

Spontaneous Periocular Ecchymosis in Children: Differential Diagnosis and Current Trends in Evaluation and Management

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Abstract

While periocular ecchymosis commonly develops following surgery or traumatic injury to the orbit, the spontaneous appearance of periocular ecchymosis in children can indicate the presence of life-threatening conditions including pediatric malignancies (neuroblastoma, rhabdomyosarcoma, leukemia) and hematologic disorders (aplastic anemia, thrombocytopenia). Vascular malformations (capillary hemangioma, lymphangioma, orbital varix), inflammatory conditions (orbital myositis, amyloidosis), pertussis, and Blue rubber bleb nevus syndrome are benign differential considerations with visual complications in certain instances. Since spontaneous periocular ecchymosis (SPE) can be encountered by pediatric subspecialists both within and outside ophthalmology, the authors present a review of the current literature integrating the clinical features, latest diagnostic investigations, and updates in management for the entities that cause spontaneous periocular ecchymosis in children. A comprehensive and current understanding of the differential diagnosis elicited by this unique ocular finding will aid the clinician in managing long-term visual consequences and coordinating with appropriate pediatric subspecialists.

Keywords: Bruising; Children; Ecchymosis; Pediatric; Periocular; Periorbital; Spontaneous

Introduction

Periocular ecchymosis, a purple discoloration of the periocular skin due to the extravasation of blood into the subcutaneous tissues, is most commonly found in the setting of periorbital trauma and surgery (Figures 1,2) [1]. The marginal, peripheral, superficial orbital, and deep orbital arcades are anastomoses of the branches of the ophthalmic and lacrimal arteries whose presence in specific fascial planes can account for ecchymosis following a variety of traumatic mechanisms or surgical interventions [2]. The superior and inferior venous drainage systems of the eyelid and orbit also communicate via a complex collateral system [2]. The propensity of ecchymosis to occur in the periocular area results from a combination of thin eyelid and periorbital skin with this rich vascular supply [2,3].

However, the spontaneous appearance of periocular ecchymosis in a child, without an attributable traumatic or surgical etiology, should alert the pediatrician and ophthalmologist to a differential diagnosis that includes both life-threatening and vision-threatening conditions (Table 1). Life-threatening conditions include pediatric malignancies such as neuroblastoma, rhabdomyosarcoma, and leukemia; as well as hematologic disorders such as aplastic anemia and thrombocytopenia [4-8]. Neuroblastoma and rhabdomyosarcoma are uncommon, with incidences ranging from 4 to 9 cases per million [9,10], but they represent 3% to 7.5% of malignancies in children, and are fatal if undiagnosed [11]. Benign vascular malformations, including hemangiomas, orbital varices, and lymphangiomas are more common entities that result in spontaneous periocular ecchymosis (SPE) in children [12-14]. Patients must be monitored for visual complications

such as amblyopia, which can occur in 43-60% of children [15]. Inflammatory conditions (orbital myositis, amyloidosis), pertussis, and Blue rubber bleb nevus syndrome are more rare differential considerations with visual complications in certain instances [16-19].



Figure 1: Traumatic periorbital ecchymosis.

Since the entities that cause spontaneous periocular ecchymosis (SPE) are observed by pediatric subspecialists both within and outside ophthalmology, this review will summarize the current literature that addresses their clinical features, diagnostic investigations, and latest management (Table 2). A comprehensive and current understanding of the conditions associated with unique ocular finding will aid the clinician in managing long-term visual consequences and coordinating with appropriate pediatric subspecialists.



Figure 2: Left upper eyelid ecchymosis following ptosis surgery.

Vascular Malformations	Malignancies	Coagulation Disorders	Inflammatory	Miscellaneous
Capillary hemangioma	Neuroblastoma	Aplastic Anemia	Orbital myositis	Pertussis
Lymphangioma	Rhabdomyosarcoma	Thrombocytopenia	Amyloidosis	Blue rubber bleb nevus syndrome
Orbital varix	Leukemia			

Table 1: Differential Diagnosis of Spontaneous Periocular Ecchymosis in a Child.

