Review

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Update on orbital vascular anomalies in pediatrics: imaging studies and management

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ABSTRACT

Orbital vascular anomalies (OVAs) are a heterogeneous group of disorders frequently found in the orbital cone, the periorbital region, or within the orbit itself. OVAs are divided into tumors and malformations. The most frequent clinical presentation is exophthalmos, associated or not with an alteration of the visual axis. They may also cause acute complications, being intralesional bleeding or cellulitis the most frequent, and chronic complications, such as amblyopia and long-term visual acuity impairment.

The development of imaging techniques, the use of new drugs, and the implementation of innovative procedures in interventional radiology have resulted in a significant improvement in the diagnostic and therapeutic approaches to these patients, essential to an accurate diagnosis and management.

Key words: *congenital anomalies; vascular malformations; hemangioma; orbital neoplasms.*

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INTRODUCTION

Vascular anomalies are a heterogeneous group of disorders frequently found in the periorbital region. The International Society for the Study of Vascular Anomalies (ISSVA) classifies them into 2 main groups: vascular tumors, which have a proliferative endothelium, and vascular malformations, which are basically localized defects of vascular morphogenesis.[1]

Infantile hemangiomas are the most common and frequent example of vascular tumors; venous malformations (VMs) and lymphatic malformations (LMs) are the most common examples in the subgroup of malformations.[2]

Orbital vascular anomalies (OVAs) are benign lesions and account for 5% to 20% of all orbital lesions in children.[2,3]

The most frequent clinical presentation of OVAs is, in general, exophthalmos, associated or not with an alteration of the visual axis (*Figure 1*). Less frequently, asymptomatic tumors are found, such as small infantile hemangiomas.[4,5] OVAs may also cause acute complications, being intralesional bleeding or cellulitis the most frequent, and chronic complications, such as amblyopia and long-term visual acuity impairment (*Figure 2*). Timely diagnosis and management are determining factors for the visual health of children.[6]

The management of these conditions has improved significantly in recent years, especially thanks to a better knowledge of them, which allows us to accurately identify and classify these lesions and decide on the best treatment option.[7–9] The most recent findings on the pathogenesis of OVAs and the development of imaging techniques and interventional procedures have led to a significant improvement in the diagnostic and therapeutic approaches to these patients.[10,11]

Figure 1. Nine-year-old female patient with an orbital venous-lymphatic malformation and exophthalmos

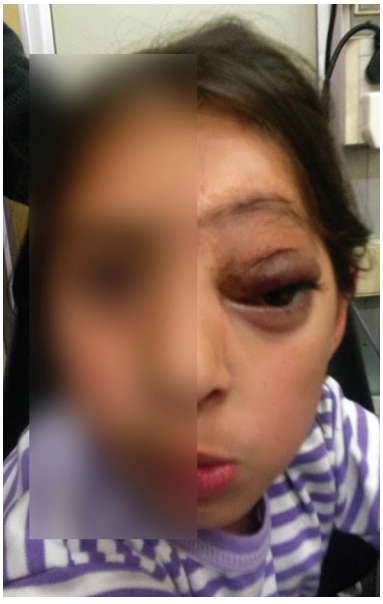
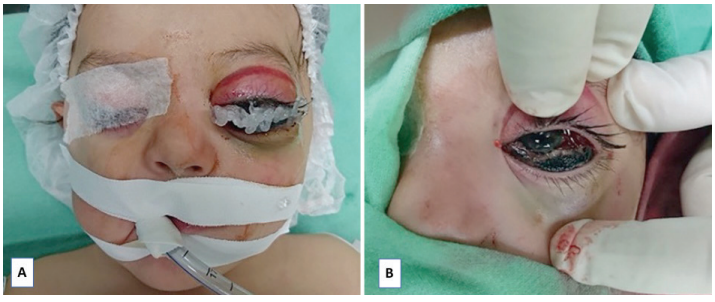


Figure 2. One-year-old male patient with retro-ocular venous-lymphatic malformation and acute episode of intralesional bleeding



CLASSIFICATION

At present, the most widely accepted classification is the one described by Mulliken and Glowacki in 1982, adopted and updated by the ISSVA (*Table 1*).[7] Based on this classification, vascular anomalies are generally divided into vascular malformations and tumors.[12,13]

Hemangiomas are the most frequent benign vascular tumors during childhood. They are subdivided into infantile hemangiomas (the most common and known type to general pediatricians) and congenital hemangiomas (so called because they are fully developed at birth). In this update, we will refer exclusively to infantile hemangiomas (IHs) because congenital hemangiomas are extremely rare in the orbit. IHs are present in 4–5% of infants. They are not present at birth; however, a precursor lesion may be present as a pale, pink or purple area with telangiectasis, which then increases in volume and turns bright red and more evident between 3 and 7 weeks of age. The lesion then proliferates for an average of 3 to 5 months and then involutes over several years.[14,15]

