A case of giant fetal intracranial capillary hemangioma cured with propranolol

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Fetal brain tumors are rare. This report describes a giant posterior fossa capillary hemangioma treated with 3 mg/kg/day of propranolol for 6 months. Total regression was confirmed at 1 year, and no additional tumors were observed during the subsequent 2 years. No side effects relating to the use of this drug were detected; thus, the authors believe that propranolol may be useful for treating all intracranial capillary hemangiomas.

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KEY WORDS capillary hemangioma; propranolol; fetal brain tumor; posterior fossa tumor; hydrocephalus; apoptosis; vascular disorders

CAPILLARY hemangiomas are common benign vascular tumors in infants who often present with skin lesions on the face, neck, and thorax.⁶ Their occurrence in the central nervous system is a rare and challenging phenomenon because of their initial proliferative phase, which causes enlargement of the lesion, with a growth peak at 6 months after birth and the theoretical possibility of spontaneous regression.^{5,6} This regression is typically observed at 4 years of age (30% of patients) and 7 years of age (80% of patients).¹¹ In our literature search, only case reports and small case series on intracranial capillary hemangiomas were found, and no uniform treatment was administered in the described cases. Surgery was performed in certain cases, whereas other cases involved clinical observation and/or treatment with steroids, thalidomide, bevacizumab, and/or temozolomide.^{3,4,13,25}

A different scenario is applicable for cutaneous hemangiomas.^{12,15,24} In particular, for such tumors, propranolol

has been the first-line treatment since Léauté-Labrèze et al.¹⁰ published a case series in 2008 that described severe infantile hemangiomas treated with this beta-blocker with excellent outcomes. To date, propranolol has not been described as a treatment for intracranial capillary hemangiomas. In this paper, we describe the first case in which an intracranial fetal capillary hemangioma has been successfully treated with propranolol.

Case Report

History and Examination

A healthy 24-year-old pregnant woman at 35 weeks of her first gestation underwent routine obstetrical ultrasonography (US) that demonstrated good fetal status but a bulky posterior fossa fetal tumor without hydrocephalus. At the 37th gestational week, a male child was delivered by cesarean section. The infant weighed 3030 g and exhibited

ABBREVIATIONS MAPK = mitogen-activated protein kinase; US = ultrasonography.

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FIG. 1. Postnatal T1-weighted MR image after a Gd injection. **Left:** Sagittal view of the tumor, revealing the voluminous mass anteriorly displacing the brainstem. **Right:** Magnetic resonance angiogram indicating the highly vascular capillary lesion.

Apgar scores of 9 and 10 at 1 and 5 minutes, respectively, a head circumference of 36 cm, and a slightly tense anterior fontanel. Neonatal transfontanellar US demonstrated the presence of a giant, homogeneous, hyperechogenic tumor in the posterior fossa that was causing anterior displacement of the brainstem and cerebellum, disjunction of the posterior fossa sutures, and hydrocephalus. A Doppler US evaluation indicated that the lesion was highly vascular and exhibited a low resistance index. Magnetic resonance imaging (MRI) revealed a large, homogeneous, Gd-enhancing lesion in the posterior fossa that was compressing the brainstem and cerebellum and appeared isointense with flow voids on T1-weighted sequences and hypointense on T2-weighted sequences (Fig. 1). Hypersignals were absent on diffusion-weighted sequences, and rich vascularity was revealed by angio-MRI.

Because of anterior brainstem displacement, intracranial pressure was relieved by placing a ventriculoperitoneal shunt in front of the large, hypervascular, life-threatening tumor in the posterior fossa that was causing hydrocephalus instead of performing an endoscopic third ventriculostomy (ETV). A Codman Hakim programmable shunt device (Codman & Shurtleff Inc.) with an aperture pressure of 5 mm Hg was used. At this time, we presumed that the tumor was an intracranial capillary hemangioma given its intense vascularization, and we therefore proceeded with propranolol treatment.