	Epidemiology	Clinical features	Investigations	Management
Vascular				
Capillary hemangioma	Incidence 1-5% [21-23]	Ocular: Superficial hemangioma (strawberry nevus) Subcutaneous hemangioma [12,21] Enlarges during first year, followed by gradual resolution [22]	Clinical diagnosis CT or MRI if deeper lesion [22]	Ocular: Monitor for local complications [22,23] Systemic: Surgery [20] Pulsed-dye laser [20] Steroids [20] Beta blockers [25]
Lymphangioma	5.6% of benign childhood tumors [26]	Ocular: Orbital, eyelid, or conjunctival vascular mass [23,26,27] Acute proptosis triggered by upper respiratory infection [27]	CT/MRI [22]	Ocular: Monitor for local complications [23,27,28] Surgical debulking [27,28] Local radiotherapy and intralesional sclerotherapy [23,28].
Orbital varix	2% of orbital tumors [29,30]	Ocular: Venous vascular mass dilates during increased venous return—crying, straining, Valsalva [29,30] Systemic: Cranioorbital or cranionasal anomalies in 5% [29]	CT/MRI. [33] Sequential CT scans with and without Valsalva maneuver demonstrate enlargement [33]	Ocular: Monitor for local complications [13,29] Surgical debulking [13,31] Endovascular catheterization [32,34].
Malignant				
Neuroblastoma	Incidence: 9 per million [10] 7.5% of pediatric cancers [11]	Ocular: Spontaneous periocular ecchymosis (SPE) [4,36,37], subconjunctival hemorrhage, proptosis, strabismus, anisocoria, heterochromia, choroidal metastasis, optic neuropathy [4,38-40]. Systemic: abdominal pain, distension, mass effect, bone pain, thrombocytopenia [4,39,44].	Blood tests for catecholamine metabolites Tissue biopsy Abdominal plain film, ultrasound, MRI for primary [35]. Whole-body MRI and nuclear medicine for staging [35]	Ocular: Monitor for local complications [13] Systemic: multimodal chemotherapy and resection of primary tumor [43,44] Adjuvant myeloablative and autologous stem cell therapies [45]
Rhabdomyosarcoma	Incidence: 4 per million [11,46] 3% of all pediatric cancers [5]	Ocular: SPE [5,9,47], palpable mass, periocular edema, ptosis, proptosis, chemosis, choroidal folds, optic disc edema [5]. Systemic: soft tissue mass	CT/MRI [49] Incisional or excisional biopsy [49] Whole body imaging with bone scan for staging [48]	Ocular/systemic: Surgical debulking, external-beam radiation, systemic chemotherapy [9,50].

Leukemia	Incidence: 3,000 children per year [52]	Ocular: infiltration to orbit, conjunctiva, iris, ciliary body, choroid, retina, optic nerve [53] Retinal vascular tortuosity and occlusion, retinal and vitreous hemorrhage, opportunistic infection, SPE6 [53], Systemic: anemia, thrombocytopenia, hyperviscosity, and immunosuppression [6,53]	Bone marrow biopsy [54] Serum electrolytes and uric acid, complete blood count, coagulation studies, metabolic and viral panel [54] Ocular exam for papilledema and cranial nerve palsies [6,53]	Ocular: Local irradiation and systemic chemotherapy (emergent if optic nerve infiltrate) [55-57] Systemic: Induction, consolidation, and maintenance chemotherapy [54]
Coagulation disorders				
Aplastic anemia	Incidence: 2 per million per year [58]	Ocular: retinal and vitreous hemorrhage, neovascularization, cotton-wool spots, SPE7 [60-62], Systemic: Anemia, neutropenia, thrombocytopenia, fatigue, pallor, recurrent infections, mucosal hemorrhage, menorrhagia, petechiae [7].	CBC, work-up for hepatitis, human immunodeficiency virus, Epstein-Barr virus	Ocular: Monitor for local complications Surgical decompression in rare cases of orbital hemorrhage [7] Systemic: allogeneic bone marrow transplantation [59,63]
Thrombocytopenia	Incidence: 4-6 children per year [64,65]	Ocular: SPE, mucosal bleeding [8] Systemic: purpura, petechial rash, mucosal bleeding, history of recent infection, epistaxis, gastrointestinal bleeding, intracranial hemorrhage [65].	Platelet count Complete blood count Peripheral blood smear [64]	Systemic: Intravenous immunoglobulin, anti-D immunoglobulin, platelet transfusions for severe cases [66]
Inflammatory				
Orbital myositis	Female predilection of 2:1 [67,68]	Ocular: Diplopia, painful proptosis, SPE, ptosis [9,69,70]	CT of orbits [69]	Ocular: systemic steroids [69] Intralesional triamcinolone with prolonged oral steroid taper [72] Radiotherapy, immunomodulatory drugs, surgical debulking for recalcitrant cases [71,72]
Amyloidosis	Incidence 9 per 100,000 [74]	Organ-dependent Ocular: periocular pain, palpable mass, SPE, ptosis, proptosis, motility restriction [17,75,78] Systemic: congestive heart failure, edema, petechiae, diarrhea, proteinuria, hepatosplenomegaly [17,75,78]	Biopsy Subcutaneous fat aspiration with Congo red staining [78]	Ocular: monitor for complications Local debulking [77] Systemic: steroids, mephalan, autologous stem cell transplantation [77,79,80]
Miscellaneous				
Pertussis	3055 cases per year in the U.S. [82]	Ocular: SPE and subconjunctival hemorrhage [81,83] Systemic: series of coughs during a single expiration, followed by a vigorous whooping inspiration [18]. Post-tussive vomiting	Clinical diagnosis [81]	Systemic: antibiotics (macrolide, trimethoprim-sulfamethoxazole) [84] Consider hospitalization if increased work of breathing, cyanosis, apnea, poor feeding.
Blue rubber bleb nevus syndrome	200 reported cases [86]	Ocular: proptosis, subconjunctival hemorrhage, SPE [19,87,88] Systemic: Cutaneous lesions resembling blue rubber blebs [85] Gastrointestinal bleeding [85]	CT / MRI Endoscopy [85]	Ocular: Monitor for local complications Surgical debulking if exposure keratopathy [88] Systemic: gastroenterology evaluation, endoscopic removal if bleeding [85]

