Klippel–Trénaunay Syndrome, Parkes Weber Syndrome

27

Antonino Cavallaro

In 1900, M. Klippel and P. Trénaunay [1] described a disease characterized by a triad of physical features: cutaneous vascular naevi, varices and venous malformations, hypertrophy of one extremity: the Klippel–Trénaunay syndrome (KTS). Owing to their color, the naevi (capillary malformations) are universally recognized as port-wine stains. This classic triad is not present in all KTS patients (Table 27.1).

Currently, KTS is defined [5] as the association of: (1) combined malformations of the capillary, venous, and lymphatic systems; (2) varicosities of unusual distribution (in particular, the lateral venous anomaly, observed during infancy and childhood); (3) limb enlargement.

Vascular naevi in none of the about 1500 cases reported in the literature involved the craniofacial region [5], as at a glance differentiation from Sturge–Weber syndrome.

Describing the characteristics observed in a large series of patients, Gloviczki and Driscoll [6] pointed to the main features of the disease: capillary malformations (port-wine stains); soft tissues and bone hypertrophy (occasionally hypotrophy) of one limb (usually lower limb); atypical, mostly lateral, varices. They recognized that KTS derives from the involvement of capillary, venous, and lymphatic systems without any significant arteriovenous shunting.

The lack of a-v shunts was categorically asserted by Lindenauer [2], as a mark of differentiation from Parkes Weber syndrome (PWS). Further observations [3, 7] confirmed the absence of significant a-v communications; these may be present, but deprived of any functional relevance [8–11].

Limb overgrowth is a typical feature in most cases of KTS; however, hypotrophy has been recorded [2, 4, 11].

Whereas varicosities may be absent, malformations in the venous system are the rule: these may be of different types consisting on segmental defects of deep veins and/or persistence of veins pertaining to the embryonic system. Servelle [3] demonstrated and successfully treated, with a 14-year follow-up, the compression of the popliteal vein by a fibrous band in a 16-year-old girl with KTS. The same author, who collected the largest world experience in this field, extensively used phlebography to study the patients, demonstrating obstructive lesions of lower limb deep veins at different levels: popliteal 51%, superficial femoral 16%, iliac 3.3%: the lesion consisted on agenesis in 8% of the patients and hypoplasia in 21%. Lindenauer [2] observed, through phlebography, absence of deep vein at popliteal and thigh level. Vein abnormalities are considered the prime cause of KTS by some authors [12, 13]. Baskerville et al. [8, 9] assert that only a minority

A. Cavallaro (✉)
Past Professor of General Surgery,
"Sapienza" University, Rome, Italy

A. Cavallaro (ed.), *Aneurysms of the popliteal artery*,
https://doi.org/10.1007/978-3-030-49687-6_27

Table 27.1 Physical features in KTS

Author, year	*N* patients	Port-wine stains	Varicosities and venous malformat.	Limb hypertr.	Three features	Two features
Lindenauer [2], 1965	18	15 (83%)	18 (100%)	11(61%)	13 (72%)	5 (28%)
Servelle [3], 1985	614	32%	36%			
Jacob [4], 1998	252	246 (98%)	182 (72%)	160 (67%)	159 (63%)	93 (37%)

of patients have true absence of deep veins and that the principal defect is superficial and/or deep veins reflux: they observed absence of valves in the deep veins in 47% of 33 patients and in 68% a large lateral venous channel, mainly valveless, representing a birth-mark. The rarity of deep vein atresia had been already reported [14, 15]. At Mayo Clinic [16], a severe involvement of lower limb veins was observed consisting on complex reflux patterns, diffuse valvular incompetence with impairment of the calf muscle pump and chronic venous hypertension. In the same institutional review, atypical veins (lateral and persistent sciatic) were very frequent. The persistence of the venous sciatic system produces an overload of the internal iliac vein, causing secondary varices in the rectum, bladder, and vagina [3].

