorrhage, coloboma, retinopathy of prematurity, ocular toxocariasis, and astrocytic hamartoma. Although in many cases the ophthalmologic evaluation and ocular sonography are sufficient for the diagnosis of the cause of leukocoria, in some cases, CT and, especially, MR imaging play an important role nonetheless. A systematic approach based on the image characteristics of the different entities and some clinical elements can help in the differential diagnosis of the cause of leukocoria.

Another factor that can help in distinguishing the most likely cause of leukocoria is the age at presentation

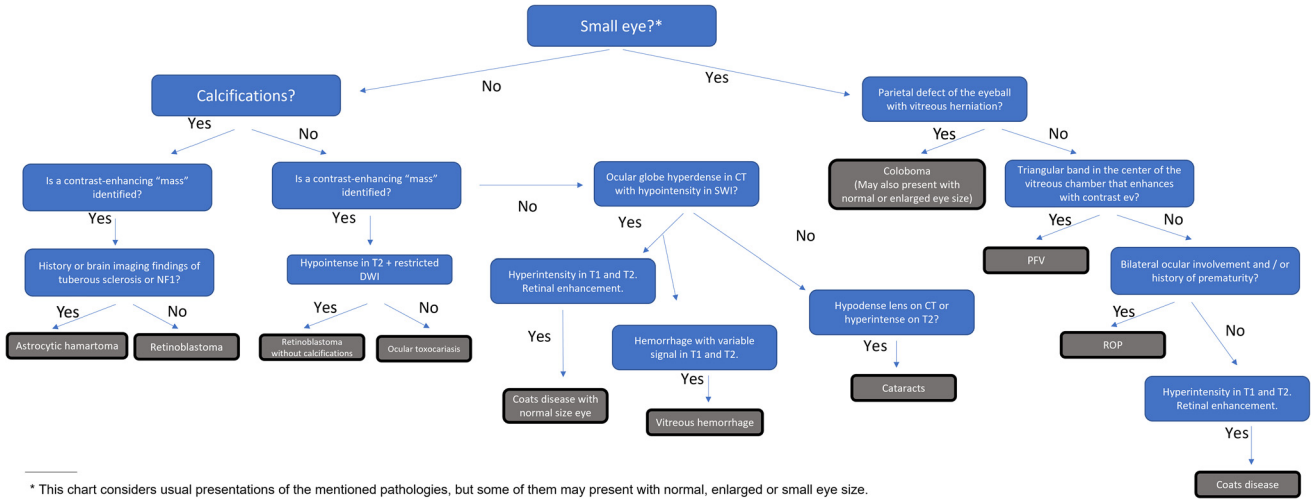

FIG 13. Proposed flowchart for diagnostic approach of a child with leukocoria.

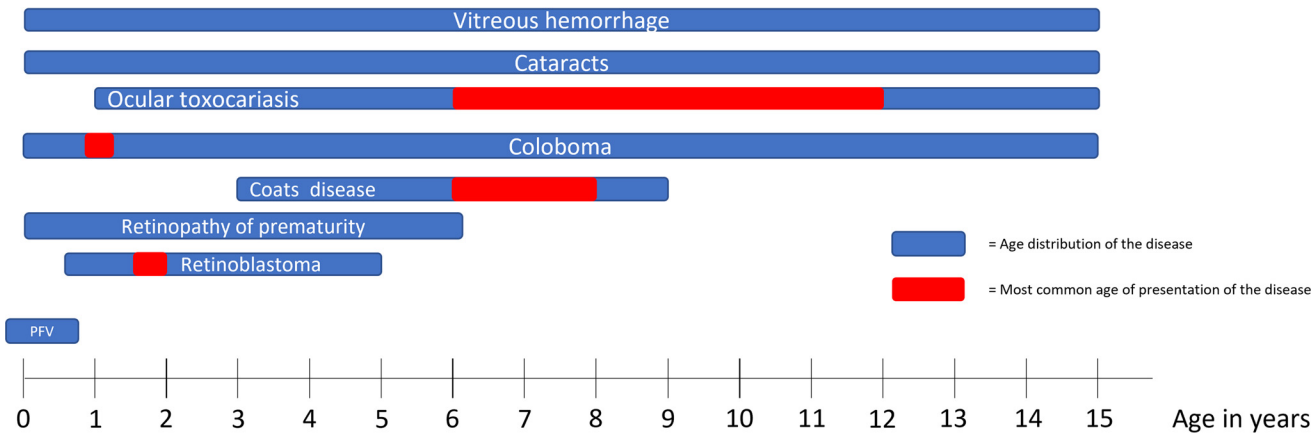

FIG 14. Ages of presentation of the different causes of leukocoria. The range of ages of the different pathologies is represented in blue, while the age at which it is most common to find each pathology is represented in red.

(Fig 14).[5] Patients with persistent hyperplastic primary vitreous present with leukocoria from or shortly after birth. ROP is generally not apparent from birth but progresses rapidly in the first few years of life. Retinoblastoma usually presents in children younger than 5 years of age, with the peak of presentation being between 18 and 24 months. Coats disease has some degree of overlap with retinoblastoma in the age of presentation, but most cases will appear between 3 and 9 years of age. There are other pathologies that can occur in a broader range, such as coloboma and ocular toxocariasis, but they peak at certain ages: coloboma at 9 months and ocular toxocariasis between 6 and 12 years of age. Finally, cataracts and vitreous hemorrhage can occur almost at any age, depending exclusively on the etiology.

CONCLUSIONS

Leukocoria is a clinical sign that may be produced by multiple conditions. Diagnostic imaging, particularly MR imaging, can be very helpful in determining the specific cause. Thus, it is important to be familiar with the imaging characteristics of the responsible entities, that along some clinical data, chief among which is the age of presentation, will guide us to the diagnosis. A correct diagnosis is vital in some cases because treatment for the underlying cause may be substantially different, and early initiation of treatment is of paramount importance in entities with poor prognosis, such as retinoblastoma.

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