On the other hand, vascular malformations are observed at birth and consist of dysplastic vascular channels. Unlike hemangiomas, vascular malformations show normal cellular proliferation, grow in parallel with the child´s development, and do not have a spontaneous involution. Based on the vascular channel involved, they are subdivided into arterial, venous, lymphatic, capillary or mixed; each has clinical and imaging features that define their presentation, management, and specific follow-up.[7,9,10]

ORBITAL AND PERIORBITAL INFANTILE HEMANGIOMAS

IHs located in the orbital and periorbital regions should be considered a possible cause of alterations in visual development in infants. Most IHs are usually extraconal, most frequently located in the upper eyelid. IHs located at a deeper level may extend across tissue planes, even intracranially through the optic canal or superior orbital fissure. The extraocular muscles and lacrimal glands are rarely involved.[16]

IHs may cause certain complications, including astigmatism, blepharoptosis, exophthalmos, and strabismus (*Figure 3*). One of the main preventable causes of blindness in children is amblyopia, which results from the visual stimulus deprivation due to the obstruction caused by this vascular tumor.[3,5]

On physical examination, lesions located in the superficial orbital or periorbital planes usually appear as reddish tumors, whereas subcutaneous lesions are usually purplish. In many cases, these lesions are not clearly visible on the skin.[17–19] In general, they do not change during crying or Valsalva maneuvers, as is the case with VMs.

In case of extension into the orbit, these lesions may cause exophthalmos with displacement of the eyeball.[17,19] Deep hemangiomas typically present with only limited skin manifestations, such as a faint blue-green discoloration, in addition to the underlying tumor.

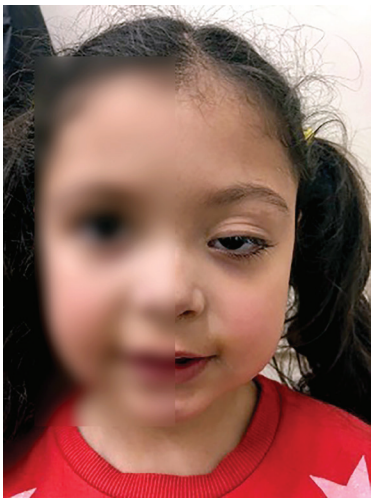
In rare cases, other less frequent complications may occur, including local bleeding, ulceration of the hemangioma, localized thrombosis, optic

Table 1. 2018 ISSVA classification for vascular anomalies

Vascular tumors	Vascular malformation
Benign	**Simple**
Infantile hemangioma	Capillary
Congenital hemangioma	Lymphatic
Tufted angioma	Venous
Pyogenic granuloma	Arterial
Locally aggressive	**Combined**
Kaposiform hemangioendothelioma	Arteriovenous fistula
Kaposi sarcoma	Arteriovenous malformation
Others	Capillary-venous malformation
Malignant	Capillary-lymphatic-venous malformation
Angiosarcoma	Venous-lymphatic malformation
Others	Capillary-lymphatic malformation

ISSVA Classification of Vascular Anomalies ©2018 International Society for the Study of Vascular Anomalies. Available at issva.org/classification

Figure 3. Four-year-old female patient with intraorbital hemangioma and secondary exophthalmos



nerve compression, and bone remodeling.[20]

IHs are frequently seen as isolated findings, but in cases with a large and segmental lesion, i.e., affecting segments of the face, skull, and cervical region, it is important to request imaging tests to rule out PHACE (posterior fossa anomalies, hemangioma, arterial anomalies, cardiac anomalies, and eye anomalies) syndrome. PHACE syndrome, defined as a neurocutaneous disorder, is associated with the presence of large hemangiomas and 1 or more structural abnormalities. Its most characteristic feature is the presence of a large skin hemangioma that may involve one or more dermatomes (*Figure 4*).[21–24]

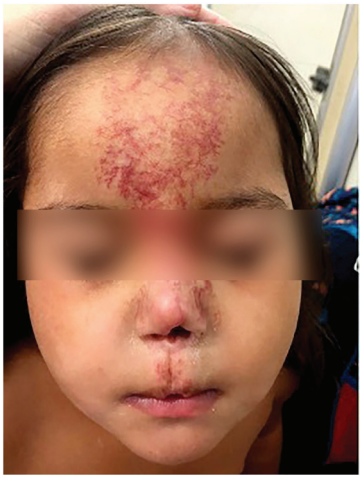
Lesions suspicious for infantile hemangiomas that do not present cutaneous stigmata should be carefully evaluated, taking into account the differential diagnosis of malignant lesions of the orbit. Such differential diagnoses include rhabdomyosarcoma, leukemic infiltrations or other malignancies (*Figure 5*).[5,25]

