



Diversity and frequency of symptoms in Klippel–Trénaunay syndrome

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Abstract

Introduction and Objective. Klippel–Trénaunay syndrome is a rare congenital disease consisting of vascular malformations, limb overgrowth, large varicose veins and port-wine stains. It is related to the mosaic variants of PIK3CA gene. Patients with KTS usually receive symptomatic treatment, such as orthopaedic correction of limb overgrowth or varicose vein treatment. This systematic review aims to summarise knowledge about the most common of anomalies presented by Klippel–Trénaunay patients. The literature review describes the anomalies present in Klippel–Trénaunay syndrome.

Review Methods. This review was created based on 21 papers found in PubMed and PubMedCentral databases after searching for 'klippel trenaunay' and 'hypertrophy/anomaly/anatomical/malformation', published between 1978–2023, as well as on Dove Press articles from 2012.

Brief description of the state of knowledge. Limb overgrowth is a dominant symptom of KTS, appearing in 67%–100% of patients. More often it affects lower limbs, although it can also appear in the upper limbs. Overgrowth is caused by vascular malformations which, on their own, are another symptom of KTS. Patients with KTS present malformations of deep veins (e.g. popliteal vein) or superficial veins (e.g. superficial femoral vein), together with embryonal veins (e.g. persisting sciatic vein). Port-wine stains can appear to up to 98% of patients, and are located mostly on the lower limbs and/or torso.

Summary. The variety of anomalies appearing in Klippel–Trénaunay syndrome is large and diversified. Collecting and summing-up information about anatomical anomalies of Klippel–Trénaunay syndrome can help both doctors and patients in the search for more meticulous diagnosis and treatment of the symptoms.

Key words

haemangioma, abnormalities, Klippel-Trenaunay-Weber Syndrome, hypertrophy

INTRODUCTION

Klippel–Trénaunay Syndrome (KTS) is a rare congenital disease, occurring with the frequency of 2–5/100 000 births, regardless of gender [1–3]. It is characterised by the presence of vascular malformations, mostly located on the limbs. Malformations affect limb growth [3]. They include skin capillaries, veins, lymphatic vessels. The direct cause of limb growth is the presence of vascular malformations in childhood [4]. It is proven that KTS is related to the presence of mosaic-activating variants in PIK3CA gene [1]. This syndrome lacks defined, uniform symptoms because of their variety. It is characterised mostly by 3 manifestations: limb overgrowth (caused by the overgrowth of bone, subcutaneous tissue and muscle), unilateral, extensive varicose veins and vascular anomalies- port-wine stains, observed postnatally. Anomalies are most often located on the lower extremities, their distant parts [5]. Usually only one limb is affected, less often there is a bilateral and asymmetrical presence of an anomaly [6]. For a proper diagnosis of KTS, the presence

of two out of three typical symptoms is necessary [1]. In literature, a case of inverse KTS ('KFS'), similar, but without the limb and muscle overgrowth, has been described [1]. Clinically, the most similar syndrome to KTS is Parkes-Weber Syndrome, often called Klippel–Trénaunay-Weber Syndrome (PWS). Different from KTS, deep malformations in PWS are arteriovenous malformations, while KTS is characterised by venous malformations only [1]. Treatment of KTS-affected patients is mostly focused on conservative and symptomatic treatment. The objective is to raise the quality of the patient's life, as there is no cure for the disease. Operational treatment is applied only in the cases of deep vein obstruction or limb-asymmetry correction [7]. KTS can affect not only the limbs, but also other organs.

The aim of this systematic review is to collect and define knowledge about the various anatomical anomalies and variations in KTS, and their frequency of occurrence in order to clarify the clinical picture of the disease and draw attention to the limitations of medical practice in its management, as well as the possibilities of relieving some of the patients' ailments.

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MATERIALS AND METHOD

To collect the data in this review, information from 21 scientific papers (20 from PubMed and PubMed Central databases, and one article from Dove Press magazine of 05 May 2012) was used. Two of 20 publications were available as scans of their paperback editions.

Primarily, a range of 40 papers found in PubMed and PubMedCentral under keywords: 'klippel trenaunay AND hypertrophy/anomaly/anatomical/malformation' were considered. However, as the analysis progressed, the range increased to include cited work with similar content. Selected papers ranged from 1978–2023 and contained studies on the patient pool (>2 patients) – 9 papers; single-patient case studies – 9 papers; available literature reviews – 3 papers; papers with combined case studies and literature reviews.