Propranolol Treatment and Clinical Course

We administered 3 mg/kg/day of propranolol every 12 hours for 6 months and monitored the infant's heart rate and arterial blood pressure, intensively at the beginning of treatment and then once a month. Imaging follow-up included US studies in the 2nd month after starting treatment and MRI examinations every 6 months. Follow-up US demonstrated partial reduction of the lesion. The first MRI examination, which was conducted during the 6th month after treatment initiation, indicated a 50% reduction in the lesion. At 1 year posttreatment, total regression of the tumor was observed. Two-year MRI confirmed total

regression of the lesion (Fig. 2). The patient exhibited normal neuromotor development, and no adverse effects of beta-blocker use were observed.

Discussion

On patient admission in the described case, we considered a teratoid/rhabdoid tumor or a medulloblastoma as possible etiologies. However, fetal tumors are rare in the posterior fossa and are generally associated with high mortality rates;¹ moreover, these tumors lack the high vascularity observed in this case. Given the intense vascu-

FIG. 2. Sagittal MR image obtained at the 2-year follow-up, demonstrating total regression of the lesion and release of the brainstem from tumor-related compression.

larization of the tumor, a simple stereotactic biopsy could have led to a catastrophic hemorrhage. Thus, the patient was treated without pathological confirmation. In-depth analyses of the radiological findings, including high vascularity, excluded a teratoid/rhabdoid tumor and a medulloblastoma and suggested the possibility of a capillary hemangioma, which is a highly vascular lesion that is rare in the intracranial compartment but extremely common in the skin.

Capillary hemangiomas—also known as infantile hemangiomas, strawberry birthmarks, or hemangiomas—are benign vascular tumors characterized by an encapsulated mass that is lobular in shape with a poorly defined capillary channel consisting of a single layer of flattened endothelium without intervening brain parenchyma.^{8,9,11,14} These tumors typically affect the skin and the soft tissues of the face, scalp, back, or chest in children,^{2,6,8,14} appearing as a single lesion in 80% of cases.^{9,11} Their reported frequency in neonates ranges from 0.05% to 5%.^{8,11} Although superficial hemangiomas are common, intracranial capillary hemangiomas are rare, and few cases of definite, probable, or possible¹⁶ congenital intracranial capillary hemangiomas have been described in the literature; published cases are listed in Table 1.^{2,3,6–9,21–23}

Intracranial capillary hemangiomas can present as asymptomatic lesions or result in cranial nerve palsy, head circumference enlargement, and elevated intracranial pressure. In addition, these lesions are frequently associated with skin hemangiomas. Only 5 of 22 reviewed cases of intracranial capillary hemangiomas did not involve an associated skin hemangioma. Moreover, intracranial hemangiomas appear to be associated with PHACE syndrome^{7,23} and exhibit a female predominance (with a male/female ratio of 1:2).^{8,11} Capillary hemangiomas are also characterized by a proliferative phase during the 1st months of life that is followed by spontaneous regression in most cases.^{5,18}

Intracranial capillary hemangiomas are characterized by isointensity or hypointensity on T1-weighted MR images, with avid uniform contrast enhancement, and by hyperintensity on T2-weighted MR images. Because capillary hemangiomas present sinusoidal vascularization, the repetition of T1-weighted MRI at a different time with Gd could show a progressive enhancement differing from that observed with other posterior fossa tumors, which do not maintain this enhancement over time. On CT scans, these tumors are characterized by isodensity to hyperdensity, a lobulated morphology, and intense contrast enhancement. Although angiography is rarely performed, such studies of these tumors reveal enlarged arterial feeders and intense contrast staining, with pooling of the contrast medium within tumoral vascular spaces.^{2,13,21,23} Doppler US of intracranial capillary hemangiomas indicates numerous intralesional and perilesional vessels, with a high-peak arterial Doppler shift.²³ The aforementioned imaging findings are not exclusive to intracranial capillary hemangiomas; in fact, these tumors must primarily be differentiated from meningiomas, hemangiopericytomas, and hemangioblastomas.

To date, as indicated in Table 1, no consensus exists regarding the treatment of intracranial capillary hemangiomas.

