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ORIGINAL
RESEARCH

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BACKGROUND AND PURPOSE: KTS is a rare limb overgrowth disorder with slow-flow vascular anomalies. This study examines the presumed association between KTS and spinal AVMs.

MATERIALS AND METHODS: We performed a MEDLINE search of articles and reviewed textbooks of spinal diseases to study the association between KTS and spinal AVM. Our goal was to ascertain the basis on which the diagnosis of KTS was established and to evaluate the evidence of its association with spinal AVMs. In addition, the data base of the Vascular Anomalies Center at Children's Hospital Boston was queried for patients with KTS, and the association with spinal AVM was investigated.

RESULTS: Twenty-four published reports on spinal AVMs in 31 patients with KTS were reviewed. None of these references provided solid evidence of the diagnosis of KTS in any patient. Clinical data were either incompatible with the diagnosis of KTS or were inadequate to establish the diagnosis. Alternative possible diagnoses (CLOVES syndrome and CM-AVM) were suggested by the first author for 9 of the patients reported in these articles. The medical records of 208 patients with the diagnosis of KTS were analyzed; not a single patient had clinical or radiologic evidence of a spinal AVM.

CONCLUSIONS: An association between KTS and spinal AVM, as posited in numerous references, is most likely erroneous. The association has neither been reliably proved in the limited published literature nor encountered in a large cohort.

ABBREVIATIONS: AVM = arteriovenous malformation; CLOVES = congenital lipomatous overgrowth, vascular malformations, epidermal nevus, and skeletal/scoliosis and spinal anomalies; CLVM = capillary-lymphaticovenous malformation; CM = capillary malformation; CM-AVM = capillary malformation-arteriovenous malformation; F = female; HHT = hereditary hemorrhagic telangiectasia; KTS = Klippel-Trenaunay syndrome; LM = lymphatic malformation; M = male; NA = not available/not applicable; VEGF = vascular endothelial growth factor; VM = venous malformation; Y = year

KTS is the most well-known overgrowth disorder associated with vascular anomalies. KTS is defined as combined slow-flow malformations (capillary, lymphatic, and venous) in an overgrown limb. During the past century, KTS has achieved prototypic status among overgrowth syndromes, with >1000 published articles and extensive documentation in the medical textbooks. Nevertheless, as with many other rare disorders and in the absence of clear diagnostic criteria, misdiagnoses and misconceptions abound.

Many published reports claimed that KTS is associated with spinal AVMs. This uncontested notion has also been

widely accepted in many specialized medical textbooks. In this communication, we set out to clarify the purported association between KTS and spinal AVM.

Materials and Methods

We conducted a literature search by using MEDLINE to identify reports of a relationship between KTS and spinal AVM. The search was done from the inception of MEDLINE through February 2010, by using combinations of the following key terms: "Klippel," "Trenaunay," "Weber," "spinal, arteriovenous," "vasculosus osteohypertrophicus," "naevus varicosus osteohypertrophicus," "hemangiectatic hypertrophy," and "congenital phlebarteriectasias." Available reports in English, French, German, Slovak, Portuguese, and Japanese were reviewed. These reports were scrutinized with particular reference to the methods used to diagnose KTS.

Available medical reference textbooks were also searched and analyzed by using the key terms noted above.

The review documented the number, age, and sex of patients; type and location of the spinal vascular anomalies; and evidence of KTS (On-line Table). Diagnostic inaccuracies were noted. Alternative diagnoses were suggested by the first author (A.I.A.).

Additionally, the data base of Vascular Anomalies Center at Children's Hospital Boston was reviewed for clinical or radiological evidence of spinal AVM in patients with KTS.

The diagnosis of KTS and the distinction from other overgrowth

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syndromes were based on the major clinical features of KTS, namely the presence of CLVM, which is associated with overgrowth of an extremity.¹⁻³

Results

The results are divided into 3 sections: published case reports, medical textbooks, and the KTS cohort from the Vascular Anomalies Center.