The involvement of the lymphatic system is a common component of KTS [3, 5, 6], sometimes manifesting as lymph oozing from the surface of capillary malformations sometimes as lymphangitis or true lymphedema. Studying by RM lymphography 31 KTS patients with lymphedema, Liu et al. [17] observed aplasia or hypoplasia of the lymphatics in 20 and hyperplasia in 11.

KTS may be defined as a slow-flow vascular malformation with a good prognosis; however, severe complications can manifest, represented by hemorrhage from the rectum or the genitourinary system [10]. Hemorrhage can derive from secondary varicosities [3] but is in general attributed to angiomatous lesions [18]. Whereas colon involvement is scantily reported [19], urogenital manifestations are not rare [20–22]. In a review of the Mayo Clinic experience 1970–2005 [23], genitourinary involvement was observed in 41/218 patients (19%) and severe hemorrhage requiring hospitalization occurred in 19 cases. Another relevant complication of KTS is the augmented risk of pulmonary embolism [24], up to 10% in children [25].

According to Cohen [5], KTS affects lower limb in 95% of the cases and upper limbs in 5%; involvement of the trunk alone is extremely rare [2, 3, 25].

KTS is considered a sporadic disease and its origin is unknown. Examples of familiarity are very rare [2, 26]. The most credited etiological hypothesis is that of a mesodermal defect during fetal development [2] producing the persistence [27] or the delayed regression [8] of the embryonic vascular system represented by a reticular network. Tijan et al. [28] identified in a mutation of the VG5Q gene a susceptibility to develop KTS; this hypothesis was contested by other researchers [29], but supported, albeit modified, by others: Hu et al. [30], studying 177 KTS patients and 477 controls, observed that two single nucleotide polymorphism of the AGGF1 (VG5Q) gene were significantly associated with susceptibility for KTS, proposing a two-hit mechanism for development of KTS, according to the concept of paradominant inheritance [31]. This molecular mechanism is still on the stage even if not universally accepted [32].

In 1918, F. Parkes Weber [33] described the syndrome which bears his eponym, relying on three main features: (1) capillary malformations; (2) arteriovenous communications; (3) overgrowth of a limb deriving from abnormal growth of bone and soft tissues. Already in 1907 [34], he had reported on patients who could have been classified as KTS patients, without any mention of arteriovenous communications. The substantial difference which characterizes PWS with respect to KTS is the presence of functionally

relevant a-v fistulae, which progress relentlessly with time, eventually causing ulcerations, cardiac failure, and amputation [10]. Currently, MR projection angiography looks a very reliable diagnostic tool for the evidentiation of a-v fistulae in order to separate KTS from PWS [35]. This is important, as PWS, being a fast flow vascular malformation, implies a prognosis substantially worse than KTS, notwithstanding the potential complications associated with the latter [2]. Already in 1956, Robertson [36], reviewing 28 cases of PWS, observed six cases of cardiac enlargement and three major amputations. In spite of these objective considerations, cases of "KTS" with a-v fistulae were repeatedly reported [37–39] and in 1962 Mullins et al. [40] proposed the term Klippel–Trénaunay–Weber syndrome (KTWS), asserting that there is no prognostic or therapeutic meaning in maintaining the differentiation into two specific entities. In effects, prognosis of PWS is really worse than that of KTS, and, after all, Parkes Weber described patients with enlarged arteries and veins, capillary and venous malformations, a-v communications, and enlargement of a limb; moreover, a lymphatic component is rarely observed [32] and the lateral venous anomaly has never been observed [5].

However, the term KTWS is frequently used [41–43], even when the patient should be undoubtedly classified as affected with PWS [44].

After the initial observations of Eerola et al. [45], a mutation of the gene RASA1 has been found both in cases of CM-AVM (capillary malformation-arteriovenous malformation) and PWS [46], apparently linked to the condition of high-flow a-v malformation; this mutation is lacking in KTS [47].

