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A.I. Alomari, D.B. Orbach, J.B. Mulliken, A. Bisdorff, S.J. Fishman, A. Norbash, R. Alokaili, D.J. Lord and P.E. Burrows

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ORIGINAL RESEARCH

A.I. Alomari
D.B. Orbach
J.B. Mulliken
A. Bisdorff
S.J. Fishman
A. Norbash
R. Alokaili
D.J. Lord
P.E. Burrows

FELLOWS' JOURNAL CLUB

Klippel-Trenaunay Syndrome and Spinal Arteriovenous Malformations: An Erroneous Association

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.

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From the Division of Interventional Radiology (A.I.A., D.B.O.) and Departments of Plastic Surgery (J.B.M.) and Surgery (S.J.F.), Children's Hospital Boston and Harvard Medical School, Boston, Massachusetts; Vascular Anomalies Center (A.I.A., D.B.O., J.B.M., S.J.F.), Children's Hospital Boston, Boston, Massachusetts; Department of Neurointerventional Radiology (A.B.), Hôpital Lariboisière, Paris, France; Department of Radiology (A.N.), Boston Medical Center and Boston University, Boston, Massachusetts; Department of Medical Imaging (R.A.), King Abdulazziz Medical City, Riyadh, Saudi Arabia; Department of Radiology (D.J.L.), Children's Hospital Westmead, Sydney, Australia; and Department of Diagnostic Imaging (P.E.B.), Texas Children's Hospital, Houston, Texas.

Please address correspondence to Ahmad I. Alomari, MD, Divisions of Vascular and Interventional Radiology, Children's Hospital Boston, 300 Longwood Ave, Boston, MA 02115; e-mail: ahmad.alomari@childrens.harvard.edu

Indicates article with supplemental on-line table and appendix.

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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

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 reports[4-27] 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 (~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 al[12] advocated the theory of "focal teratogenesis" for these complex cases. The latter refers to an early embryonic insult with a metameric vascular expression. 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 metameric origin of the syndrome, are discussed. The authors of *Surgical Neuroangiography* consider KTS, a slow-flow venolymphatic disorder, one of the cerebrofacial venous metameric 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 metameric 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 metameric distribution of the birthmark.[32] Happle[42] 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 erndostatin.[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 al[45] 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 al[46] 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, Servelle[31] 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 AVMs[55]; none had spinal AVMs.

HHT is an autosomal dominant disease. Its major features are recurrent epistaxis, cutaneous ad 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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