In particular, the various therapies for these tumors include surgical removal, systemic steroid therapy, thalidomide, intralesional triamcinolone, bevacizumab, temozolomide, interferon, and clinical observation.^{2,3,6–9,21–23,25} The same variations in treatment were observed for capillary hemangiomas in the skin until 2008, when Léauté-Labrèze et al.¹⁰ described 11 patients with complicated infantile hemangiomas who were treated with propranolol and exhibited dramatic lesion regression within a short time period with minimal adverse effects. Subsequently, many authors began to examine propranolol and its role in capillary hemangioma treatment and have suggested this beta-blocker as a first-line treatment for severe infantile capillary hemangiomas.^{12,15,24}

Propranolol is a nonselective beta-adrenergic receptor antagonist that appears to promote vasoconstriction in capillary hemangiomas, reducing blood flow within these lesions and causing skin capillary hemangiomas to change color and soften. This beta-blocker appears to inhibit angiogenesis by decreasing the expression of proangiogenic growth factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), most likely by inactivating the extracellular signal-related kinase/mitogen-activated protein kinase (ERK/MAPK) cascade. Another potential underlying mechanism of propranolol's antiangiogenic effects is its reduction of matrix metalloproteinase-9 (MMP-9) expression, which leads to the inhibition of endothelial cell tubulogenesis.^{18,20} Moreover, propranolol promotes the induction of apoptosis in capillary endothelial cells by blocking apoptosis inhibition by beta-adrenergic agonists (mediated by MAPK and the caspase cascade) and thereby increasing apoptosis rates.^{17,18}

Ghosh and Ghosh⁴ reported the use of propranolol in a 6-week-old female infant with cutaneous and intraspinal-extradural capillary hemangiomas, who exhibited an excellent response. Strahle et al.¹⁹ suggested the theoretical possibility of using propranolol to treat intracranial capillary hemangiomas based on the evident success of propranolol treatment for skin lesions and the occurrence of fewer adverse effects from propranolol treatment relative to steroid, thalidomide, bevacizumab, and temozolomide therapies. The most frequent side effects of propranolol use are low blood pressure, bradycardia, bronchospasm, and hypoglycemia. Although capillary hemangiomas can spontaneously regress, when the tumor mass compresses brain tissue (such as in the brainstem, as detailed in the described case), treatment must be provided to relieve this compression because spontaneous total regression could take a long time. Surgical removal can be life-threatening given the intense vascularization of these tumors as well as a patient's low weight and young age. Given this consideration and the knowledge that propranolol could cause the regression of capillary hemangiomas during the proliferative phase, we began to administer propranolol to a neonate with a giant, life-threatening intracranial capillary hemangioma. Our treatment produced subtotal regression by the 6-month follow-up and total regression by the 1-year follow-up, and the treated patient exhibited normal cognitive and motor development.

TABLE 1. Summary of congenital, likely congenital, and possibly congenital intracranial capillary hemangioma

Authors & Year	Age at Diagnosis (wks), Sex	Clinical Findings	Imaging Findings	Presence of Skin Hemangiomas	Intracranial Localization	Pathology Confirmed	Treatment	FU
Tortori-Donati et al., 1999	4, F	Absent	T1W Gd enhancing	Rt side of face & lips	Rt uncohippocampal region	NA	Wait & see	Involution of both extracranial & intracranial lesion
	6, F	Absent	T1W Gd enhancing	Lt side of face & orbit	Lt CPA, leptomeningeal enhancement at cerebellar surface	NA	Wait & see	Involution of both extracranial & intracranial lesion, leptomeningeal enhancement disappeared
	4, F	Absent	T1W Gd enhancing	Rt side of face & orbit	Lt CPA	NA	Systemic steroid therapy	Lost at FU
Le Bihannic et al., 2005	6, M	Lt hemiparesis	Signs of hemorrhage	Rt upper eyelid & thigh	Rt temporal lobe	Yes	None	Death
Karikari et al., 2006	12, M	Absent	T1W Gd enhancing	Absent	Fourth ventricle & extending through lt CPA cistern	Yes	Surgery	GTR & recovery from neurological deficits
Judd et al., 2007	6, F	Absent	Intense enhancement following administration of Gd	Rt orbit	CPA	No	Intralesional triamcinolone	Significant involution
	8, F	Absent	Intense enhancement following administration of Gd	Lt orbit	Internal carotid artery	No	Intralesional triamcinolone	Significant involution
	3, F	Rt facial paresis	Intense enhancement following administration of Gd	Rt orbit	CPA	No	Systemic steroid therapy	Significant involution
	3, F	Absent	Intense enhancement following administration of Gd	Rt orbit	CPA	No	Systemic steroid therapy	Significant involution
Uyama et al., 2008	16, F	Enlarged head circumference	T1W hypersignal & Gd enhancing & mixed signal on T2W	Skin, pleura, liver, spleen, pancreas, kidneys & vagina	Lt cerebellar hemisphere	Yes	Systemic steroid therapy followed by surgery	GTR
Frei-Jones et al., 2008	At birth, F	Lt CN VII palsy	Mass hyperintense on T2W, contrast-enhancing on T1W & areas of hemorrhage	Absent	Large heterogeneous mass spanning middle cranial fossa, temporal bone, & posterior fossa	Yes	Thalidomide 4 mg/kg	Initial increase in tumor size until 5 mos old, followed by 95% decrease in initial size at 20 mos
Daenekindt et al., 2008	7, M	Enlarged head circumference	Large heterogeneous extraaxial contrast-enhancing mass	Absent	Rt temporal fossa	Yes	Preop embolization & surgery	GTR