Arterial aneurysms have been reported both in KTS and PWS. In some cases, it is difficult to assess a specific etiology or to rule out a coincidental occurrence with other vascular diseases. Peculiar microscopy findings seem to characterize some cases of aneurysm in KTS. Nakamura et al. [18] described aneurysm of the transverse cervical artery due to the weakening of the arterial wall by invasion from a surrounding hemangiomatous lesion. Particularly intriguing is the histology in the case of popliteal aneurysm reported by Akagi et al. [48]: disrupted and disordered elastic fibers in an extremely thinned media. The authors suggest that this picture could represent a specific arterial lesion of KTS. On the other side, some of the aneurysms observed in KTS are clearly atherosclerotic (as the aortic aneurysm reported by Kaladji et al. [49] and the popliteal aneurysm operated on for acute ischemia by Komai [50]). The genesis of aneurysmal lesions in PWS could be correlated with the overload and the increased turbulence consequent to a-v fistulae; diffuse dilation of all the arteries of the involved limb has been described [51].

Aneurysms observed in KTS involved the renal artery [20, 52] and cerebral arteries [53–55]. In PWS (or KTWS) were reported aneurysms at different sites: cerebral arteries [56–58]; renal artery [59]; brachial artery [60]; iliac and femoral arteries [61].

Details of aneurysms of the popliteal artery observed in KTS and PWS are illustrated in Table 27.2.

Table 27.2 Popliteal artery aneurysm in KTS and PWS

Author, year	Patient	Symptoms	Treatment and outcome
1. Akagi[a] [48], 2006	F, 35 years	Local pain	Partial excision, femorotibial vein bypass; OK 7 years
2. Komai[a] [50], 2006	M, 48 years	Acute isch.	Aneurysmectomy, popliteotibial vein graft
3. Pourhassan[a] [62], 2007	M, 49 years		
4. Ferrero[b] [51], 2011	M, 27 years		Coil emboliz. a-v fistulae + stent graft; OK 8 years
5. Plaza-Martinez[b] [63], 2011	M, 61 years	Asympt.	Stent graft; OK 1 year

1. Aneurysm involving the distal superficial femoral and the popliteal arteries; diagnosed 2 years before, when asymptomatic. 2. Atherosclerotic aneurysm. 3. Patient with aneurysms of renal, splenic, and superior mesenteric arteries. 4. Aneurysm of the superficial femoral involving the proximal popliteal artery; several a-v fistulae at the last control

