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Top 5 Diagnoses Not to Miss in Children

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This issue of *Ophthalmology Rounds* focuses on 5 of the most important eye conditions in children that should not be missed. Any clinician who sees children should be familiar with these potentially vision and life-threatening diseases. This article summarizes the clinical presentation, differential diagnosis, assessment, and management of the key pediatric causes of leukocoria, epiphora, ptosis, proptosis, and neurological disease.

1. White Pupillary Reflex

Leukocoria, also known as a "white pupil," results from the reflection of light off a media opacity or retinal lesion during direct fundus illumination. It may first be observed in flash photography or detected by the child's family or pediatrician. Any child with an abnormal red reflex should be referred urgently to an ophthalmologist, as it is imperative not to miss the life-threatening diagnosis of retinoblastoma. While the differential diagnosis of leukocoria includes cataract, familial exudative vitreoretinopathy, toxocariasis, retinopathy of prematurity, and coloboma, key considerations include persistent fetal vasculature (PFV) and Coats disease.

Retinoblastoma is the most common primary intraocular malignancy of childhood, with a worldwide incidence of 1 in 15 000–20 000 live births.[1] About 23 children are diagnosed each year in Canada.[2] The tumour arises in the developing retina following inactivation of both copies of the *RB1* gene, a tumour-suppressor located at chromosome 13q14.2.[3,4] This leads to loss of functional retinoblastoma protein and uncontrolled cell division. The origin of retinoblastoma may be a cone precursor cell, which remains within the inner nuclear layer.[5,6]

Retinoblastoma presents as a small, round, grey intraretinal tumour that initially undergoes symmetrical growth.[7] Over time, the growth becomes lobulated due to clonal growth differences. As the disease progresses, the tumour may breach the inner limiting membrane and lead to vitreous seeding, or extend into the subretinal space causing subretinal seeding and exudative retinal detachment (Figure 1A). Signs of advanced disease include phthisis bulbi, anterior chamber invasion, elevated intraocular pressure (IOP) with neovascularization, hyphema, or aseptic orbital cellulitis.[8] The tumour can spread via the optic nerve or subarachnoid space to the central nervous system, invade adjacent orbital structures, and disseminate hematogenously via the choroid, most commonly to bone marrow.

When retinoblastoma is suspected, a complete clinical examination under anesthesia (EUA) including IOP measurement, anterior segment evaluation and indirect ophthalmoscopy with scleral indentation should be performed.[2] B-scan ultrasonography shows typical calcification. Useful imaging modalities include RetCam™, fluorescein angiography and ultrasound biomicroscopy for assessing anterior involvement.[9,10] Optical coherence tomography (OCT) aids in detecting small tumours and evaluating foveal architecture, which influences management decisions.[11] Magnetic resonance imaging (MRI) of the brain and orbits assesses for extraocular or optic nerve involvement, as well as intracranial midline embryonic tumours. Computed tomography (CT) is no longer recommended given the increased risk of second primary neoplasms following radiation exposure in children with germline mutations. Molecular genetic testing dictates the frequency of EUAs to monitor for new ocular tumours and surveillance for second neoplasms.[2]

Staging of the disease extent at presentation helps to select appropriate therapy and predict outcomes. The Reese-Ellsworth classification was originally used to predict eye salvage following external-beam radiation therapy.[12] The International Intraocular Retinoblastoma Classification later staged eyes from Group A (very low risk) through E (very high risk) and predicted outcomes following systemic chemoreduction and focal therapies.[7] The 8th edition of the American Joint Committee on Cancer Tumor, Node, Metastasis and Heritable trait (TNMH) system was introduced recently to stage for overall prognosis.[8]

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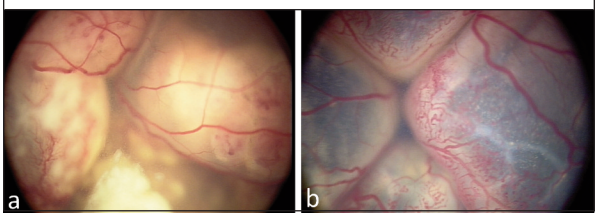
Figure 1. 1A: A funnel-shaped exudative retinal detachment overlying tumour with both vitreous and subretinal seeds in a child with retinoblastoma. **1B:** Fundus photograph of a child with Coats disease. Note the total exudative retinal detachment and prominent retinal telangiectasia.