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TABLE 1. Summary of congenital, likely congenital, and possibly congenital intracranial capillary hemangioma

Authors & Year	Age at Diagnosis (wks), Sex	Clinical Findings	Imaging Findings	Presence of Skin Hemangiomas	Intracranial Localization	Pathology Confirmed	Treatment	FU
Viswanathan et al., 2009	3, F	Congestive heart failure, head circumference enlargement	Isointense on T1W, hyperintense on T2W, homogeneous avid contrast, flow voids	Lt perimastoid soft tissues	Quadrigeminal plate cistern, pineal region, lt CPA	No	Systemic steroid therapy	Decreased tumor vol
	9, F	Lt periorbital swelling	CT only: dense, heterogeneous contrast enhancement	Lt zygomatic fossa, preorbital/orbital soft tissues & parotid	Lt cavernous sinus, Meckel cave & prepontine cistern	No	Systemic steroid therapy	NA
	16, F	Head circumference enlargement	Isointense on T1W & T2W, flow voids, homogeneous contrast enhancement	Lt parieto-temporal scalp	Fourth ventricle, lt foramen of Luschka	No	Systemic steroid therapy	Decreased tumor vol
	12, F	Lt ptosis	Slightly hyperintense on T1W & T2W, flow voids, homogeneous contrast enhancement	Lt forehead, periorbital soft tissues, & orbit	Fourth ventricle	No	First interferon & then systemic steroid therapy	Decreased tumor vol
	7, F	Rt proptosis	Slightly hyperintense on T1W & T2W, flow voids, homogeneous contrast	Rt parietal soft tissues	Rt temporal fossa & cavernous sinus	No	Systemic steroid therapy	Decreased tumor vol
	7, M	Absent	Isointense on T1W, hyperintense on T2W, avid contrast, flow voids	Rt face & neck, occiput, posterior auricular soft tissues	Fourth ventricle, rt foramen of Luschka	No	Systemic steroid therapy	Decreased tumor vol
	3, M	Absent	Isointense on T1W & T2W, avid contrast, flow voids	Rt preauricular region	Rt CPA & fourth ventricle	No	Corticosteroid w/ minimal response, then interferon	Decreased tumor vol w/ interferon
	12, F	Head circumference enlargement	Isointense on T1W, slightly hyperintense on T2W, homogeneous contrast enhancement, flow voids	Rt facial region	Rt cavernous sinus & CPA	No	Systemic steroid therapy	Decreased tumor vol
Jalloh et al., 2014	At birth, M	Rapidly expanding head circumference, irritability, & seizures	Well-defined enhancing lobulated tumor	None	Lt middle fossa	Yes	Surgery	GTR
Present case	33 wks' gestation, M	Absent	Hyperechogenic lesion in posterior fossa w/o hydrocephalus on US	None	Posterior fossa	No	Propranolol	Total regression of lesion at 1 yr

CN = cranial nerve; CPA = cerebellopontine angle; FU = follow-up; GTR = gross-total resection; T1W = T1-weighted; T2W = T2-weighted.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Cavalheiro, Costa. Acquisition of data: Cavalheiro, Costa. Analysis and interpretation of data: all authors. Drafting the article: Cavalheiro, Costa. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Cavalheiro. Administrative/technical/material support: Cavalheiro.

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