Table 2: Characteristics and management of the entities that cause spontaneous periocular ecchymosis.

Methods

Articles were retrieved by searches of the US National Library of Medicine at the National Institutes of Health and the PubMed OLDMEDLINE subset (Cumulated Index Medicus and the Current List of Medical Literature). The search period was 1955-2014. Search terms included periorbital, periocular, ecchymosis, purpura, raccoon eyes, aplastic anemia, thrombocytopenia, hemangioma, lymphangioma, orbital varix, metastatic neuroblastoma, rhabdomyosarcoma, leukemia, amyloidosis, orbital myositis, pertussis, and blue rubber bleb nevus syndrome. The literature review was completed in full compliance with the Human Investigations Committee of the Yale University School of Medicine with informed consent signed by the parents of patients permitting the utilization of de-identified patient images.

Vascular Malformations

Capillary hemangioma

Capillary hemangioma is a proliferation of vascular endothelial cells and pericytes forming a capillary unit [20]. It is the most common benign orbital tumor in childhood, with incidence between 1% and 5% [21-23], and occurs frequently in females, premature infants and children of multiple-gestation pregnancies [24].

Clinical features: The most common presentation is the superficial hemangioma or strawberry nevus of the eyelid, consisting of a bright red, elevated nodule (Figure 3). In contrast, subcutaneous and orbital hemangiomas feature a deep, bluish hue that can resemble an ecchymosis (Figure 4a) [12,21]. It appears in the first few weeks of life with enlargement during the next year, followed by gradual resolution, which occurs in 75% of children by age 7 without treatment [22].



Figure 3: Superficial capillary hemangioma: bright red, elevated nodule with sharp borders.

Chief investigations: Diagnosis is typically clinical and does not require imaging or histology. Deeper lesions may require computerized tomography (CT) of the orbits which demonstrates a well-circumscribed, enhancing, lobulated mass. Magnetic resonance imaging (MRI) demonstrates slight hypo-intensity on T1 sequences and slight hyper-intensity on T2 sequences with serpiginous flow voids (Figures 4b,4c) [22].

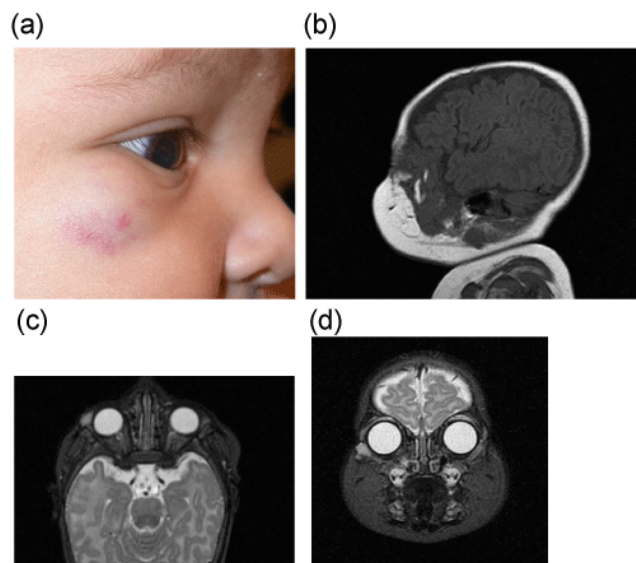


Figure 4: **A)** Subcutaneous capillary hemangioma with deep bluish hue and soft borders. **B)** Well-circumscribed, lobulated mass with serpiginous flow voids at the infero-lateral orbital rim on T1-weighted MRI, sagittal view. **C,D)** The lobulated lesion has thin septae and slight hyperintensity on T2-weighted sequences (axial, coronal views).