Retinoblastoma can be fatal if left untreated. The goals of care are, first, to save the child's life, followed by eye and vision salvage. Treatment is dictated by the staging, laterality of disease and genetic status, and should involve a multidisciplinary team including pediatric oncology. Focal therapies (laser photocoagulation for posterior or cryotherapy for peripheral tumours) are used for treating small tumours that spare the optic nerve and fovea, while larger or vision-threatening tumours may require systemic chemoreduction with focal consolidation.[13] Enucleation serves as a definitive treatment for advanced unilateral tumours.[2] Intravitreal melphalan has shown success in control of vitreous seeding.[14] Finally, intra-arterial chemotherapy has emerged as a treatment for select patients.[15]

Differential diagnosis

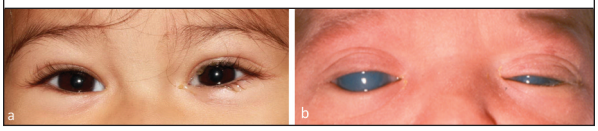
PFV is an isolated, sporadic congenital malformation caused by arrest of the normal regression of the fetal vasculature. It is typically unilateral and can present with a spectrum of anterior and posterior segment manifestations, including microphthalmos and elongated ciliary processes. The most common sign is leukocoria, which is secondary to dense retrolental plaque and cataract formation.[16]

Coats disease is the most clinically challenging disease to differentiate from retinoblastoma.[17,18] It is usually unilateral and presents in males at a median age of 5 years.[19] Coats disease is an idiopathic, nonhereditary retinal telangiectasia with associated intraretinal and subretinal lipid exudation. Advanced cases present with exudative retinal detachment and mimic retinoblastoma (Figure 1B). Fundus examination in both upright and supine positions, to visualize the inferior retina, is important to distinguish these conditions.[18] FA and ultrasonography may be useful adjuncts. While laser and intravitreal anti-vascular endothelial growth factor therapies have been reported, enucleation is the safest management option in advanced cases with diagnostic uncertainty.[18]

2. The Tearing Eye

Nasolacrimal duct obstruction, typically the result of a thin membrane present at the distal valve of Hasner, is the most common cause of epiphora and periocular crusting in infants (Figure 2A). Since 90% resolve spontaneously within the first year of life, conservative management with lacrimal massage is preferred.[20] Persistent obstruction after 1 year of age warrants probing and, when necessary, balloon catheter dilation, silicone tube intubation, or dacryocystorhinostomy.[20] While tearing in children can also be a sign of conjunctivitis, keratitis, or

Figure 2. 2A: This child presented with a left nasolacrimal duct obstruction. Note the epiphora and periocular crusting. **2B:** Infant with congenital glaucoma. Note the buphthalmos and corneal opacification.



lid abnormalities such as epiblepharon, the most important etiology that must not be missed is primary congenital glaucoma (PCG).

The Childhood Glaucoma Research Network classifies childhood glaucoma as PCG, juvenile open angle glaucoma, glaucoma associated with acquired conditions, nonacquired systemic syndromes (eg, Marfan, Sturge-Weber, or Lowe), nonacquired ocular anomalies (eg, Axenfeld Rieger syndrome, aniridia, or Peters anomaly), and glaucoma following cataract surgery.[21] PCG is an isolated goniodysgenesis leading to increased resistance to aqueous outflow. It is the most common type of childhood glaucoma and presents with the classic triad of epiphora, photophobia, and blepharospasm. PCG can be further classified as neonatal (≤1 month), infantile (>1-24 months), and late-onset (>2 years).[21]

Examination of the tearing infant should include assessment of visual acuity (VA), pupils, and IOP, preferably before general anesthesia induction. IOP can also be measured in clinic using the Icare® tonometer.[22] In infants, elevated IOP (>12 mmHg in newborns) leads to distention of the cornea, paired curvilinear breaks in Descemet membrane known as Haab striae, corneal edema, and buphthalmos (Figure 2B). Horizontal corneal diameter (HCD) and axial length (AL) are greater than age-matched controls, with HCD more sensitive in identifying congenital glaucoma.[23] HCD >11 mm in a newborn and >13 mm at any age is suggestive of PCG. Serial AL measurements are useful to monitor the course of PCG, as AL may decrease or parallel normal growth with improvement in IOP.[24] Pachymetry, anterior segment examination, and gonioscopy should also be performed. Circumferential cupping with a cup-to-disc ratio >0.3 or asymmetry >0.2 is suggestive of PCG. Cycloplegic refraction shows a myopic shift with progressive axial elongation.