Imaging studies

The natural evolution of IHs is very characteristic, they grow in phases. First, the proliferative phase, which begins during the third trimester of pregnancy, in the womb, and continues during the first weeks of life. This phase is characterized by intense vascularization of the lesion. Between 1 and 5 years old, the plateau phase occurs, where the hemangioma remains stable and slowly begins to decrease in size. Finally, after 5 years old, the involution phase occurs, where the hemangioma generally disappears and is replaced almost entirely by fibroadipose tissue.[3,5,14]

These phases correlate well with the most useful imaging method for these lesions. A

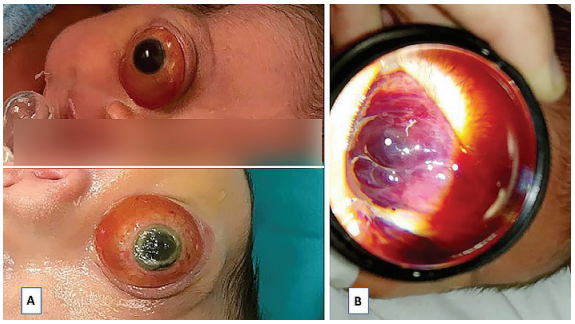
Figure 4. Three-year-old female patient with PHACE syndrome and facial hemangioma > 5 cm in diameter



Doppler ultrasound should be the first imaging test requested. Superficial lesions can be adequately delimited, without extension to deep planes and without involvement of adjacent structures. An ultrasound is sufficient to assess the extent of the lesion and its characteristics, thus avoiding more complex and costly studies, such as magnetic resonance imaging (MRI).

A morphological and color Doppler ultrasound shows solid, limited lesions with variable echogenicity, which present intense vascularization during the proliferative phase. During the involution phase, atrophy occurs and the lesion is replaced by fibroadipose tissue. At this stage, a Doppler ultrasound shows decreased blood flow and increased echogenicity of the

Figure 5. Two-month-old male patient with rhabdomyosarcoma. On examination with a 20-diopter magnifying glass, a bright red, multilobulated lesion that displaces the eyeball and protrudes through the ocular cleft is observed

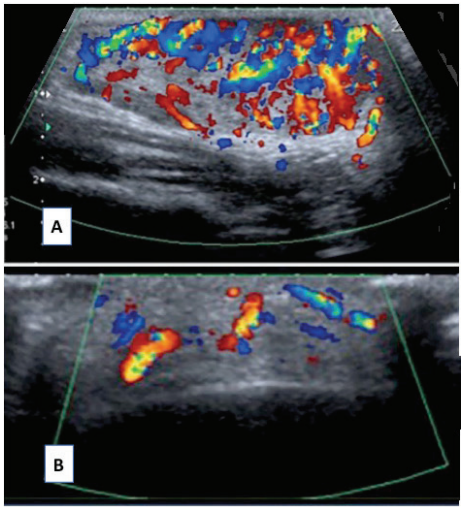


lesion, given the adipose replacement (*Figure 6*).[26]

An MRI is an excellent imaging diagnostic tool, which should only be indicated in cases where the diagnostic doubt persists or a more comprehensive assessment of the extension of the lesion is necessary, and when the ultrasound shows extension to the retro-orbital region and/or the lesion boundaries cannot be adequately defined. This is because, most of the time, an MRI requires general anesthesia to be adequately performed in infants and toddlers (*Figure 7*).[3–5,15,16]

In the proliferative phase, IHs appear as well-defined, lobulated isointense lesions in T1, as hyperintense and homogeneous lesions in T2, with homogeneous enhancement in the post-contrast series. During the involution phase, there is a decrease in vascular flow, visible by a reduction in the post-contrast enhancement, and

Figure 6. Infantile hemangioma. Color Doppler ultrasound. A: Longitudinal section, proliferative phase (hypervascularization). B: Longitudinal section, involution phase (adipose replacement, reduced Doppler signal)



an increase in fibroadipose tissue, rendering the lesion more heterogeneous.[27]

Management

The multidisciplinary approach and advances in treatment options have resulted in better management of orbital hemangiomas in recent decades. Most cases without a risk for amblyopia, optic nerve involvement, or corneal injury should managed conservatively with clinical and ultrasound follow-up. In cases in which it is necessary to prevent potential complications of hemangioma, propranolol is currently considered the drug of choice; leaving surgery as a last resort. Propranolol is a beta-blocker approved by the United States Food and Drug Administration (FDA) for the treatment of infantile hemangiomas with a risk for complications. The response rate for the administration of propranolol has been reported to be 90–95% within a few weeks of starting treatment. It is administered orally at 1–3 mg/kg/day. Treatment is usually necessary for 6 months.[28]

In standard practice, prior to treatment, a complete clinical history should be taken—with special emphasis on the history of cardiac and lung conditions—and a physical and cardiac examination should be performed, including heart rate (HR) and blood pressure (BP) measurements. The greatest effect of oral propranolol on HR and BP is observed 1 to 3 hours after administration, so these vital signs should be monitored after the first dose, especially in younger children. Monitoring can be performed on an outpatient basis, although sometimes hospitalization may be necessary.