Published Case Reports

There were 24 published reports⁴⁻²⁷ of the association between KTS and spinal AVM available for our review, with a total of 31 patients (sex: 17 male, 9 female, 5 undocumented; age range, 9–67 years [On-line Table]). On the basis of clinical history, imaging studies, and photographs in these articles, the diagnosis of KTS was either incorrect (22 articles, 27 patients) or unsupported by the given data (2 articles, 4 patients). One article reported the association between KTS and spinal “cavernous malformation” in 1 patient.¹⁸

The locations of the spinal lesions were thoracic ($n = 9$), thoracolumbar ($n = 9$), cervicothoracic ($n = 4$), cervical ($n = 1$), lumbar ($n = 1$), lumbosacral ($n = 1$), and unspecified ($n = 6$). The types of the reported vascular lesions were spinal cord AVM ($n = 10$), “hemangioma/angioma/vascular tumor” ($n = 6$), spinal cord fistula ($n = 3$), paraspinal AVM ($n = 1$), thrombosis of the anterior spinal artery ($n = 1$), dural fistula ($n = 1$), posterior extramedullary AVM ($n = 1$), spinal cord cavernous malformation ($n = 1$), or not specified ($n = 7$).

Alternative diagnoses suggested in 8 patients included CM-AVM ($n = 5$) and CLOVES syndrome ($n = 4$). None of the articles reviewed clearly described the combined extremity CLVM anomalies that characterize KTS. The focus of most reports was on the spinal vascular malformation and its clinical sequelae.

The commonly cited reasons for inappropriately diagnosing these patients with KTS included the following: variable forms of limb and truncal overgrowth, multiple vascular malformations, cutaneous vascular birthmarks, lymphedema, and varicosity. The features reported in these patients that are not compatible with the diagnostic criteria of KTS (as discussed above) included arterial lesions (suggested by the high-flow lesions angiographically or clinically), atypical distribution of the vascular anomalies (eg, foot, trunk, face, and quadrilateral involvement), unusual associated findings (eg, deafness, pulmonary nodules, and lymphedema), and the lack of major components of KTS (particularly the lymphatic malformations).

Textbooks

The association between KTS and spinal AVM was mentioned in 36 medical textbooks available for our review (On-line Appendix). All these references essentially cited the published case reports found in MEDLINE. With 1 exception (see below), no new cases were systematically presented in any of these books.

KTS Cohort from the Vascular Anomalies Center

A total of 208 patients with the diagnosis of KTS were found in the data base of the Vascular Anomalies Center at Children’s

Hospital Boston. None of these patients had clinical or radiologic evidence of spinal AVM. Although dedicated spinal imaging studies were not routinely obtained on these patients, asymptomatic spinal AVMs are extremely uncommon ($\sim 1\%$).²⁸

Discussion

Diagnostic inaccuracy is common in overgrowth disorders,²⁹ particularly when vascular anomalies are also present. Due to the rarity, complexity, and some overlap among these conditions, establishing a diagnosis can be challenging.

KTS (Online Mendelian Inheritance in Man, 149000; <http://www.ncbi.nlm.nih.gov/omim>) is a relatively uncommon sporadic disorder that primarily consists of the following: 1) a slow-flow vascular malformation: CMs (port-wine stain), venous malformations (marginal/lateral and embryonic venous veins), and lymphatic malformation (both microcystic and macrocystic types); and 2) hypertrophy of fatty and osseous components of a limb.³⁰ KTS typically occurs in the lower extremity and may occasionally be bilateral or affect the upper extremity.³¹ Unlike the Parkes Weber syndrome, arteriovenous communications are not a feature of KTS.^{32,33} Unfortunately, KTS has often been used as a generic diagnosis referring to a heterogeneous group of vascular anomalies with overgrowth.

Historical Background

Original Description of KTS. KTS was described more than 100 years ago by 2 French physicians: Maurice Klippel (1858–1942) and Paul Trenaunay (1875–?), though some initial observations were published by the French zoologist Isidore Geoffroy Saint-Hilaire (1805–1861).³⁴

Klippel and Trenaunay reported a patient with a combination of clinical features including an extensive “nevus,” congenital varices (phlebectasia), and hypertrophy of the soft tissues and bone of the lower extremity.³⁵ The bony structures were overgrown in length and width. The soft-tissue component was predominantly composed of thickened subcutaneous fat and vascular tissue. Cutaneous manifestations ranged from smooth birthmark to “wrinkled” desquamated plaques with ulcers. The authors collectively named this disorder “Du naevus variqueux ostéohypertrophique.” In the present day refined terminology, the “nevus” refers to cutaneous CM (port-wine stain), and the other cutaneous manifestations are lymphatic malformations (vesicles).

Hence, the combination of slow-flow vascular malformations, CLVM, in an overgrown limb constitutes the backbone of what is now known as KTS.