RESULTS

Bone and soft-tissue hypertrophy is one of 3 types of malformations resulting in Klippel-Trénaunay syndrome diagnosis. One of the studies conducted on the pool of 786 patients diagnosed with KTS found that the difference of length between healthy (shorter) and affected (elongated) limb was present in 100% of cases [8]. Other studies pointed to 84% [5] and 67% [9] of frequency of limb hypertrophy; therefore, this defect can be considered as one of the 3 main anomalies of KTS, but not necessarily in setting a diagnosis although it is a dominant defect. Tissue overgrowth usually affects one of the lower limbs [5] and is described as overgrowth of bone and soft tissue, which can increase in size by the coarsening of bone layers, venous hypertension [10], or oedema caused by lymph stasis caused by compression or obstruction. Upper extremities are less frequently affected by the disease – in 24.9% of cases, or 11% in situations where an upper limb is the only one affected [14].

Malformations of this type can result in other distortions of bone and cartilage tissue, such as scoliosis, osteoporosis and osteopenia, limb axis disorders, joint contractures [5], lower [11] and upper [19] limb syndactyly. Soft tissue overgrowth and connected deformations can sometimes affect the exterior genital area, where it can result in cryptorchidism, phimosis and problems with micturition [12]. Cases of facial soft tissue overgrowth and bone malformations have also been described, mostly in the areas of the mandible and maxilla, which can also be restricted laterally [2].

Other types of anomalies in KTS are venous and lymphatic malformations. According to different studies they can appear in 36% [8] or 72% [9] of patients diagnosed with KTS in a study group. Venous malformation can appear as large varicose veins, located on the hypertrophic or oedematous tissue, on parts or even entire hypertrophic limbs (such as thick and winding superficial vein characteristic for KTS) [18]), as well as chest [11], genital area and proximal internal organs- urinary bladder, ureters and urethras [12]. Cases of significant bleeding from the digestive tract, caused by large malformations of blood vessels of the organs have also been described [16, 17]. Such variations can appear from the stomach to the descending colon and, in one described case, accompanied by multiple spleen haemangiomas [17]. Malformations can affect both deep venous structures – popliteal vein in 51% of cases, superficial –



Figure 1. Upper limb length disparity and port wine stain in a 24-year-old patient with KTS



Figure 2. Limb length disparity, varicose veins and malformations in 24-year-old patient with KTS

superficial femoral vein in 16% of cases, or both – in 29% of cases. [8] To a lesser extent, iliac veins (3%) or inferior vena cava (1%) can be affected [8]. Patients with KTS can also manifest persistent embryonic veins which, if present postnatally, are considered a pathology. A study conducted on 70 patients with KTS showed that embryonic veins were present in 17.1% of the group – 12 people [13]. The study focused on the lateral marginal vein; however, this anomaly can be accompanied by persistent sciatic vein [13], located near the sciatic nerve. Another study claims that persistent veins are present in 72% of KTS patients [9].



Figure 3. Left foot hypertrophy in 24-year-old patient with KTS

The last element of the Klippel-Trénaunay triad are port-wine stains. There are sources referring to as 'flat angiomas' [8], although most of the newly-published papers prefer the term 'port-wine stains' while describing haemangiomas that do not shrink with age and (in most cases) cover the hypertrophic limb, gluteal region of the same side if the lower limb is affected, and the trunk – both anterior and posterior sides of the corpus can be affected [11]), and sometimes even the neck with the unilateral stain formation on both limbs and trunk [2]. They can appear in 98% of patients according to one study [9] or 32% in the other cases, and referred to as the previously 'flat angiomas' [8].



Figure 4. State post-corrective osteotomy of third digit of right hand in 24-year-old patient with KTS

All 3 KTS symptoms are not usually observable in all patients; for example, the triad can be present in 63% of the studied pool, while the remaining 37% presented only 2 of 3 symptoms [9]. Diagnosed Klippel-Trénaunay syndrome does not exclude the patients from the risk of developing other rare ailments, described in singular instances, such as:

- newly-developed periosteal bone formation, potentially linked to KTS [15];

- broad, numerous lymphatic haemangiomas of underscribed relation to KTS, based on the uniqueness of the case [11];
- osseous haemangioma that developed in patient's frontal bone, affecting the superior sagittal sinus, which is an uncommon and probably the only published instance of a patient with a cranial location of haemangioma in a KTS patient [20];
- a case of a giant uterus weighing 6.3 kgs, with leiomyomatosis and diffuse vascular malformations [21].