Management: Periocular hemangiomas must be monitored by the pediatric ophthalmologist for astigmatism, ptosis and amblyopia. Furthermore, orbital lesions can result in proptosis, exposure keratopathy, strabismus, and optic neuropathy [22,23]. These complications can cause anisometropic and deprivational amblyopia in 43-60% of patients with capillary hemangioma [15]. Surgery, pulsed-dye laser, systemic and intralesional corticosteroids, and immunomodulators have traditionally been used to hasten resolution of the lesion. More recent reports demonstrate the success of systemic and topical beta blockers [20], though life-threatening side effects (bradycardia, hypotension, bronchospasm, hypoglycaemia) can occur with systemic propranolol administration [25].

Lymphangioma

Lymphangioma is a rare hamartoma composed of lymphatic and venous vasculature that represents 5.6% of benign childhood tumors [26]. It is commonly diagnosed in the first or second decade of life, with most cases seen before 2 years of age [26,27].

Clinical features: Ocular involvement can include the orbit, eyelid, or conjunctiva; non-ocular lymphangiomas are most commonly seen in the head and neck [23,26,27]. Acute episodes of proptosis and pain with orbital lymphangioma are often triggered by an upper respiratory tract infection (Figure 5) [27]. Spontaneous hemorrhage within the tumor can manifest as spontaneous periocular ecchymosis (SPE) [14].

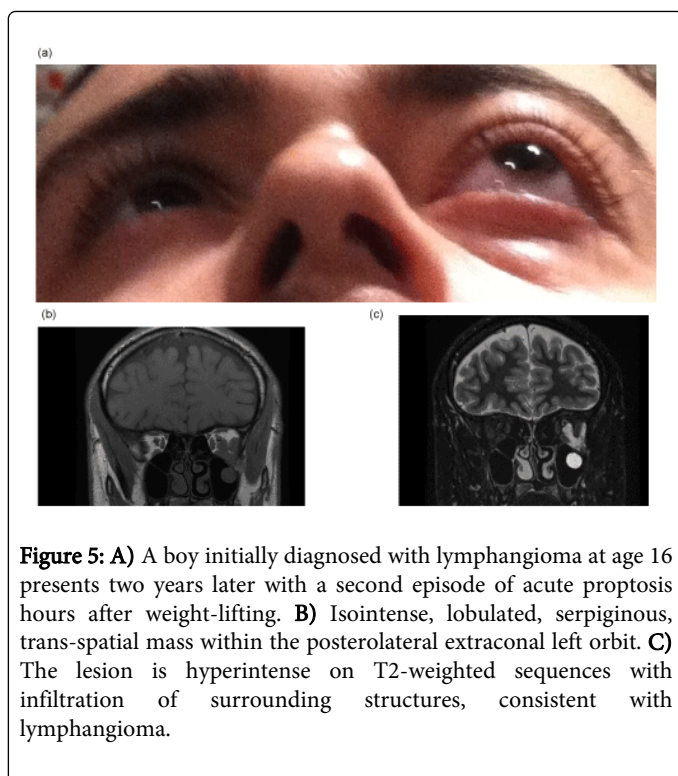


Figure 5: A) A boy initially diagnosed with lymphangioma at age 16 presents two years later with a second episode of acute proptosis hours after weight-lifting. B) Isointense, lobulated, serpiginous, trans-spatial mass within the posterolateral extraconal left orbit. C) The lesion is hyperintense on T2-weighted sequences with infiltration of surrounding structures, consistent with lymphangioma.

Chief Investigations: An infiltrative, cystic mass with lobular areas of layered blood can be seen on CT and MRI of the orbits (Figures 5b, 5c) [22]. Biopsy demonstrates vascular channels with lymphatic fluid, but is not considered necessary for diagnosis [28].