Most patients do not relapse once treatment is completed, but a small number of children may show new tumor growth requiring reinstitution of propanolol.[28,29]

The local administration of timolol maleate 0.5% has also been described; it causes less systemic adverse effects, but is also less effective. Its use is limited to superficial lesions.[30]

ORBITAL AND PERIORBITAL VASCULAR MALFORMATIONS

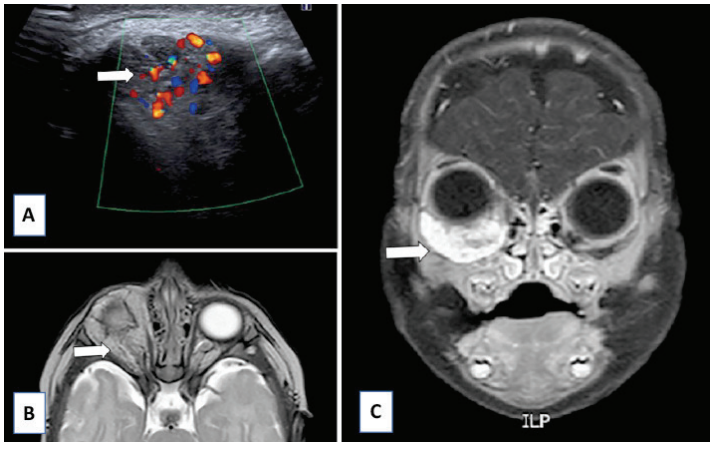
Classification and diagnosis

Vascular malformations are localized, congenital defects of vascular development. They may involve arteries, veins and/or lymphatic vessels. Based on hemodynamics, they can also be classified into high-flow and low-flow malformations. They are more frequent in the head and neck; and although they are rare in the orbit, they may involve the orbit, the periorbital region, and the eye cone.[8,10]

Being a congenital disease, they may be evident from birth or manifest later during development and grow in parallel with the patient, without involuting. In some cases, they become evident only at puberty, since the increase in estrogen and testosterone directly influences the malformations due to the presence of receptors for these hormones.[9,11]

No cases of high-flow (arteriovenous) orbital malformations have been reported, so we limit ourselves to describe low-flow malformations

Figure 7. Orbital hemangioma. A: Ultrasound, longitudinal section, at the level of the orbit. On color Doppler examination, a heterogeneous, hypervascular lesion is observed. B: Magnetic resonance imaging of the same patient, T2 sequence, axial section without contrast. Slightly hyperintense lesion involving the right orbital region and extending to the eye cone. C: T1 sequence, coronal section with gadolinium. Lesion with homogeneous enhancement in the lower right orbital region



involving the orbit (lymphatic and venous). It is worth noting that the combined lesion –venous-lymphatic malformation (VLM)– is the most common type at this level.[5]

Venous-lymphatic malformations

LMs consist of cystic dilatations of lymphatic channels lined by vascular endothelium. There is usually no communication with the functional systemic lymphatic system, although lesions often vary in size in the context of a systemic viral disease.[8,9]

VMs are the most frequent type of vascular anomalies in general. They are caused by an alteration in the development of the vascular endothelium, generating abnormal veins that lack functional valvular mechanisms, with alterations in blood flow leading to progressive dilatation, blood stasis, and subsequent acute or chronic thrombosis (phleboliths). In many cases, during an acute event of thrombosis, they become evident, due to the resulting inflammation and pain.[31]

VLMs account for up to 4% of all orbital lesions referred to tertiary care pediatric centers.[5] They are usually single lesions on the head and neck and may involve the skin, subcutaneous cellular tissue, muscle, and mucous membranes.

These are compressible lesions, which may vary in size with Valsalva maneuvers. In some cases, they may also increase in size suddenly after trauma, with episodes of intralesional bleeding, partial resections, and even due to hormonal influence during puberty and/or pregnancy.[32]

Orbital VLMs are usually not visible at birth, but in most cases become clinically evident in the first 10 years of life.[5,6] The main symptoms include the presence of a mass, exophthalmos, displacement of the eyeball, bleeding and/or pain. Such increase in size may be associated with episodes of thrombosis or bleeding within the lesion and a deformity may appear suddenly and result in a significant cosmetic alteration (*Figure 8*).[5,6,33]