[a]KTS

[b]PWS or KTWS

References

1. Klippel M, Trénaunay P. Du naevus variqueux ostéo-hypertrophique. Arch Gen Méd. 1900;185:641–72.
2. Lindenauer S. The Klippel-Trénaunay syndrome: varicosity, hypertrophy and hemangioma with no arteriovenous fistula. Ann Surg. 1965;162:303–14.
3. Servelle M. Klippel and Trénaunay syndrome. 768 operated cases. Ann Surg. 1985;201:365–73.
4. Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Gloviczki P. Klippel-Trenaunay syndrome: spectrum and management. Mayo Clin Proc. 1998;73:28–36.
5. Cohen MM Jr. Vascular update: morphogenesis, tumors, malformations, and molecular dimensions. Am J Med Genet. 2006;146A:2013–38.
6. Gloviczki P, Driscoll DJ. Klippel-Trenaunay syndrome: current management. Phlebology. 2007;22:291–8.
7. Servelle M, Zolotas E, Soulie J, Andrieux J, Cornu C. Syndrome de Klippel et Trenaunay: malformations des veines iliaques, fémorale et poplitée. Arch Mal Coeur Vaiss. 1965;58:1187–97.
8. Baskerville PA, Ackroyd JS, Browse NL. The etiology of the Klippel-Trenaunay syndrome. Ann Surg. 1985;202:624–7.
9. Baskerville PA, Ackroyd JS, Thomas LM, Browse NL. The Klippel-Trenaunay syndrome: clinical, radiological and haemodynamic features and management. Br J Surg. 1985;72:232–6.
10. Roebuck DJ. Klippel-Trenaunay and Parkes-Weber syndromes. Am J Roentgenol. 2004;14:311–2.
11. Oduber CE, Van der Horst CM, Hennekam RC. Klippel-Trenaunay syndrome: diagnostic criteria and hypothesis on etiology. Ann Plast Surg. 2008;60:217–23.
12. Hutchinson WJ, Burdeaux BD. The influence of stasis on bone growth. Surg Gynecol Obstet. 1954;99:413–20.
13. Poulet J, Ruff F. Les dysplasies veineuses congénitales des membres. Presse Méd. 1969;77:163–9.
14. Coget JM, Merlen JF. Klippel-Trénaunay: syndrome ou maladie? Phlebologie. 1980;33:37–43.
15. Van der Stricht J. Syndrome de Klippel et Trénaunay et phacomatoses. Phlebologie. 1980;33:21–30.
16. Delis KT, Gloviczki P, Wennberg PW, Rooke TW, Driscoll DJ. Hemodynamic impairment, venous segmental disease, and clinical severity scoring in limbs with Klippel-Trenaunay syndrome. J Vasc Surg. 2007;45:561.567.
17. Liu NF, Lu Q, Yan ZK. Lymphatic malformation is a common component of Klippel-Trenaunay syndrome. J Vasc Surg. 2010;52:1557–63.
18. Nakamura K, Onitsuka T, Koga Y, Shirata K, Tsuchida Y, Nabeshima K, Sumiyoshi A. Aneurysm of the transverse cervical artery occurring in association with a cavernous hemangioma as a complication of Klippel-Trenaunay syndrome: report of a case. Surg Today. 1995;25:978–81.
19. Ghahremani GG, Kangarloo H, Volberg F, Meyers MA. Diffuse cavernous hemangioma of the colon in the Klippel-Trenaunay syndrome. Radiology. 1976;118:673–8.
20. Campistol JM, Agusti C, Torras A, Campo E, Abad C, Revert L. Renal hemangioma and renal artery aneurysm in the Klippel-Trenaunay syndrome. J Urol. 1988;140:134–6.
21. Zini L, Amara N, Graziana JP, Villers A, Mazeman E. Klippel-Trenaunay syndrome and multiple vesical hemangiomas: treatment with Neodymium:YAG laser. Prog Urol. 2001;11:1282–4.
22. Furness PD 3rd, Barqawi AZ, Bisignani C, Decter RM. Klippel-Trenaunay syndrome: 2 case reports and a review of genito-urinary manifestations. J Urol. 2001;166:1418–20.
23. Husmann DA, Rathburn SR, Driscoll DJ. Klippel-Trenaunay syndrome: incidence and treatment of genito-urinary sequelae. J Urol. 2007;177:1244–9.
24. Huiras EE, Barnes CJ, Eichenfield LF, Pelech AN, Drolet BA. Pulmonary thromboembolism associated with Klippel-Trenaunay syndrome. Pediatrics. 2005;116:e596–600.
25. Samuel M, Spitz L. Klippel-Trenaunay syndrome: clinical features, complications and management in children. Br J Surg. 1995;82:757–61.
26. Aelvoet GE, Jorens PG, Roelen LM. Genetic aspects of the Klippel-Trenaunay syndrome. Br J Dermatol. 1992;126:602–3.
27. Bourde C. Classification des syndromes de Klippel-Trénaunay et de Parkes-Weber d'après les données angiographiques. Ann Radiol. 1974;17:153–60.
28. Tian X-L, Kadaba R, You S-A, Liu M, Timur AA, Yang L, Chen Q, Szafranski P, Rao S, Wu L, Housman DE, Di Corleto PE, Driscoll DJ, Borrow J, Wang Q. Identification of an angiogenic factor that when mutated causes susceptibility to Klippel-Trenaunay syndrome. Nature. 2004;427:640–5.
29. Barker KT, Foulkes WO, Schwartz CE, Labadie C, Monsell F, Houlton RS, Harper J. Is the E133K allele of VG5Q associated with Klippel-Trenaunay syndrome and other overgrowth syndromes? J Med Genet. 2006;43:613–4.
30. Hu Y, Seidelmann SB, Timur AA, Shen PH, Driscoll DJ, Wang OK. Identification of association of common AGGF1 variants with susceptibility for Klippel-Trenaunay syndrome using the Structure Association Program. Ann Hum Genet. 2008;72(Pt 5):636–43.
31. Happle R. Lethal genes surviving by mosaicism: a possible explanation for sporadic birth defects involving the skin. J Am Acad Dermatol. 1987;16:899–906.
32. Killion E, Mohan K, Lee EI. A review of vascular syndromes: genetics and common syndromes. Semin Plast Surg. 2014;28:64–8.
33. Parkes WF. Hemangioectatic hypertrophy of limbs – congenital phleboarteriectasis and so-called congenital varicose veins. Br J Child Dis. 1918;15:13–171.
34. Parkes WF. Angioma formation in connection with hypertrophy of limbs and hemihypertrophy. Br J Dermatol. 1907;19:231–5.