Frederick Parkes Weber later described a condition of an overgrown limb with CM, but in contradistinction to KTS, extensive arteriovenous fistulas of the affected leg with significant clinical hemodynamic sequelae made up the hallmark of Parkes Weber syndrome.³⁶⁻³⁸ While both KTS and Parkes Weber syndrome occur sporadically and both have vascular anomalies and overgrowth affecting predominantly the lower extremities, these 2 entities should be considered separate disorders because their clinical manifestations and types of complications are quite different.³

Reported Association of KTS and Spinal AVM. The misconception that KTS is associated with spinal AVM has been

uncontested in the literature for decades, with the case report by Den Hartog Jager in 1949 being one of the earliest published references.²¹ However, the notion of such a relationship between KTS and spinal AVM can primarily be attributed to 2 prominent French neuroradiologists: René Djindjian (1918–1977) at the Hôpital Lariboisière and Pierre Lasjaunias (1948–2008) at the Hôpital Bicêtre.

Prototype Article. In 1977, an association between KTS and spinal AVM was described by the pioneering group of French neurointerventionalists led by Djindjian.¹² All 5 patients reported were children (4–19 years of age) with intramedullary spinal AVM, presenting with subarachnoid hemorrhage. The diagnosis of KTS was established on the basis of the presence of varices and cutaneous “angioma.” However, cutaneous birthmarks were lacking in 2 patients, and the authors did not mention a lymphatic component in any of these patients. Although all patients had vascular anomalies, there is no evidence that any met the basic clinical description for KTS (Table). In the “Discussion” of this article, the authors quoted (and contradicted) the prior work of André,³⁹ whose thesis on vascular anomalies stated that KTS lacks a neural element. Djindjian et al¹² advocated the theory of “focal teratogenesis” for these complex cases. The latter refers to an early embryonic insult with a metamerically expressed vascular anomaly. However, this theory seems less germane, given recent advances in the genetic studies of the vascular anomalies and overgrowth syndromes associated with complex vascular anomalies, allowing us to differentiate seemingly similar vascular lesions and to reveal their genetic etiology (see below).

Prototype Textbook

Although the association between KTS and spinal AVM has never, to our knowledge, been definitively demonstrated in the literature, this erroneous linkage has been extensively cited by many textbooks.

Surgical Neuroangiography is a well-known 4-volume textbook by Lasjaunias et al. The series is one of the most comprehensive often-cited clinical neurovascular references. In it, many aspects of KTS, including theories about the embryonic and metamerically expressed origin of the syndrome, are discussed. The authors of *Surgical Neuroangiography* consider KTS, a slow-flow venolymphatic disorder, one of the cerebrofacial venous metamerically expressed syndromes with associated spinal cord AVMs and arterial aneurysms. They also describe KTS as a “bone disease with the vascular expression of a bone-related growth factor.”⁴⁰ However, the authors contradict their own nosologic category and also list KTS as one of the spinal arteriovenous metamerically expressed syndromes, with an incidence of spinal AVMs of 5%.⁴⁰

Two cases presumed to have KTS and spinal AVM are discussed in *Surgical Neuroangiography*. The first is that of a 12-year-old boy with a spinal cord AVM noted on spinal MR imaging and angiography.⁴⁰ The clinical and radiologic data provided showed no evidence of KTS. The other case is presented elsewhere in the book, with angiographic images of the spinal cord and foot.⁴¹ The foot angiogram demonstrated multiple arteriovenous fistulas with marked tortuosity and dilation of the tibial arterial feeders, but no capillary, lymphatic, or venous anomalies and no hypertrophy.

Classification of Spinal AVMs

The classification of spinal AVMs proposed by Rodesch et al,¹³ which relies primarily on the experience at Hôpital Bicêtre, was founded on the proposed embryonic basis of the vascular insult. The authors divided spinal cord AVMs into 3 categories: genetic hereditary, genetic nonhereditary, and single lesions. Of the 155 patients reviewed, 5 were included in the genetic nonhereditary subcategory, of whom 3 were thought to have had KTS, and 2, Parkes Weber syndrome. However, no clinical or imaging data were provided to substantiate these diagnoses.

Etiologic Aspects of KTS

Klippel and Trenaunay originally suggested a congenital spinal cord anomaly as the etiologic basis for what they thought was a metamerically distributed birthmark.³² Happle⁴² proposed the more intriguing theory of paradominant inheritance, in which individuals heterozygous for the mutation would have no symptoms and the mutation could be transmitted unperceived through many generations. The phenotype would only manifest when an additional postzygotic mutation occurs, giving rise to loss of the corresponding wild-type allele, resulting in a cellular clone, either homozygous or hemizygous for the mutation.