The treatment of PCG is primarily surgical, with IOP-lowering medications used as adjunctive therapy. Angle surgery such as goniotomy (ab interno), which requires a relatively clear cornea, and trabeculotomy (ab externo) allow aqueous access to the Schlemm canal.[25] Other surgical options include trabeculectomy with adjunctive mitomycin C, combined trabeculotomy-trabeculectomy, glaucoma drainage devices, and cyclophotocoagulation. IOP reduction can lead to improved corneal edema and stabilization or reversal of optic nerve cupping. Concurrent correction of refractive errors and amblyopia therapy is essential. Long-term monitoring of children with PCG is critical to assess for progression.

3. More Than Just a Droopy Lid

Roughly 75% of childhood ptosis is simple congenital ptosis, which may require surgical correction but is not associated with any serious underlying disease;[26] however, rare but dangerous cases of ptosis should not be missed. Three

potentially life-threatening conditions in children can present with ptosis: Horner syndrome, oculomotor palsy, and myasthenia gravis (MG).

Horner syndrome

Horner syndrome is due to a lesion of the sympathetic nerve pathway. It is known for the classic "osis" triad of ipsilateral ptosis, miosis, and anhydrosis. Children with Horner syndrome generally have 1-2 mm of upper eyelid ptosis (due to denervation of the Muller muscle) associated with a characteristic "reverse ptosis" in which the lower eyelid is higher due to denervation of the lower lid retractors. Parents often report that the eye looks "smaller" as opposed to noting the eyelid changes (Figure 3A). The anisocoria is greater in dim illumination and associated with dilation lag of the miotic pupil. Heterochromia, another important finding, indicates that the Horner syndrome is congenital or early-onset. In order to confirm the diagnosis, instill 4% cocaine drops into each eye; anisocoria ≥0.8 mm after 1 hour accurately confirms the diagnosis. There is no need to measure the change in anisocoria, just the post-cocaine difference.[27] A more easily accessible alternative to cocaine is 0.5%–1% topical apraclonidine, which will reverse the anisocoria in Horner syndrome;[28-30] however, apraclonidine can cause extreme drowsiness in infants and is therefore contraindicated in infants <6 months and should be used cautiously in children <2 years.[31]

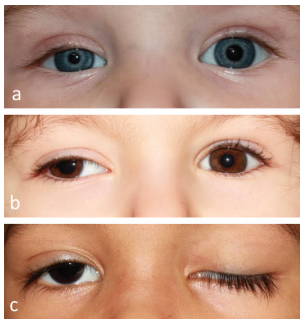
If the cause of Horner syndrome is known (eg. perinatal trauma, neck/cardiothoracic surgery) or there is heterochromia in an older child, no further work-up is required. If there is no known cause, a thorough assessment for neuroblastoma is mandatory as there is a significant risk of a mass lesion along the sympathetic pathway.[32] Urine catecholamines, abdominal ultrasound, and chest x-ray are useful and easily accessible tests, but the definitive test to rule out neuroblastoma is a head, neck, and chest MRI with contrast.[32]

Oculomotor (cranial nerve III) palsy

The oculomotor nerve innervates several important muscles, including 4 of the 6 extraocular muscles (medial/superior/inferior recti muscles and inferior oblique), the levator palpebrae superioris, and the sphincter pupillae muscle via the ciliary ganglion. As such, a complete oculomotor palsy causes severe ptosis, a blown pupil, and large-angle exotropia with moderate hypotropia. However, injury to the oculomotor nerve may not affect all muscles and the weakness may be partial. Therefore, in any case of ptosis, it is crucial to be vigilant for any associated signs of cranial nerve III injury (Figure 3B).

The most common cause of an isolated oculomotor palsy in children is congenital, followed by trauma, which collectively make up about two-thirds of all cases.[33] The remaining cases are due to infection/inflammation, tumour, aneurysm, and ophthalmoplegic migraine. Unless the cause is known, all cases require an urgent MRI / MR angiography and neurological assessment. Following an acute injury, the oculomotor nerve may recover and so surgical repair of ptosis and strabismus should be delayed ≥6 months. However, complete ptosis combined with large-angle strabismus is highly amblyogenic, so young children with oculomotor palsy need to be monitored closely for amblyopia.[34]

Figure 3. Potentially life-threatening conditions that can present with ptosis. **3A:** Right Horner syndrome with mild ptosis, reverse ptosis, and miosis. **3B:** Right oculomotor palsy with moderate ptosis, large-angle exotropia, hypotropia, and a dilated pupil. **3C:** Myasthenia gravis with bilateral, asymmetric ptosis.