35. Ziyeh S, Spreer J, Rossler J, Strecker R, Hochmuth A, Schumacker M, Klisch J. Parkes Weber or Klippel-Trenaunay syndrome? Non-invasive diagnosis with MR projection angiography. Eur Radiol. 2004;14:2025–9.
36. Robertson DJ. Congenital arteriovenous fistulae of the extremities. Ann R Coll Surg Engl. 1956;18:73–98.
37. Cullity TB. Hypertrophy of the leg with associated vascular abnormality (the Klippel-Trenaunay syndrome): report of a case. Med J Aust. 1951;2:773–6.
38. Bouvrain G, Bourthoumieux A. Le rétentissement cardiaque du syndrome de Klippel-Trénaunay. Arch Mal Coeur Vaiss. 1957;50:626–35.
39. Galicer RF, Nerio CN. Sindrome de Klippel-Trenaunay (Presentacion de 3 cases). Prensa Med Argent. 1956;43:3259–63.
40. Mullins JF, Naylor D, Redetski J. The Klippel-Trenaunay-Weber syndrome. Arch Dermatol. 1956;86:202–6.
41. Koch G. Zur Klinik, Symptomatologie, Pathogenese und Erbpathologie des Klippel-Trénaunay-Weber Syndrom. Acta Genet Med Gemellol. 1956;5:326–70.
42. Schönenberg H, Redermann M. Klippel-Trénaunay-Weber syndrom. Klin Paediatr. 1972;184:449–60.
43. Kondo T, Tanaka K, Fujii T, Akita S. Klippel-Trenaunay-Weber syndrome associated with intra-abdominal lymphangioma requiring multiple surgical interventions. Ann Plast Surg. 1997;39:435–7.
44. Patil V, Patil S, Ichalakaranji R, Bhadragoudra J, Devani R. Klippel-Trenaunay-Weber syndrome: a case report. Int J Biomed Adv Res. 2014;5:396–7.
45. Eerola I, Boon LM, Mulliken JB, Burrows PE, Dompmartin A, Watanabe S, Vanwijck R, Vikkula M. Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. Am J Med Genet. 2003;73:1240–9.
46. Ravencu N, Boon LM, Mulliken JB, Enjolras O, Cordisco MR, Burrows PE, Clapuyt P, Hammer F, Dubois J, Baselga E, Brancati F, Carder R, Quintal JM, Dallapiccola B, Fischer G, Frieden IJ, Garzon M, Harper J, Johnson-Patel J, Labrèze C, Martorell L, Paltiel J, Pohl A, Prendiville J, Quere I, Siegel DH, Valente EM, Van Hagen A, Van Hest L, Vaux KK, Vicente A, Chitayat D, Vikkula M. Parkes Weber syndrome, vein of Galen aneurysmal malformation, and other fast-flow vascular anomalies are caused by RASA1 mutations. Hum Mutat. 2008;29:959–65.
47. Revencu N, Boon LM, Dompmartin A, Rieu P, Busch WL, Dubois J, Forzano F, Van Hagen JM, Halbach S, Kuechler A, Lachmeijer AM, Lahde J, Russell L, Simola KO, Mulliken JB, Vikkula M. Germline mutations in RASA1 are not found in patients with Klippel-Trenaunay syndrome or capillary malformations with limb overgrowth. Mol Syndromol. 2013;4:173–8.
48. Akagi D, Ishii S, Kitagawa T, Nagawa H, Miyata T. Popliteal arterial aneurysm associated with Klippel-Trenaunay syndrome: case report and literature review. J Vasc Surg. 2006;43:1287–9.