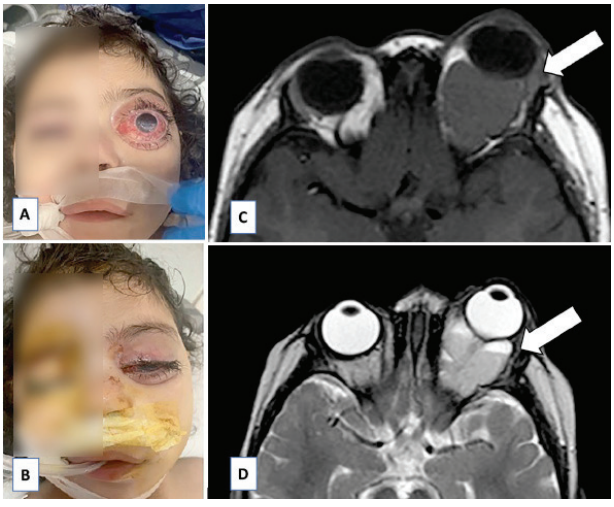
Bleeding occurs in more than half of these patients, may be recurrent, be associated with exophthalmos, and lead to optic neuritis by a mechanism of inflammation and compression.[5,6]

Imaging studies

Imaging features will depend on the evolution of the lesion. In general, there may be multiple cysts containing lymph, blood, or hemoglobin degradation products, especially if bleeding was the presenting clinical symptom (*Figure 9*). On the whole, for all vascular anomalies, Doppler ultrasound and MRI are the imaging studies of choice for the correct and comprehensive assessment and follow-up of patients with this condition. Most patients with VLMs will require both studies at least once.[34,35]

A Doppler ultrasound should always be the first study performed. It will show heterogeneous images, with mixed echogenicity, i.e., anechoic areas corresponding to predominantly lymphatic cystic areas and echogenic areas that may

Figure 8. Two-year-old female patient with retro-ocular venous-lymphatic malformation. A: Intralesional bleeding episode that required percutaneous drainage. B: Immediately post-drainage, correction of exophthalmos is evident. C: Magnetic resonance imaging, T1 sequence, axial section, showing isointense lesion. D: T2 sequence, axial section, showing hyperintense lesion (arrows)



correspond to areas of tissue inflammation associated, in some cases, with diffuse bleeding. Phleboliths, calcium deposits typical of VMs, may be observed as echogenic images with acoustic shadowing in cases of predominantly venous VLMs. In patients with predominantly lymphatic VLMs, the presence of intracystic bleeding may be identified and changes in the echogenicity of the fluid in lymphatic lesions may be observed.[35]

An MRI is helpful to assess the extent and relationship to adjacent structures. Recommended sequences are T1 (pre- and post-contrast) and T2 weighted images, with fat saturation. Typically, images may have an intermediate signal intensity in T1 and a hyperintense signal in T2 in relation to its content or the presence of bleeding or thrombosis. A gadolinium injection usually shows a diffuse enhancement of venous channels, unlike purely LMs, which usually do not have such enhancement. With T2 weighted images, phleboliths appear as focal areas of hypointense signal (*Figure 10*).[36]

Management

Treatment is indicated in case of repeated episodes of exophthalmos, the presence of pain and/or for aesthetic reasons. Unlike hemangiomas, approximately 50% of orbital VLMs can be managed conservatively once the diagnosis is made. Episodes of exophthalmos and acute inflammation generally have a good response to the initial treatment with oral corticosteroids.[5,6]

Beyond medical-drug treatment, the first invasive treatment option is percutaneous sclerotherapy.[9] This procedure is performed under general anesthesia. The initial step consists of an ultrasound- or CT-guided puncture of the orbital lesion, depending on the case. Once the lesion has been approached, the hemodynamics and angioarchitecture of the lesion are studied by means of phlebography, followed by sclerotherapy, i.e., the injection of sclerosing agents (most commonly, sodium tetradecyl sulfate, doxycycline, bleomycin) that cause inflammation and subsequent damage to the endothelium, resulting in fibrosis. This fibrosis leads to retraction and decrease in lesion size and less frequent pain and bleeding events (*Figure 11*).[9,37–40]

These percutaneous procedures have displaced surgery in recent years, although in very complex cases, the combination of sclerotherapy and surgery may be necessary.[33,38]

The use of oral anti-angiogenic drugs such as sirolimus (or rapamycin) has demonstrated to be effective and safe in patients with complex vascular malformations. In some cases, it is possible to combine oral sirolimus with sclerotherapy and/or surgery. There is increasingly more scientific bibliography supporting this option, which shows excellent results in the short- and medium-term. An example of this are orbital malformations with extensive intraconal involvement, in which sclerotherapy is not enough to treat the whole lesion and surgery would not allow the complete resection due to the complex anatomy of tissues adjacent to the lesion.[12,41–44]

