Overgrowth Syndromes With Vascular Anomalies

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Overgrowth syndromes with vascular anomalies encompass entities with a vascular anomaly as the predominant feature vs those syndromes with predominant somatic overgrowth and a vascular anomaly as a more minor component. The focus of this article is to categorize these syndromes phenotypically, including updated clinical criteria, radiologic features, evaluation, management issues, pathophysiology, and genetic information. A literature review was conducted in PubMed using key words "overgrowth syndromes and vascular anomalies" as well as specific literature reviews for each entity and supportive genetic information (e.g., somatic mosaicism). Additional searches in OMIM and Gene Reviews were conducted for each syndrome. Disease entities were categorized by predominant clinical features, known genetic information, and putative affected signaling pathway. Overgrowth syndromes with vascular anomalies are a heterogeneous group of disorders, often with variable clinical expression, due to germline or somatic mutations. Overgrowth can be focal (e.g., macrocephaly) or generalized, often asymmetrically (and/or mosaically) distributed. All germ layers may be affected, and the abnormalities may be progressive. Patients with overgrowth syndromes may be at an increased risk for malignancies. Practitioners should be attentive to patients having syndromes with overgrowth and vascular defects. These patients require proactive evaluation, referral to appropriate specialists, and in some cases, early monitoring for potential malignancies. Progress in identifying vascular anomaly-related overgrowth syndromes and their genetic etiology has been robust in the past decade and is contributing to genetically based prenatal diagnosis and new therapies targeting the putative causative genetic mutations.

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Introduction

What is a syndrome and why does it matter? A syndrome is a defined constellation of clinical findings that helps direct the practitioner in a proactive approach, toward an appropriate evaluation and management plan, and referral to appropriate specialists. Associating the patterns in a syndrome guides clinical expectations and may lead to identification of a genetic mutation that may elucidate causative signaling mechanisms, enable prenatal testing and screening of family members (if genomic), and potentially enable targeted medical therapy. Indeed this has been the case for many syndromes. This article will review those syndromes associated with overgrowth and vascular anomalies. Overgrowth, or excessive proliferation of an organ or tissue, can be focal or diffuse, symmetrical or asymmetrical, and affect one or more germ layers. Overgrowth can be apparent at birth or postnatally, may be static, may continue in parallel with the overall growth of a patient, or may be progressive.

Background Information

"Vascular Anomalies" encompass a heterogeneous group of vascular lesions, with focal aberrations of vascular development or vascular proliferation. The updated (2014) classification for vascular anomalies International Society for the Study of Vascular Anomalies (ISSVA) provides a comprehensive framework (Table 1; www.issva.org). Vascular anomalies are divided into proliferative lesions (hemangiomas, tufted angiomas, kaposiform hemangioendothelioma, pyogenic granuloma, and malignant vascular tumors, not fully discussed in this review) and static lesions (vascular malformations—capillary, venous, arteriovenous, lymphatic, or in combination), which can become more pronounced in the setting of trauma, hormonal stimulation, and/or infection. Hemangiomas are further divided into three subtypes: (1) rapidly involuting congenital hemangiomas (RICH), which grow in utero and gradually involute postnatally. (2) "Infantile Hemangiomas," the most common, which are minimally evident at birth, rapidly grow over the

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TABLE 1. ISSVA classification of vascular anomalies, 2014 (copyright licensed under Creative Commons)

Vascular anomalies				
Vascular tumors	**Vascular malformations**			
	Simple	**Combined**	**Of major named vessels**	**Associated with other anomalies**
Benign	Capillary malformations	Capillary–venous, capillary–lymphatic, lymphatic venous, capillary–lymphatic–venous, capillary–arteriovenous, and capillary–lymphatic–arteriovenous	(Aka "channel-type" or "truncal" vascular malformations)	For example, Klippel–Trenaunay
Locally aggressive or borderline	Lymphatic malformations			Sturge–Weber
Malignant	Venous malformations		Further characterized by involvement of artery, lymphatic, or vein and by anomaly of origin, course, number, length, diameter, etc.	Maffucci
	Arteriovenous malformations			CLOVES
	Arteriovenous fistula			Proteus
				Bannayan–Riley–Ruvalcaba
				Others

See www.issva.org for interactive comprehensive classification.

ensuing several months and gradually involute (not always completely). (3) Non-involuting congenital hemangiomas (NICH), which grow in utero, however, neither grow nor involute postnatally. Only infantile hemangiomas are characterized by GLUT-1 staining during all phases, a diagnostic tool.[1] Vascular malformations are present at birth (but not always evident) and grow in parallel with the growth of the patient. Early detection, proper evaluation, and appropriate diagnosis are crucial.

Hemangioma syndromes include PHACES (posterior fossa anomalies, segmental hemangioma, arteriopathies, cardiac anomalies, eye anomalies, and sternal or other midline anomalies),[2] SACRAL syndrome (spinal dysraphism, anogenital, cutaneous, renal and urologic anomalies, lumbosacral hemangioma),[3] and LUMBAR syndrome (lower body hemangioma, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies).[4] Vascular anomaly syndromes include CLOVES (congenital lipomatous overgrowth, vascular malformation, epidermal nevus, scoliosis),[5] Klippel–Trenaunay syndrome (capillary–lymphatic–venous malformation with limb hypertrophy), blue rubber bleb nevus syndrome (generalized small venous malformations), Proteus syndrome,[6,7] Ollier disease/Maffucci syndrome (hemangioendothelioma and enchondromatosis), Sturge–Weber syndrome (facial capillary malformation with pial angiomatosis and glaucoma), Parkes Weber Syndrome (similar to Klippel–Trenaunay with arteriovenous shunting), Hereditary Hemorrhagic Telangiectasia (multifocal arteriovenous malformations), Gorham's syndrome (lymphangiomatosis with osteolysis),[8] and several lymphatic anomaly/lymphedema syndromes. PTEN-related vascular anomaly syndromes include Cowden syndrome and Bannayan–Riley–Ruvalcaba syndromes.[9] Genetic mutations have been identified for a number of vascular malformation syndromes, lending insight into their etiology.

Unfortunately, it is not well appreciated that not every vascular anomaly is a hemangioma, and strewn through the medical literature, the term "hemangioma" is loosely stated. A thorough history focusing on the age of presentation, clinical behavior and growth cycle of the lesion, physical examination, and appreciation of patterns of distribution help define the diagnosis of a true hemangioma (as described above).

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Questions aiding the diagnosis of a vascular anomaly include the following: What is the age of the patient? How large is the lesion? Is it focal or segmental? Is it single or are there multiple lesions? Are there any associated or impending symptoms [i.e., airway compromise, ptosis (eyelid lag), ulceration, infection, bleeding, high-flow state, functional limitation, headaches, and tinnitus]? Is it progressing or improving? Does it become larger with straining or in a dependent position? Is there a bruit or thrill?

Questions aiding the diagnosis of a vascular anomaly syndrome include the following: Are there skeletal/digital abnormalities (extra, sandal-gap, or webbed fingers or toes)? Is the head disproportionately large or small? Are any other organs abnormally developed (e.g., brain, heart, kidneys, and eyes)? Are there any