49. Kaladji A, Zamreek A, Pinel G, Gérard F, Leguernier A, Cardon A. Klippel-Trenaunay syndrome associated with abdominal aortic aneurysm. Eur J Vasc Endovas Surg EXTRA. 2012;23:e29–30.
50. Komai H. Regarding popliteal arterial aneurysm associated with Klippel-Trenaunay syndrome: case report and literature review (letter). J Vasc Surg. 2006;44:1377–88.
51. Ferrero E, Ferri M, Viazzo A, Carbonatto P, Molinaro V, Suita R, Nessi F. Parkes-Weber syndrome and giant superficial femoral artery aneurysm. Treatment by endovascular therapy and follow-up of 8 years. Ann Vasc Surg. 2011;25:384e9–384e15.
52. Ogden CW, Jackson JE. The Klippel-Trenanunay syndrome associated with renal artery aneurysm. Br J Urol. 1993;71:617–8.
53. Spallone A, Tcherekayev VA. Simultaneous occurrence of aneurysm and multiple meningioma in Klippel-Trenaunay parients: case report. Surg Neurol. 1996;45:241–4.
54. De Blasi B, Zenzola A, Lanzilotti CM, Resta M, Caputi O, Lamberti P, Simone F. An unusual association of intracranial aneurysm and oesophageal duplication in a case of Klippel-Trenaunay syndrome. Neuroradiology. 2000;42:930–2.
55. Kim YW, Kim N, Hwang J-M, Choung H-K, Khwarg SI. Teaching neuroimages: multiple giant intracranial aneurysms in Klippel-Trenaunay syndrome. Neurology. 2013;81:e17–8.
56. Taira T, Tamura Y, Kawamura H. Intracranial aneurysm in a child with Klippel-Trenaunay-Weber syndrome: case report. Surg Neurol. 1991;36:303–6.
57. Ouellet MC, Sevick RJ, Tranmer BI, Lester WM. Thrombosed fusiform basilar aneurysm associated with Klippel-Trenaunay-Weber syndrome. Can Assoc Radiol J. 1997;48:28–32.
58. Star A, Fuller CE, Landas SK. Intracranial aneurysms in Klippel-Trenaunay-Weber syndrome: case report. Neurosurgery. 2010;66:E1027–8.
59. Sharma S. Multifocal intradural spinal AVF and renal artery aneurysm in a case of Klippel-Trenaunay syndrome (KTS). Neuroimaging. 2010;20:386–9.
60. Bartels C, Claeys L, Ktenidis K, Horsch S. F. P. Weber syndrome associated with a brachial artery aneurysm: case report. Angiology. 1995;46:1039–42.
61. Ugurlucan M, Yerebakan C, Alpagut U, Tireli E, Dayioglu E. Klippel-Trénaunay-Weber syndrom. Wien Med Wochenschr. 2008;158:402–4.
62. Pourhassan S, Grotemeyer D, Klat V, Sandmann W. Das Klippel-Trénaunay Syndrom bei gleichzeitigem Vorliegen von Viszeralarterienaneurysmen. Vasa. 2007;35:124–9.
63. Plaza-Martinez A, Ortiz-Monzón E, Gomez-Palonés FJ, Genovés-Gasco B, Martinez-Perelló I, Martinez-Parreño C. Popliteal artery aneurysm in a patient with Klippel-Trenaunay-Weber syndrome. Ann Vasc Surg. 2011;25:838e13–6.