DIFFERENTIAL DIAGNOSES OF ORBITAL VASCULAR ANOMALIES

In clinical practice, invasive tumors of the orbit are observed, such as congenital fibrosarcoma.[11] This malignant tumor lesion usually presents in neonates and infants as palpable masses, with healthy skin, although some reports mention lesions with purplish skin and even ulcers that

Figure 9. Ultrasound of orbital lymphatic malformation. Multiple macrocysts (arrows) separated by septa are observed

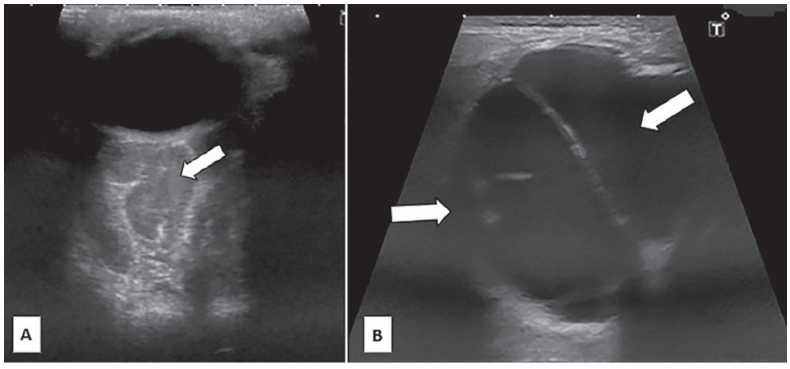
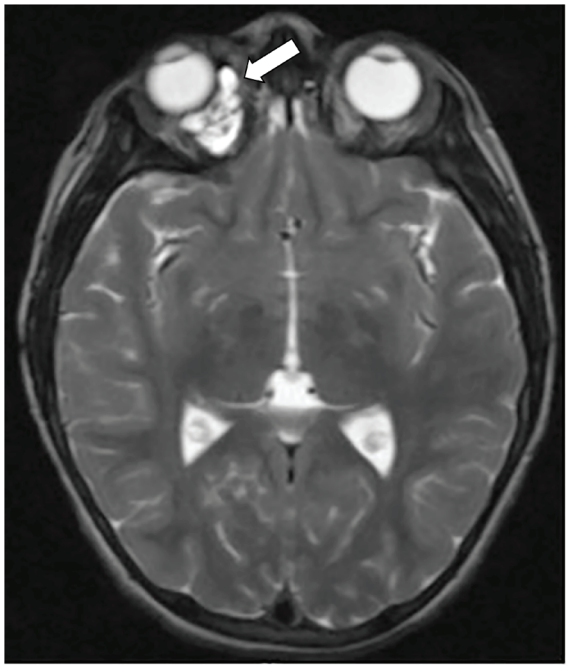


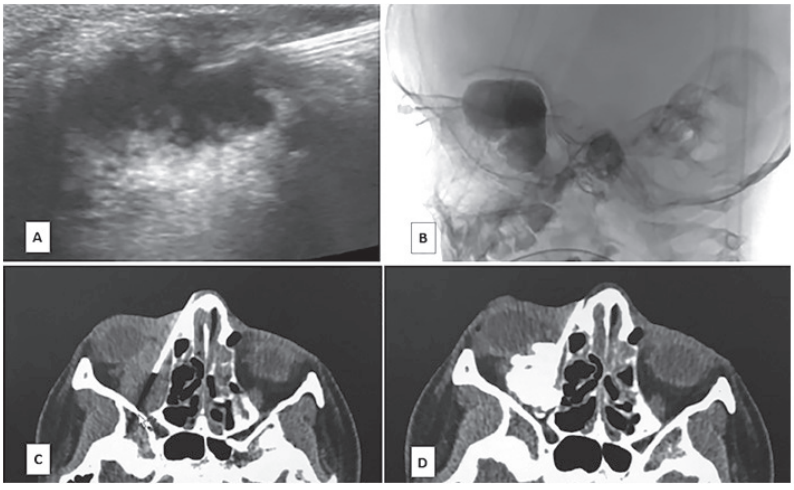
Figure 10. Magnetic resonance imaging, T2 sequence, axial section, showing hyperintense retro-ocular lesion



may be confused with hemangiomas.[45] The initial clinical presentation of neuroblastoma, rhabdomyosarcoma, and retinoblastoma with an exophytic growth pattern may also be very similar to that of some OVAs, so these differential diagnoses should be kept in mind.[2,11,41,45] As a general rule, malignant lesions grow rapidly and cause the remodeling of adjacent bone planes, which is uncommon in AVOs.[33–35] In any cases where the treating specialists have doubts about the benignity of the lesion, a biopsy should be indicated to rule out a malignant lesion.[2]

In summary, basic knowledge of vascular anomalies and vascular conditions of the orbit would help pediatricians with the early detection of OVAs; this would accelerate consultation and eventual referral to a center with appropriate tools for a multidisciplinary