Management: While asymptomatic cases are observed, the pediatric ophthalmologist must monitor for proptosis, ptosis, strabismus, astigmatism and amblyopia [23,27,29]. Visual loss can also result from expansion or acute hemorrhage of an orbital lymphangioma with optic nerve compression [27,29]. In these situations, surgical debulking is indicated but technically challenging due to the diffusely infiltrative and hemorrhagic nature of the tumor, and recurrence after surgery is common [27,29]. Other evolving therapies that require additional investigation are local radiotherapy and intralesional sclerotherapy [23,29].

Orbital varix

Orbital varix, composed of dilated venous channels, is another benign vascular growth in children and represents 2% of orbital tumors [28,30]. This plexus of thin-walled, distensible vessels communicates with the normal orbital veins; unlike the lymphangioma which is hemodynamically-isolated [27].

Clinical features: The venous plexus dilates during maneuvers that increase venous return, including crying or straining in the child [28,31]. Children with orbital varices may complain of pain, visual disturbance or diplopia [28]. Ophthalmic exam can reveal proptosis that increases with crying, orbital hemorrhage, periocular ecchymosis, motility disturbance, and optic nerve swelling or atrophy in severe cases [13,28,32]. Varices are typically confined to the orbit, but significant craniocorbital or cranionasal anomalies are present in 5% of cases [28].

Chief investigations: Like lymphangioma, the diagnosis is radiographic rather than histologic and involves CT or MRI of the orbits [33]. Sequential CT scans with and without Valsalva maneuver demonstrate a change in size to aid the radiologist in distinguishing this from other orbital vascular tumors. Enhancement with contrast matches venous structures in the cavernous sinus.

Management: Asymptomatic varices require no intervention. Indications for surgery include pain, cosmetic deformity, exposure keratopathy, and optic neuropathy [13,28]. As with lymphangioma, surgical debulking poses technical challenges due to close relationships with normal structures, direct communication with the cavernous sinus, and recurrence after subtotal excision [32,33]. Endovascular catheterization of the varix through the jugular vein and cavernous sinus is a recent and less invasive alternative [32,34].

Malignancies

Neuroblastoma

Neuroblastoma is an aggressive pediatric sympathetic nervous system malignancy that arises from neural crest cells in the adrenal medulla or paraspinal sympathetic tissue [4,35]. Although it is an uncommon tumor with an incidence of nine cases per million children, it accounts for 7.5% of all cancers occurring in children aged less than fifteen [10,11]. Orbital metastasis represents 10-20% of metastatic neuroblastoma cases [4,36,37].

Clinical features: While abdominal pain and distension are common symptoms of primary neuroblastoma, SPE is a hallmark of orbital metastasis, seen in 20-40% of children with the malignancy [4,36,37]. Other ocular manifestations include proptosis, strabismus, anisocoria, heterochromia, choroidal metastasis, and optic neuropathy [4,38-40]. Given the aggressive nature of the tumor, children often present with widely metastatic disease, including bone marrow metastasis leading to thrombocytopenia and subconjunctival haemorrhage [4], and other systemic metastasis often manifesting with mass effect and bone pain [36,41]. Paraneoplastic neurologic manifestations including cerebellar ataxia, opsoclonus and myoclonus have been reported [42].

Chief investigations: Diagnosis is initially suggested by blood tests for catecholamine metabolites and confirmed by tissue biopsy. Plain film and ultrasound can demonstrate an intra-abdominal mass with possible calcification [35]. Abdominal/thoracic MRI is best for determining the organ of origin, and whole-body MRI and nuclear medicine studies with metaiodobenzylguanidine (MIBG) are useful for staging [35].

Management: Ophthalmic involvement represents Stage IV disease, for which multimodal systemic chemotherapy and resection of the primary tumor are the mainstays of treatment [43,44]. Adjuvant myeloablative and autologous stem cell therapies are being investigated [45]. The pediatric ophthalmologist's role encompasses workup, diagnosis, biopsy and management of visual consequences [4].

Rhabdomyosarcoma

Rhabdomyosarcoma is a highly malignant mesenchymal tumor that constitutes 3% of all cancers in children below fifteen years of age [5]. It is the most common soft tissue tumour with an incidence of four per

million children [11,46]. Primary orbital rhabdomyosarcoma represents 9% of cases [23].

Clinical features: Although rhabdomyosarcoma can arise from mesenchymal tissue throughout the body, SPE is a hallmark presenting sign of orbital rhabdomyosarcoma [5,9,47]. Palpable mass, periocular edema, ptosis, proptosis, and chemosis, choroidal folds and optic disc edema can also be found [5]. The more common embryonal histologic subtype frequently involves the superonasal orbit and portends a much better 5-year survival than the alveolar subtype which often originates in the inferior orbit [9,48,49].