The complex signaling pathways implicated in the process of blood vessel formation and maturation are regulated by numerous protein factors including but not limited to the VEGFs, such as VEGF-A, VEGF-B, VEGF-C, and VEGF-D, and their receptors VEGFR-1, VEGFR-2, and VEGFR-3; receptor tyrosine kinases (eg, Tie1 and Tie2, and Tie2 ligands Ang1 and Ang2); integrins and their ligands (bFGF, FGF-2); platelet-derived growth factor; transforming growth factor- β ; thrombospondin-1; metalloproteinase inhibitors; angiostatin; and endostatin.⁴³ The identification of several mutations causing vascular malformations has helped to better delineate the spectrum of presentation of each subtype and to newly recognize clinical entities.⁴⁴ While several mutations have been recently identified to cause vascular anomalies (such as the *RASA1* mutation for CM and *Glomulin* and *TIE2* mutations for venous malformation, and so forth), there is no clear evidence so far that KTS is linked to any genetic aberration. Tian et al⁴⁵ proposed that genetic defects in the *VG5Q* protein, a potent angiogenesis-promoting protein, cause susceptibility to KTS. However, only 5 of 130 patients with KTS studied had this variant. Barker et al⁴⁶ subsequently identified 9 carriers of the same genetic alteration among 275 healthy individuals, throwing major doubts about the validity of this theory.

Differential Diagnosis of KTS

Some features of KTS can overlap other overgrowth disorders such as Parkes Weber syndrome, Proteus syndrome, CM-AVM, CLOVES syndrome, Cobb syndrome, and Bannayan-Riley-Ruvalcaba syndrome.

Parkes Weber syndrome is an extensive faint capillary stain on an overgrown limb, with diffuse slowly progressive multiple arteriovenous microfistulas, ulceration, and cardiac failure.⁴⁷ In contrast to KTS, the vascular malformations in Parkes Weber syndrome are fast-flow and involve arterial malformations; lymphatic involvement is rare.⁴³ Spinal AVM has not been reported to be a feature of Parkes Weber syndrome.

Parkes Weber syndrome is thus not a type of KTS with AVM because these 2 conditions are clinically and radiologically distinct. The triple eponym Klippel-Trenaunay-Weber syndrome should thus be abandoned. On a review of large cohort of 786 patients with KTS, Servelle³¹ distinguished between the pattern of venous ectasia noted in Parkes Weber syndrome, which is due to arteriovenous shunts, and the inherent venous anomalies of KTS. Recently, some patients with a clinical pattern of Parkes Weber syndrome have been found to have a mutation in the *RASA1* gene (CM-AVM).⁴⁸

Cobb syndrome consists of a cutaneous capillary stain and a spinal AVM in the same metamere.⁴⁹ It can be distinguished from KTS in a straightforward manner through the lack of classic combined slow-flow malformations in a limb.

CLOVES syndrome is a recently delineated overgrowth disorder that includes congenital lipomatous overgrowth, vascular malformations, epidermal nevi and skeletal/spinal anomalies, scoliosis, and seizures.^{50,51} In this disorder, spinal and paraspinal AVMs are common and are responsible for significant morbidity.⁵¹ The presence of a large truncal mass, skeletal anomalies, and high-flow vascular anomalies provides a clinical distinction from KTS.

CM-AVM is an autosomal dominant disorder caused by a mutation in the *RASA1* gene and characterized by the presence of multiple CMs without overgrowth.⁴⁸ AVM occurs in approximately 12% of the patients and may involve the CNS.

Bannayan-Riley-Ruvalcaba syndrome is a *PTEN*-hamartoma disorder characterized by macrocephaly, lipomatosis, pigmented penile macules, vascular malformations, mental/developmental delay, Hashimoto thyroiditis, and assorted tumors.⁵² A spectrum of vascular anomalies, including paraspinal AVM, has been documented in more than half of these patients.⁵³

Proteus syndrome is a rare mosaic progressive sporadic disorder with a spectrum of clinical features, including connective tissue nevus, epidermal nevus, disproportionate progressive overgrowth, and tumors, among others.⁵⁴ While slow-flow vascular malformations are reported to be common in Proteus syndrome, AVMs are uncommon, with only 1 unambiguously affected patient having been described as having intracranial AVMs⁵⁵; none had spinal AVMs.