Figure 5. Vascular malformation of right leg in 24-year-old patient with KTS

DISCUSSION

Based on the literature included in this review, it can be concluded that in Klippel-Trénaunay syndrome is the most common of anomalies involving limb hypertrophy [5, 8, 9], venous malformations (especially popliteal vein and superficial femoral vein, as well as superficial veins of the lower limb; less common are malformations of iliac veins and inferior vena cava [8], as well as persistent embryonal and sciatic veins [9,13]) and haemangiomas [8, 9]. Selected papers show large inconsistencies in the frequency of anomalies, which indicates the necessity of a more detailed, broader research of the topic. Also, while instances of rare ailments present in KTS patients are described, they remain isolated cases and are not part of a typical picture of patients affected by this syndrome. [11, 15, 20, 21].

CONCLUSIONS

Klippel-Trénaunay syndrome is associated with numerous anatomical anomalies which vary in frequency and clinical significance. Unilateral limb overgrowth can result in negative consequences for posture, mobility, or the vertebral column, and development of the pectoral and pelvic girdles. Abnormal course and structure of veins can result in obstruction and thrombotic episodes, necessitating surgical and pharmacological assistance. Accompanying variations of organ vascularisation can lead to its enlargement and diagnostic and therapeutic difficulties. Despite the rarity of occurrence, KTS should be continuously researched; its characteristics, symptoms and complications described with more detail in hopes of more detailed diagnostic process and further development of therapeutic methods used

Table 1. Frequency of anatomical anomalies presented in Klippel-Trénaunay syndrome in selected literature

	Servelle M (1985). Klippel and Trénaunay's syndrome. 768 operated cases. [8]	Schoch JJ, Nguyen H, Schoch BS, Anderson KR, Stans AA, Driscoll D, Tollefson M (2019). Orthopaedic diagnoses in patients with Klippel-Trénaunay syndrome. [5]	Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Głowiczki P (1998). Klippel-Trénaunay syndrome: Spectrum and management. [9]	Oduber CE, Young-Afat DA, Van Der Wal AC, Van Steensel MA, Hennekam RC, Van Der Horst CM (2013). The persistent embryonic vein in Klippel-Trénaunay syndrome. [13]
Limb length disparity	100%	84%	67%	-
Vascular malformations	36%	-	72%	-
Including popliteal vein	51%	-	-	-
Including superficial femoral vein	16%	-	-	-
Including popliteal and femoral veins	29%	-	-	-
including iliac veins	3%	-	-	-
Including inferior vena cava	1%	-	-	-
Present persistent embryonic veins	-	-	72%	17.1%
Hemangiomas	32%	-	98%	-

to help affected patients and raising their quality of life. Further studies on the clinical manifestation of syndrome help in relieving their complaints, for example, by surgical interventions in varicose veins treatment [19], as well as compensation of limb disparities by epiphysiodesis [9]. Large disproportions and development remain in the literature data collected over the years of research of KTS, perhaps pointing to a need of more detailed, uniform studies on the topic.

Disclosures

All authors have read and agreed with the published version of the manuscript.

Conflict of interest. The authors declare no conflict of interest.