Myasthenia gravis (MG)

While rare in children, MG does occur and can be a diagnostic challenge. MG is a disorder of the neuromuscular junction that causes weakness, often presenting with ptosis and/or strabismus. The ptosis is highly variable (Figure 3C) and can be mistaken for more common conditions such as simple congenital ptosis.[35] The eye movements also do not follow a consistent pattern and can imitate any pattern of ocular misalignment. Given the variability in clinical presentation, the key clinical features of MG are fatigability and fluctuation. The ptosis and strabismus change throughout the day and will characteristically be worse with use/exercise and better with rest; however, the finding of "worse at the end of the day" is not pathognomonic of MG. MG does not affect the pupil and so any pupillary findings such as anisocoria strongly indicate a different underlying etiology.

When MG is suspected, acetylcholinesterase inhibitor antibodies should be ordered and the child should be referred to neurology for further testing.[36,37] It is crucial not to miss ocular MG, as most children who present with ocular findings will eventually go on to develop generalized weakness and, in severe cases, are at risk of respiratory failure and death.[38]

4. When the Problem Lies Behind the Eye

The onset of proptosis in a child warrants urgent evaluation to rule out an infectious, inflammatory, vascular, or neoplastic orbital process. Ask about recent trauma, upper respiratory or sinus disease, and immunocompromise. The examination should identify orbital signs such as ptosis, eyelid edema, conjunctival chemosis, restricted extraocular movements, and increased resistance to retropulsion, as well as signs of compressive optic neuropathy.

Orbital cellulitis

Orbital cellulitis is an infection involving the tissues posterior to the orbital septum. The most common etiology is ethmoidal sinusitis,[39] but penetrating orbital trauma should be excluded. Children present with eyelid erythema and edema, proptosis, external ophthalmoplegia, chemosis, fever, lethargy, and pain. Prompt diagnosis, hospitalization, and initiation of broad-spectrum intravenous (IV) antibiotics and daily follow-up are crucial.

CT orbit can assess the extent of sinusitis and the presence of subperiosteal abscess (SPA).[39] This occurs secondary to accumulation of purulent material between the orbital bone and periorbita. Culture-positive cases from SPAs demonstrate single microbial aerobic infections (*Streptococcus* and *Staphylococcus*) in children <9 years.[40] Children aged 9–14 years show a transition toward more complex infections, while those >15 years show polymicrobial aerobic and anaerobic (*Bacteroides*) infections, with an average of 5 different species isolated per abscess.[40]

The Chandler classification of orbital cellulitis includes Group I (inflammatory eyelid edema), Group II (orbital cellulitis), Group III (subperiosteal abscess), Group IV (orbital abscess), and Group V (posterior extension leading to cavernous sinus thrombosis, frank meningitis, or brain abscess).[41]

The mainstay of treatment is broad-spectrum IV antibiotics and nasal decongestants. The antibiotics should be tapered to oral following clinical improvement. While conservative management is appropriate for small SPAs, surgical drainage should be considered if there is inadequate response to medical management after 24-48 hours, evidence of optic nerve compromise, or a worsening clinical course.[42] Patients requiring surgery tend to be older (>6 years), have larger abscesses (>10 mm), and require longer admissions.[42] The size of the SPA on CT orbit is significantly correlated with management outcome; an SPA volume >3.8 mL is associated with a 71% probability of requiring surgery.[39] Finally, oral prednisone 1 mg/kg daily for 7 days has been shown to be beneficial and a standardized starting point of C-reactive protein <4 mg/dL has been proposed.[43]

Rhabdomyosarcoma (RMS)

Acute onset of unilateral painless proptosis, ptosis, and lid edema or ecchymoses in a child should raise the suspicion of RMS, the most common pediatric primary orbital malignancy. RMS is a neoplasm of primitive mesenchyme expressing skeletal muscle differentiation. Primary ophthalmic RMS originates most commonly in the orbit, followed by the conjunctiva, uveal tract and eyelid, and presents at a mean age of 10 years.[44] The most common orbital site is the superonasal quadrant.[45] On CT, the tumour has an irregular shape with homogenous soft tissue density, moderately well-defined margins and shows contrast enhancement.[45] On MRI the tumour is isointense on T1 and hyperintense on T2 relative to muscle (Figures 4A, 4B).[45]