HHT is an autosomal dominant disease. Its major features are recurrent epistaxis, cutaneous and mucosal telangiectasias, and visceral AVMs. In a retrospective study of 13 patients with spinal AVMs presenting at younger than 2 years of age, HHT was seen in 6 patients.⁵⁶ In contrast to KTS, HHT is not associated with fatty overgrowth or with lymphatic, capillary, or venous malformations within an extremity.

We may thus conclude that the unsubstantiated association between KTS and spinal arteriovenous metameric syndrome has stemmed from a small number of case reports and has unfortunately been sustained among physicians in the clinical neurosciences, as well as through documentation in major textbooks. Of all the articles reviewed, we have shown that none documented an unambiguous case of KTS. Of course, the utility of published cases on rare disorders is wholly dependent on accurate diagnosis.²⁹

Diagnostic inaccuracies, particularly in complex conditions having manifestations in numerous organ systems, may result from lack of knowledge or experience in dealing with

rare disorders, confusion in terminology, and overlapping phenotypic features.²⁹ We advocate a collaborative multidisciplinary approach to the management of patients with overgrowth disorders and complex vascular anomalies.

Conclusions

On the basis of this retrospective review of the literature and of a large cohort of patients, we argue that the association between KTS and spinal AVM has no solid foundation. Unfortunately, this misconception has evolved into a difficult-to-refute tenet. Regardless, until proved otherwise, spinal AVM is not a feature of KTS and an alternative appropriate diagnosis of patients should be sought.

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References

- Garzon MC, Huang JT, Enjolras O, et al. **Vascular malformations. Part II. Associated syndromes.** *J Am Acad Dermatol* 2007;56:541–64
- Mulliken JB, Fishman SJ, Burrows PE. **Vascular anomalies.** *Curr Probl Surg* 2000;37:517–84
- Cohen MM Jr. **Klippel-Trenaunay syndrome.** *Am J Med Genet* 2000;93:171–75
- Rohany M, Shaibani A, Arafat O, et al. **Spinal arteriovenous malformations associated with Klippel-Trenaunay-Weber syndrome: a literature search and report of two cases.** *AJNR Am J Neuroradiol* 2007;28:584–89
- Alexander MJ, Grossi PM, Spetzler RF, et al. **Extradural thoracic arteriovenous malformation in a patient with Klippel-Trenaunay-Weber syndrome: case report.** *Neurosurgery* 2002;51:1275–78, discussion 1278–79
- Brunaud V, Delerue O, Muller JP, et al. **Klippel-Trenaunay syndrome and ischemic neurologic complications** [in French]. *Rev Neurol (Paris)* 1994;150:50–54
- Nakstad PH, Hald JK, Bakke SJ. **Multiple spinal arteriovenous fistulas in Klippel-Trenaunay-Weber syndrome treated with platinum fibre coils.** *Neuroradiology* 1993;35:163–65
- Kojima Y, Kuwana N, Sato M, et al. **Klippel-Trenaunay-Weber syndrome with spinal arteriovenous malformation: case report.** *Neurol Med Chir (Tokyo)* 1989;29:235–40
- Szajner M, Weill A, Piotin M, et al. **Endovascular treatment of a cervical paraspinal arteriovenous malformation via arterial and venous approaches.** *AJNR Am J Neuroradiol* 1999;20:1097–99
- Arai Y, Takagi T, Matsuda T, et al. **Myelopathy due to scoliosis with vertebral hypertrophy in Klippel-Trenaunay-Weber syndrome.** *Arch Orthop Trauma Surg* 2002;122:120–22
- Benhaïem-Sigaux N, Zerah M, Gherardi R, et al. **A retromedullary arteriovenous fistula associated with the Klippel-Trenaunay-Weber syndrome: a clinicopathologic study.** *Acta Neuropathol* 1985;66:318–24
- Djindjian M, Djindjian R, Hurth M, et al. **Spinal cord arteriovenous malformations and the Klippel-Trenaunay-Weber syndrome.** *Surg Neurol* 1977;8:229–37
- Rodesch G, Hurth M, Alvarez H, et al. **Classification of spinal cord arteriovenous shunts: proposal for a reappraisal—the Bicêtre experience with 155 consecutive patients treated between 1981 and 1999.** *Neurosurgery* 2002;51:374–79, discussion 379–80
- Schulz H, Neumann J. **Angiodysgenetic necrotizing myelopathy (Foix-Alajouanine) and hypertrophic hemangiectasis (Klippel-Trenaunay-Weber) as a combined malformation disease** [in German]. *Psychiatr Neurol Med Psychol (Leipz)* 1966;18:217–23
- Forster C, Kazner E. **Spinal angioma with paraplegia in a case of Klippel-Trenaunay-Syndrome** [in German]. *Neuropadiatrie* 1973;4:180–86
- Gourie-Devi M, Prakash B. **Vertebral and epidural hemangioma with paraplegia in Klippel-Trenaunay-Weber syndrome: case report.** *J Neurosurg* 1978;48:814–17
- Carter DA, Kim K, Brinker RA. **Extradural tumor causing spinal cord compression in Klippel-Trenaunay-Weber syndrome.** *Surg Neurol* 1995;43:257–60