Chief investigations: Work-up requires orbital imaging to determine the extent of the lesion, followed by prompt incisional or excisional biopsy [49]. CT demonstrates soft tissue density that enhances with contrast. Bony erosion can be seen. MRI demonstrates iso-intensity to adjacent muscle with possible hemorrhagic and necrotic areas in alveolar subtypes [48]. Whole body imaging with bone scan is recommended for metastatic work-up [48].

Management: After tissue diagnosis is confirmed, rhabdomyosarcoma is treated with surgical debulking, external-beam radiation and systemic chemotherapy [9,50]. Children with primary embryonal rhabdomyosarcoma localized to the orbit have a 95% survival rate at 5 years, compared to the 75% 5- year survival rate attributed to the alveolar cell type [49,50].

Leukemia

Acute leukemia, the malignant proliferation of lymphocytes, is the most common pediatric malignancy, with peak incidence at 2-5 years of age [51]. It is classified according to acute vs. chronic duration of activity and myelogenous vs. lymphocytic predominance of cellular proliferation. Acute lymphoblastic leukemia (ALL) is diagnosed in approximately 3,000 new children each year [52].

Clinical features: Ophthalmic involvement can manifest as direct leukemic infiltration to the orbit, conjunctiva, iris, ciliary body, choroid, retina and optic nerve [53]. Even without direct infiltration, the systemic abnormalities including anemia, thrombocytopenia, hyperviscosity, and immunosuppression can result in secondary ophthalmic manifestations such as retinal vascular tortuosity and occlusion, retinal and vitreous hemorrhage, opportunistic infection, and SPE (Figure 6) [6,53].

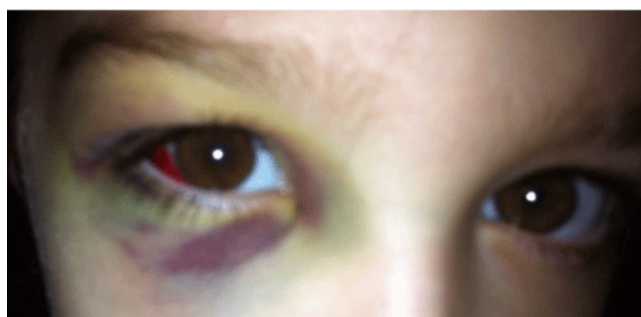


Figure 6: 9-year-old female with spontaneous periocular ecchymosis and subconjunctival hemorrhage in the setting of acute lymphoblastic leukemia.

Chief investigations: Bone marrow biopsy is required for phenotype, cytogenetics, and risk stratification [54]. Work-up should also include serum electrolytes and uric acid, complete blood count (CBC), coagulation studies, renal and liver function, and baseline viral titers.

Management: The treatment of ALL requires a multi-drug chemotherapeutic regimen divided into induction, consolidation, and maintenance phases that include CNS prophylactic therapy [54]. The pediatric ophthalmologist assists in detecting extramedullary disease as papilledema and cranial nerve palsies are important signs of CNS involvement [6,53]. Children with ocular leukemic infiltrates are treated with local irradiation and systemic chemotherapy [55,56]. Leukemic optic nerve infiltration is considered an ophthalmic emergency that requires emergent radiation [57].

Coagulation Disorders

Aplastic anemia

Aplastic anemia is a life-threatening pancytopenia with an incidence of two cases per million per year and a two-year mortality rate of 40% [58]. Pathophysiology involves immune-mediated bone marrow destruction triggered by viral infection, hepatitis, drugs, toxins or genetic predisposition [58,59]. By definition, infiltrative bone marrow disease is absent.

Clinical features: Anemia, neutropenia and thrombocytopenia result in fatigue, pallor recurrent infections, mucosal hemorrhage, menorrhagia, petechiae, and rarely SPE [7]. Retinal and vitreous hemorrhage, neovascularization, and cotton-wool spots have also been reported [60-62].

Chief investigations: CBC demonstrates pancytopenia with decreased reticulocytes, which is confirmed by bone marrow aspiration. Work-up for hepatitis, human immunodeficiency virus, and Epstein-Barr virus should be performed [58].

Management: Allogeneic bone marrow transplantation remains the preferred treatment for children [59,63]. The pediatric ophthalmologist's role is supportive with early referral to the hematologist-oncologist. In rare cases of spontaneous orbital haemorrhage, surgical decompression may be indicated [7].