Figure 11. Percutaneous treatment of ocular venous-lymphatic malformation. A: Ultrasound-guided puncture of the superficial component. B: Contrast injection under radioscopic control. C and D: CT-guided puncture and control following sclerosing agent injection (bleomycin)



approach. The different specialists involved (radiologists, interventionalists, ophthalmologists, dermatologists, among others) will be able to use appropriate diagnostic methods and treatment options for each lesion so as to preserve each patient´s visual health. ■

REFERENCES

1. ISSVA International Society for the Study of Vascular Anomalies. Classification of Vascular Anomalies. 2018. [Accessed on: November 15th, 2021]. Available at: https://www.issva.org/classification
2. Castillo BV Jr, Kaufman L. Pediatric tumors of the eye and orbit. *Pediatr Clin North Am*. 2003; 50(1):149-72.
3. Haik BG, Karcioglu ZA, Gordon RA, Pechous BP. Capillary hemangioma (infantile periocular hemangioma). S*urv Ophthalmol*. 1994; 38(5):399-426.
4. Very M, Nagy M, Carr M, Collins S, Brodsky L. Hemangiomas and vascular malformations: analysis of diagnostic accuracy. *Laryngoscope*. 2002; 112(4):612-5.
5. Sullivan TJ. Vascular Anomalies of the Orbit--A Reappraisal. *Asia Pac J Ophthalmol (Phila)*. 2018; 7(5):356-63.
6. Barnacle AM, Theodorou M, Maling SJ, Abou-Rayyah YL. Sclerotherapy treatment of orbital lymphatic malformations: a large single-centre experience. *Br J Ophthalmol*. 2016; 100(2):204-8.
7. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. *Plast Reconstr Surg.* 1982; 69(3):412-22.
8. Merrow AC, Gupta A, Patel MN, Adams D. 2014 Revised classification of vascular lesions from the International Society for the Study of Vascular Anomalies: radiologic-pathologic update. *Radiographics*. 2016; 36(5):1494-516.
9. Sierre S, Teplisky D, Lipsich J. Malformaciones vasculares: actualización en diagnóstico por imágenes y tratamiento. *Arch Argent Pediatr*. 2016; 114(2):167-76.
10. Wassef M, Blei F, Adams D, Alomari A, et al. Vascular anomalies classification: recommendations from the International Society for the Study of Vascular Anomalies. *Pediatrics.* 2015; 136(1):e203-14.
11. Enjolras O. Classification and management of the various superficial vascular anomalies: hemangiomas and vascular malformations. *J Dermatol.* 1997; 24(11):701-10.
12. Adams DM, Ricci KW. Vascular Anomalies: Diagnosis of Complicated Anomalies and New Medical Treatment Options. *Hematol Oncol Clin North Am*. 2019; 33(3):455-70.
13. Monroe EJ. Brief Description of ISSVA Classification for Radiologists. *Tech Vasc Interv Radiol*. 2019; 22(4):100628.
14. Munden A, Butschek R, Tom WL, Marshall JS, et al. Prospective study of infantile haemangiomas: incidence, clinical characteristics and association with placental anomalies. *Br J Dermatol*. 2014; 170(4):907-13.
15. Baselga Torres E, Bernabéu Wittel J, van Esso Arbolave DL, Febrer Bosch MI, et al. Consenso español sobre el hemangioma infantil. *An Pediatr (Barc)*. 2016; 85(5):256-65.
16. Low CM, Stokken JK. Typical Orbital Pathologies: Hemangioma. *J Neurol Surg B Skull Base*. 2021; 82(1):20-6.
17. Xue L, Sun C, Xu DP, Liu ZM, Wang XK. Clinical Outcomes of Infants With Periorbital Hemangiomas Treated With Oral Propranolol. *J Oral Maxillofac Surg*. 2016; 74(11):2193-9.
18. Alniemi ST, Griepentrog GJ, Diehl N, Mohney BG. Incidence and clinical characteristics of periocular infantile hemangiomas. *Arch Ophthalmol.* 2012; 130(7):889-93.
19. Tavakoli M, Yadegari S, Mosallaei M, Aletaha M, et al. Infantile Periocular Hemangioma. *J Ophthalmic Vis Res*. 2017; 12(2):205-11.
20. Spence-Shishido AA, Good WV, Baselga E, Frieden IJ. Hemangiomas and the eye. *Clin Dermatol*. 2015; 33(2):170-82.
21. Frieden IJ, Reese V, Cohen D. PHACE syndrome. The association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities. *Arch Dermatol*. 1996; 132(3):307-11.
22. Metry DW, Garzon MC, Drolet BA, Frommelt P, et al. PHACE syndrome: current knowledge, future directions. *Pediatr Dermatol*. 2009; 26(4):381-98.
23. Garzon MC, Epstein LG, Heyer GL, Frommelt P, et al. PHACE Syndrome: Consensus-Derived Diagnosis and Care Recommendations. *J Pediatr.* 2016; 178:24-33.e2.
24. Rotter A, Samorano LP, Rivitti-Machado MC, Oliveira ZNP, Gontijo B. PHACE syndrome: clinical manifestations, diagnostic criteria, and management. *An Bras Dermatol*. 2018; 93(3):405-11.
25. Tu Y, Jakobiec FA, Leung K, Freitag SK. Distinguishing Benign from Malignant Circumscribed Orbital Tumors in Children. *Semin Ophthalmol*. 2018; 33(1):116-25.
26. Spierer O, Neudorfer M, Leibovitch I, Stolovitch C, Kessler A. Colour Doppler ultrasound imaging findings in paediatric periocular and orbital haemangiomas. *Acta Ophthalmol*. 2012; 90(8):727-32.
27. Albanese G, Mohandas P, Wells L, Ravenscroft J, et al. Orbital infantile haemangioma: radiological features and treatment - case series and literature review. *Orbit*. 2019; 38(1):67-71.
28. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, et al. Propranolol for severe hemangiomas of infancy. *N Engl J Med*. 2008; 12;358(24):2649-51.
29. Koka K, Mukherjee B, Agarkar S. Effect of oral propranolol on periocular Capillary Hemangiomas of Infancy. *Pediatr Neonatol*. 2018; 59(4):390-6.
30. Kramer D, Cossio ML, Downey C. Hemangiomas de la infancia tratados con timolol maleato al 1% en crema. *Rev Chil Pediatr.* 2016; 87(1):69-70.
31. Vikkula M, Boon LM, Mulliken JB. Molecular genetics of vascular malformations. *Matrix Biol*. 2001; 20(5-6):327-35.
32. Legiehn GM, Heran MK. Venous malformations: classification, development, diagnosis, and interventional radiologic management. *Radiol Clin North Am.* 2008; 46(3):545-97, vi.
33. Waner M, O TM. Multidisciplinary Approach to the Management of Lymphatic Malformations of the Head and Neck. *Otolaryngol Clin North Am*. 2018; 51(1):159-72.
34. Restrepo R. Multimodality imaging of vascular anomalies. *Pediatr Radiol*. 2013; 43(Suppl 1):S141-54.
35. Dubois J, Alison M. Vascular anomalies: what a radiologist needs to know. *Pediatr Radiol*. 2010; 40(6):895-905.
36. Flors L, Leiva-Salinas C, Maged IM, Norton PT, et al. MR imaging of soft-tissue vascular malformations: diagnosis, classification, and therapy follow-up. *Radiographics*. 2011; 31(5):1321-40; discussion 1340-1.
37. Kumar S, Kumar V, Kumar S, Kumar S. Management strategy for facial venous malformations. *Natl J Maxillofac Surg*. 2014; 5(1):93-6.
38. Berenguer B, Burrows PE, Zurakowski D, Mulliken JB. Sclerotherapy of craniofacial venous malformations: complications and results. *Plast Reconstr Surg*. 1999; 104(1):1-11; discussion 12-5.
39. Burrows PE, Mason KP. Percutaneous treatment of low flow vascular malformations. *J Vasc Interv Radiol*. 2004; 15(5):431-45.