18. Pichierri A, Piccirilli M, Passacantilli E, et al. **Klippel-Trenaunay-Weber syndrome and intramedullary cervical cavernoma: a very rare association—case report.** *Surg Neurol* 2006;66:203–06, discussion 206
19. Tan EC, Takagi T, Nagai H. **Spinal arteriovenous malformations in Klippel-Trenaunay-Weber syndrome: case report** [in Japanese]. *No Shinkei Geka* 1990;18:877–81
20. Rosenblum B, Oldfield EH, Doppman JL, et al. **Spinal arteriovenous malformations: a comparison of dural arteriovenous fistulas and intradural AVM's in 81 patients.** *J Neurosurg* 1987;67:795–802
21. Den Hartog Jager WA. **About two new forms in the group of the phacomatoses.** *Folia Psychiatr Neurol Neurochir Neerl* 1949;52:356–64, 4 pl
22. Eber AM, Streicher D, Dupuis M, et al. **Klippel-Trenaunay-Weber syndrome and medullary angioma** [in French]. *Rev Otonéuroophthalmol* 1976;48:239–41
23. Pitagoras de Mattos J. **Klippel-Trenaunay-Parkes-Weber syndrome with spinal cord angioma in** [in Portuguese]. *Arq Neuropsiquiatr* 1975;33:278–85
24. Vajda P, Brozmanova M. **Klippel-Trenaunay syndrome with a developmental defect and hemangioma of the spinal cord** [in Czech]. *Cesk Neurol Neurochir* 1983;46:114–19
25. Jyoichi T, Hasegawa T, Yoshida M, et al. **A case of Klippel-Trenaunay-Weber syndrome associated with a short affected leg, spinal AVM and disseminated intravascular coagulation** [in Japanese]. *Nippon Naika Gakkai Zasshi* 1989;78:678–79
26. Fukutake T, Kawamura M, Moroo I, et al. **Cobb syndrome and Klippel-Trenaunay-Weber syndrome** [in Japanese]. *Rinsho Shinkeigaku* 1991;31:275–79
27. Sharma S. **Multifocal intradural spinal AVF and renal artery aneurysms in a case of Klippel Trenaunay Syndrome (KTS).** *J Neuroimaging* 2009 Aug 7. [Epub ahead of print]
28. Lasjaunias P, Berenstein A, Ter Brugge KG. *Spinal Arteriovenous Malformations in Surgical Neuroangiography: Clinical and Endovascular Treatment Aspects in Adult.* Berlin: Springer-Verlag; 2004
29. Turner JT, Cohen MM Jr, Biesecker LG. **Reassessment of the Proteus syndrome literature: application of diagnostic criteria to published cases.** *Am J Med Genet A* 2004;130A:111–22
30. Mulliken J, Young AE. *Vascular Birthmarks, Hemangiomas and Malformations.* Philadelphia: W.B. Saunders; 1988
31. Servelle M. **Klippel and Trenaunay's syndrome: 768 operated cases.** *Ann Surg* 1985;201:365–73
32. Baskerville PA, Ackroyd JS, Browse NL. **The etiology of the Klippel-Trenaunay syndrome.** *Ann Surg* 1985;202:624–27
33. Lindenauer SM. **The Klippel-Trenaunay syndrome: varicosity, hypertrophy and hemangioma with no arteriovenous fistula.** *Ann Surg* 1965;162:303–14
34. Ruggieri M, Castroviejo IP, Rocco C. *Neurocutaneous Disorders: Phakomatoses and Hamartoneoplastic Syndromes.* New York: Springer-Verlag; 2008
35. Klippel M, Trenaunay P. **Du naevus variqueux osteohypertrophique.** *Arch Gen Med* 1900;185:641–72
36. Parkes WF. **Angioma formation in connection with hypertrophy of limbs and hemi-hypertrophy.** *Br J Dermatol* 1907;19:231
37. Parkes WF. **Haemangiectatic hypertrophies of the foot and lower extremity.** *Med Press* 1908;136:261