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REFERENCES

- Pavone P, Marino L, Cacciaguerra G, et al. Klippel-Trenaunay Syndrome, Segmental/Focal Overgrowth Malformations: A Review. *Children (Basel)*. 2023;10(8):1421. <https://doi.org/10.3390/children10081421>
- Daume L, Renz C, Trento G, Kleinheinz J. Klippel-Trenaunay-Weber syndrome: Oro-dental manifestations and management. *Int J Surg Case Rep*. 2023;110:108690. <https://doi.org/10.1016/j.ijscr.2023.108690>
- Funayama E, Sasaki S, Oyama A, Furukawa H, Hayashi T, Yamamoto Y. How Do the Type and Location of a Vascular Malformation Influence Growth in Klippel-Trénaunay Syndrome?: Plastic and Reconstructive Surgery. 2011;127(1):340–346. <https://doi.org/10.1097/PRS.0b013e3181f95b4c>
- Mattassi R. Differential diagnosis in congenital vascular-bone syndromes. *Semin Vasc Surg*. 1993;6(4):233–244.
- Schoch JJ, Nguyen H, Schoch BS, et al. Orthopaedic diagnoses in patients with Klippel-Trenaunay syndrome. *J Child Orthop*. 2019;13(5):457–462. <https://doi.org/10.1302/1863-2548.13.190065>
- Alwalid O, Makamure J, Cheng QG, et al. Radiological Aspect of Klippel-Trénaunay Syndrome: A Case Series With Review of Literature. *Curr Med Sci*. 2018;38(5):925–931. <https://doi.org/10.1007/s11596-018-1964-4>
- Phillips GN, Gordon DH, Martin EC, Haller JO, Casarella W. The Klippel-Trenaunay Syndrome: Clinical and Radiological Aspect. *Radiology*. 1978;128(2):429–434. <https://doi.org/10.1148/128.2.429>
- Servelle M. Klippel and Trénaunay's syndrome. 768 operated cases. *Ann Surg*. 1985;201(3):365–373. <https://doi.org/10.1097/0000658-198503000-00020>
- Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Głowiczki P. Klippel-Trénaunay syndrome: spectrum and management. *Mayo Clin Proc*. 1998;73(1):28–36. [https://doi.org/10.1016/S0025-6196\(11\)63615-X](https://doi.org/10.1016/S0025-6196(11)63615-X)
- Asghar F, Aqeel R, Farooque U, Haq A, Taimur M. Presentation and Management of Klippel-Trenaunay Syndrome: A Review of Available Data. *Cureus*. 2020;12(5):e8023. <https://doi.org/10.7759/cureus.8023>
- Mneimneh S, Tabaja A, Rajab M. Klippel-Trenaunay Syndrome with Extensive Lymphangiomas. *Case Rep Pediatr*. 2015;2015:581394. <https://doi.org/10.1155/2015/581394>
- Vicentini FC, Denes FT, Gomes CM, Danilovic A, Silva FA, Srougi M. Urogenital involvement in the Klippel-Trenaunay-Weber syndrome. Treatment options and results. *Int Braz J Urol*. 2006;32(6):697–703; discussion 703–704. <https://doi.org/10.1590/s1677-55382006000600011>
- Oduber CE, Young-Afat DA, Van Der Wal AC, Van Steensel MA, Hennekam RC, Van Der Horst CM. The persistent embryonic vein in Klippel-Trénaunay syndrome. *Vasc Med*. 2013;18(4):185–191. <https://doi.org/10.1177/1358863X13498463>
- Zwerink L, Praster R, Van Der Vleuten C. Prevalence and inventory of venous anatomical abnormalities in the arms of patients with combined capillary, venous and lymphatic malformations (Klippel-Trénaunay syndrome). *Phlebology*. 2021;36(7):549–554. <https://doi.org/10.1177/0268355521989873>
- Fang X, Zhang W, Yu Z, Kuang F, Huang B, Duan H. Periosteal new bone formation in Klippel-Trénaunay syndrome: a case report. *BMC Pediatr*. 2020;20(1):388. <https://doi.org/10.1186/s12887-020-02298-0>
- Cha SH, Romeo MA, Neutze JA. Visceral Manifestations of Klippel-Trénaunay Syndrome. *RadioGraphics*. 2005;25(6):1694–1697. <https://doi.org/10.1148/rg.256055042>
- Wang ZK, Wang FY, Zhu RM, Liu J. Klippel-Trenaunay syndrome with gastrointestinal bleeding, splenic hemangiomas and left inferior vena cava. *World J Gastroenterol*. 2010;16(12):1548–1552. <https://doi.org/10.3748/wjg.v16.i12.1548>
- Choudhary MG, Sehra. A case report and brief literature review of Klippel-Trénaunay syndrome. *RRN*. Published online May 2012:21. <https://doi.org/10.2147/RRN.S30689>
- Zavacka M, Pobehova J, Gibarti K, Frankovicova M. Patients with Klippel-Trenaunay syndrome. *Bratisl Lek Listy*. 2016;117(10):601–604. https://doi.org/10.4149/bll_2016_116
- Yousif S, Lampe G, Pattavilakom A. Large frontal osseous hemangioma with dural sinus involvement in a patient with Klippel-Trenaunay syndrome: A rare case report. *Surg Neurol Int*. 2018;9:205. https://doi.org/10.4103/sni.sni_244_18
- Di Buono G, Ricupati F, Vella R, Saverino M, Amato G, Agrusa A. Giant uterus in a patient with Klippel-Trenaunay syndrome. Report of a case. *Int J Surg Case Rep*. 2022;96:107376. <https://doi.org/10.1016/j.ijscr.2022.107376>