Thrombocytopenia

Immune thrombocytopenia (ITP), previously known as idiopathic thrombocytopenic purpura, is now recognized as an immune-mediated platelet disorder that occurs more commonly in children than adults, with peak pediatric incidence of 4-6 children per year, often between two and five years of age [64,65].

Clinical features: Cutaneous petechial rash and purpura can involve any part of the body. Mucosal bleeding and SPE are less common findings [8]. Recent infection is present in 60% of patients, and most children are otherwise healthy [65]. In severe cases, profound epistaxis, gastrointestinal bleeding, and intracranial haemorrhage can occur.

Chief investigations: ITP implies a platelet count less than 100,000/microliter and is a diagnosis of exclusion [64]. CBC and peripheral blood smear therefore are otherwise unremarkable.

Management: Isolated cutaneous ITP requires no intervention as most cases resolve within 3 months [66]. Severe cases require a

combination of intravenous immunoglobulin (IVIG), anti-D immunoglobulin, and platelet transfusions. While dedicated ocular treatment is not typically indicated [8], the ophthalmologist's role involves early disease recognition and referral to a pediatric haematologist.

Inflammatory

Orbital myositis

Orbital myositis is inflammation of the extraocular muscles that commonly affects young adults and children with a female predilection of 2:1 [67,68]. While often a form of primary idiopathic orbital inflammation, it has also been reported secondary to respiratory tract infections, Lyme disease, Varicella-zoster, Whipple's disease, polymyositis, psoriatic arthropathy, systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, Kawasaki disease, and Crohn's disease [67].

Clinical features: Inflammation most often affects the horizontal recti and presents with diplopia, painful proptosis, and/or SPE [9,69]. Levator involvement can present with ptosis [70].

Chief investigations: Orbital CT scan demonstrates enlargement of the extraocular muscle and tendon [69]. Unusual cases are biopsied. Laboratory studies are indicated if secondary orbital myositis is suspected due to the aforementioned systemic autoimmune entities.

Management: Systemic steroids are the first-line ocular therapy for symptomatic relief and prevention of muscle fibrosis [69,71]. Clinical improvement is seen within days in 67% of patients. Intralesional triamcinolone with a prolonged oral steroid taper has also been used successfully in a 5-year-old [72]. Radiotherapy, immunomodulatory drugs, and surgical debulking are reserved for recalcitrant cases [71,72].

Amyloidosis

Amyloidosis refers to the deposition of insoluble fibrils in the extracellular spaces of organs and tissues [73]. While classically a disease of the elderly with an incidence of 9 cases per 100,000 and a 2:1 male predilection [74], there are recent reports of morbidity in adolescents in the setting of lymphoproliferative disorders, chronic inflammatory diseases including juvenile idiopathic arthritis (JIA), and cyclic neutropenia [17,75-78].

Clinical features: The major sites of amyloid deposition are the kidneys, heart and liver. Ocular involvement most commonly involves the eyelids with signs and symptoms that include periocular pain, palpable mass, SPE, ptosis, proptosis, and motility restriction [17,75-78].

Chief investigations: Tissue diagnosis from biopsy of the involved organ is diagnostic. More recently, subcutaneous fat tissue aspiration with Congo red staining has been sensitive and specific in patients with multi-organ involvement [78].

Management: In addition to local surgical debulking, management of periocular amyloidosis requires control of the underlying inflammation [77]. However, complete debulking often cannot be achieved, and recurrence is common [77]. Recent success has been reported with high-dose mephalan and autologous stem cell transplantation in adults, but more study is needed for applicability to pediatric amyloidosis [79,80].

Miscellaneous

Paroxysmal cough in pertussis

Bordetella pertussis, a Gram-negative coccobacillus, classically causes whooping cough in infants and young children. Recently, however, there is a resurgence of cases in previously vaccinated adolescents as immunity wanes [81]. The National Notifiable Diseases Surveillance System in the US reports an average of 3,055 infant pertussis cases and 19 infant pertussis deaths each year [82].

Clinical features: Nonspecific upper respiratory symptoms are seen in the initial catarrhal phase for one to two weeks. During the paroxysmal phase, the hallmark paroxysm is a series of coughs during a single expiration. Small lung volumes during these spells, particularly in children, lead to a vigorous whooping inspiration. Increased venous pressure during Valsalva can cause SPE and subconjunctival hemorrhage [18,81,83]. After 2 to 3 months, a gradual decrease in frequency and severity of the cough is seen in the convalescent phase [83].