38. Parkes WF. **Haemangiectatic hypertrophy of limbs: congenital phlebarteriectasis and so-called congenital varicose veins.** *Br J Child Dis* 1918;15:13–17
39. Andre JM. **Les angiodysplasies. systématisées.** *L'Expansion Scientifique.* Paris 1973
40. Lasjaunias P, Ter Brugge KG, Berenstein A. *Surgical Neuroangiography: Clinical and Interventional Aspects in Children.* Vol. 3. New York: Springer-Verlag; 2006
41. Berenstein A, Lasjaunias P, Ter Brugge K. *Surgical Neuroangiography: Clinical and Endovascular Treatment Aspects in Adults,* Berlin: Springer-Verlag; 2004:771
42. Danarti R, Konig A, Salhi A, et al. **Becker's nevus syndrome revisited.** *J Am Acad Dermatol* 2004;51:965–69
43. Timur AA, Driscoll DJ, Wang Q. **Biomedicine and diseases: the Klippel-Trenaunay syndrome, vascular anomalies and vascular morphogenesis.** *Cell Mol Life Sci* 2005;62:1434–47
44. Brouillard P, Vikkula M. **Genetic causes of vascular malformations.** *Hum Mol Gene* 2007;16(spec no. 2):R140–09. Epub 2007 Jul 31
45. Tian XL, Kadaba R, You SA, et al. **Identification of an angiogenic factor that when mutated causes susceptibility to Klippel-Trenaunay syndrome.** *Nature* 2004;427:640–45
46. Barker KT, Foulkes WD, Schwartz CE, et al. **Is the E133K allele of VG5Q associated with Klippel-Trenaunay and other overgrowth syndromes?** *J Med Genet* 2006;43:613–14. Epub 2006 Jan 27
47. Mulliken JB, Marler JJ, Burrows PE, et al. **Reticular infantile hemangioma of the limb can be associated with ventral-caudal anomalies, refractory ulceration, and cardiac overload.** *Pediatr Dermatol* 2007;24:356–62
48. Eerola I, Boon LM, Mulliken JB, et al. **Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations.** *Am J Hum Genet* 2003;73:1240–49
49. Maramattom BV, Cohen-Gadol AA, Wijdicks EF, et al. **Segmental cutaneous hemangioma and spinal arteriovenous malformation (Cobb syndrome): case report and historical perspective.** *J Neurosurg Spine* 2005;3:249–52
50. Sapp JC, Turner JT, van de Kamp JM, et al. **Newly delineated syndrome of congenital lipomatous overgrowth, vascular malformations, and epidermal-nevi (CLOVE syndrome) in seven patients.** *Am J Med Genet A* 2007;143A:2944–58
51. Alomari AI. **Characterization of a distinct syndrome that associates complex truncal overgrowth, vascular, and acral anomalies: a descriptive study of 18 cases of CLOVES syndrome.** *Clin Dysmorphol* 2009;18:1–7
52. Marsh DJ, Kum JB, Lunetta KL, et al. **PTEN mutation spectrum and genotype-phenotype correlations in Bannayan-Riley-Ruvalcaba syndrome suggest a single entity with Cowden syndrome.** *Hum Mol Genet* 1999;8:1461–72
53. Tan WH, Baris HN, Burrows PE, et al. **The spectrum of vascular anomalies in patients with PTEN mutations: implications for diagnosis and management.** *J Med Genet* 2007;44:594–602
54. Cohen MM Jr. **Proteus syndrome: an update.** *Am J Med Genet C Semin Med Genet* 2005;137C:38–52
55. Biesecker L. **The challenges of Proteus syndrome: diagnosis and management.** *Eur J Hum Genet* 2006;14:1151–57
56. Cullen S, Alvarez H, Rodesch G, et al. **Spinal arteriovenous shunts presenting before 2 years of age: analysis of 13 cases.** *Childs Nerv Syst* 2006;22:1103–10