Histopathology is required to confirm the diagnosis. The International Classification of Rhabdomyosarcoma includes 6 histopathological subtypes: embryonal – botryoid, embryonal – spindle cell, embryonal – not otherwise specified, alveolar – solid variant, anaplasia – diffuse, and undifferentiated sarcoma.[46] The Surgical-Pathologic Grouping System of the Intergroup Rhabdomyosarcoma Study (IRS) includes groups I through IV, based on the extent of the tumour and the presence of complete resection, microscopic or gross residual disease following surgery.[47] This is an important predictor of treatment outcome. RMS can also be staged by the IRS TNM system, which dictates management. Given the tendency for local invasion and recurrence, as well as hematogenous and lymphatic metastases, management includes combinations of surgical resection, systemic chemotherapy, and radiotherapy.[44,48]

5. The Brain

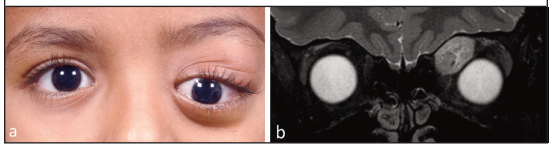
The onset of serious neurological disease is often marked by characteristic ophthalmic signs and symptoms. The key to not missing a neurological etiology is a consistent, systematic approach to the history and examination that incorporates screening for important "red flags" of optic nerve and intracranial disease.

On history, important symptoms of neurological disease include headaches, double vision, eye pain (particularly with eye movement), and the loss of colour vision or VA. In any child with headaches, ask about associated symptoms of high intracranial pressure, including nausea, vomiting, pulsatile tinnitus, transient visual obscurations, and diplopia.[49] With diplopia, it is crucial to differentiate between monocular and binocular versions; binocular diplopia is a red flag for neurological disease and disappears when one eye is closed. The simultaneous loss of VA and colour vision is typical of optic nerve disease, and pain with eye movement is highly suggestive of optic neuritis.[50]

A thorough examination is indispensable in children, who may be unable to accurately verbalize symptoms of neurological disease. At minimum, the examination should include testing of VA, pupils, visual fields, eye movements, and a dilated fundus examination with particular attention to the optic nerve.

VA testing should be age appropriate to avoid errors due to poor understanding or cooperation.[51,52] If VA is asymmetric, check for a relative afferent pupillary defect, which is a sensitive sign of unilateral optic nerve disease. Assess the pupils for anisocoria, which is an important sign of Horner syndrome and oculomotor palsy. If the child is cooperative, check visual fields for a homonymous or bitemporal hemianopia, which are both red flags for neurological disease and often go unnoticed by children. When checking eye movements, assess all cardinal positions of gaze to look for evidence of a cranial nerve III, IV, or VI palsy. A cranial nerve IV palsy usually presents as a head tilt away from the side of the palsy and/or vertical binocular diplopia. In particular, look for a hypertropia that increases with contralateral gaze and ipsilateral head tilt (ie, the 3-step test).[53] Cranial nerve VI palsies usually present with an

Figure 4. 4A: This child presented with rapid-onset proptosis without signs of infection or inflammation. **4B:** Magnetic-resonance imaging showed a superonasal enhancing orbital mass, which was diagnosed as rhabdomyosarcoma on biopsy.



abduction deficit, but may also manifest as an esotropia that is greater in side gaze (lateral incomitance) or at distance (divergence insufficiency).[54,55]

Finally, a dilated fundus examination is crucial, as both optic nerve edema and atrophy indicate neurological disease. Bilateral optic nerve edema without vision loss is highly suggestive of papilledema, especially when accompanied by symptoms of high intracranial pressure.[49] There is significant clinical overlap between mild papilledema and pseudopapilledema (eg, optic disc drusen), so ocular imaging such as B-scan ultrasound and OCT can be very helpful in differentiating true papilledema from pseudopapilledema. Bilateral optic disc edema can also occur secondary to systemic conditions such as malignant hypertension, so a general review of systems is important.[56] Optic atrophy is a key finding in many intracranial and optic nerve diseases. While optic atrophy is easily detected when severe, mild optic atrophy can be particularly subtle. In these cases, OCT can be very helpful, as studies of healthy children have found that an average retinal nerve fiber layer thickness <84 µm is usually abnormal (ie, below the 99th percentile).[57,58]

If an acute neurological disease is suspected, an urgent MRI of the brain and orbit and a neurological assessment is usually warranted. With papilledema, an MRV should be added to look for sinus venous thrombosis. In some cases where the issue is likely longstanding, such as a congenital cranial nerve IV palsy, further work-up may be unnecessary, and the patient can simply be followed or referred to neuro-ophthalmology for assessment.

Conclusion

A child presenting with leukocoria, epiphora, ptosis, proptosis or neurological red flags should prompt the clinician to assess for vision and life-threatening conditions. It is important to have a structured approach to the evaluation of children of different ages and to be aware of investigations and initial management options for these key diagnoses.

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