Chief investigations: Pertussis is a clinical diagnosis, defined as acute cough lasting at least 14 days with either paroxysmal episodes, inspiratory whooping, or post-tussive vomiting [81].

Management: Pertussis is treated with a 1-2 week course of macrolide antibiotics or trimethoprim-sulfamethoxazole [84]. Antibiotic therapy eradicates the organism from the host but often without measurable alteration in the course or duration of symptoms. The outpatient clinician must maintain a low threshold for hospitalization of the child while monitoring for increased work of breathing, cyanosis, apnea, and poor feeding. Ocular treatment is not typically indicated.

Blue rubber bleb nevus syndrome

Blue rubber bleb nevus syndrome (BRBNS) is a rare congenital entity consisting of distinctive venous malformations in the skin and gastrointestinal tract that can result in bleeding and chronic anemia [85]. Approximately 200 cases have been reported in the literature [86].

Clinical features: Cutaneous lesions with characteristic appearance resembling blue rubber blebs are present in early childhood, with gastrointestinal bleeding of varying severity in subsequent years. Ophthalmic BRBNS findings include proptosis, subconjunctival hemorrhage, and SPE [19,87,88].

Chief investigations: Systemic CT, MRI and endoscopy are used to identify visceral lesions [85]. Histopathology demonstrates dilated vascular spaces lined by both endothelium and fibrous tissue.

Management: Since gastrointestinal bleeding in BRBNS can be profound and fatal, the pediatric ophthalmologist should be alert to the diagnosis in a patient with characteristic cutaneous and ophthalmic findings for appropriate gastroenterology evaluation. Ocular treatment with surgical debulking is indicated if exposure keratopathy results from proptosis [88].

Traumatic periocular ecchymosis

The differential diagnosis elicited by spontaneous periocular ecchymosis is considered in a child after traumatic etiologies have been ruled out. The traumatic causes of periocular ecchymosis in

children include abusive head trauma (AHT), skull base fracture, periocular surgery, and open globe injuries.

AHT refers to the cranial, cerebral, and spinal injuries that can result from blunt force trauma, shaking, or a combination of forces [89]. These injuries cause significant morbidity and mortality in infants with an incidence of 17 per 100,000 person-years [90]. The injuries result in mortality in as many as 30% of victims, and survivors are left with severe cognitive, motor, visual, and behavioural disabilities [91]. Vitreous, subhyaloid, intraretinal, and subretinal haemorrhages; macular folds, and retinoschisis are cardinal ophthalmic signs of AHT [92], with periocular ecchymosis and edema observed in 15% cases [93]. The diagnosis of AHT carries social and legal ramifications and requires a comprehensive workup by a pediatrician trained in child abuse, working in collaboration with neurosurgery, neurology, radiology, and ophthalmology.

Skull base fracture is another important cause of pediatric morbidity and mortality that results from severe head trauma [94,95]. Reported incidence ranges from 3.5% to 24% in patients with head trauma [96,97]. Subdural and epidural hematoma, dural laceration with rhinorrhoea, dural fistulae, and concurrent fracture of the paranasal sinuses and cribriform plate are also common findings [94,95]. Recognition of skull base fractures by the clinician is also significant due to the associated risks of meningitis [1] and fatal complications if using a nasogastric tube [98]. Diagnosis of skull base fracture and its aforementioned complications often requires imaging with high-resolution computerized tomography [94,95]; but in the appropriate setting, clinical signs can be used to aid in rapid diagnosis. Periocular ecchymosis is observed in 21-52% of patients with skull base fracture [94,95,99]. Neurosurgical evaluation and management are paramount [94,95].

Ecchymosis following periocular surgery, particularly ptosis repair in children, occurs due to a rich vascular supply in combination with thin eyelid skin, and is an alarming finding for the unsuspecting parent [2,3]. Finally, adnexal and orbital injuries that can result in periocular ecchymosis have been reported in 25.7% of patients with open globe injuries [100]. An increased likelihood for adnexal injury in patients with rupture rather than penetrating mechanism has been shown [100,101]. Globe integrity therefore should be confirmed in the evaluation of a child with traumatic periocular ecchymosis, especially in the setting of blunt trauma.

Conclusion

Spontaneous periocular ecchymosis in children elicits a broad differential diagnosis of vision-threatening and life-threatening conditions that often necessitate the collaboration of multiple pediatric disciplines. Thorough history and physical and additional ocular findings will guide the clinician in appropriate diagnostic work-up and coordination with pediatric subspecialists.

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