40. Legiehn GM, Heran MK. A Step-by-Step Practical Approach to Imaging Diagnosis and Interventional Radiologic Therapy in Vascular Malformations. *Semin Intervent Radiol*. 2010; 27(2):209-31.
41. Szhafir I, Teplisky D, Lambert G, Affranchino N, et al. The Impact of Adjuvant Sirolimus Therapy in the Surgical Management of Scrotal Slow-Flow Vascular Malformations. *Urology*. 2021; 147:270-4.
42. Alba-Linero C, García-Lorente M, Rachwani-Anil R, Luque-Aranda G, et al. Treatment of orbital lymphatic malformation with oral sirolimus: a case report. *Arq Bras Oftalmol.* 2022; S0004-27492022005006218.
43. Purt B, Rana HS, Whitescarver TD, Chou E. Novel treatment of recurrent orbital venolymphatic malformation with sirolimus and rivaroxaban. *Orbit.* 2021; 1-8. [In press].
44. Shoji MK, Shishido S, Freitag SK. The Use of Sirolimus for Treatment of Orbital Lymphatic Malformations: A Systematic Review. *Ophthalmic Plast Reconstr Surg.* 2020; 36(3):215-21.
45. Chung EM, Smirniotopoulos JG, Specht CS, Schroeder JW, Cube R. From the archives of the AFIP: Pediatric orbit tumors and tumorlike lesions: nonosseous lesions of the extraocular orbit. *Radiographics*. 2007; 27(6):1777-99.