Special Article

Klippel-Trenaunay Syndrome: A Review Article

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Klippel-Trenaunay syndrome is a vascular malformation associated with limb overgrowth[1]. The name of the disease came from two French men: Maurice Klippel and Paul Trenaunay. There is an equal incidence of Klippel–Trenaunay Syndrome in men and women[2]. The syndrome typically affects only on one lower limb[3]; however, cases with more than one affected limb are occasionally found[2,4,5].

Keywords: Klippel-Trenaunay syndrome, Treatment, Diagnosis

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The pathophysiology of Klippel-Trenaunay syndrome is related to PIK3CA, which causes blood or lymph vessels to proliferate improperly[2,6,7]. Activating somatic mutations of PIK3CA involving the amino acids E542, E545, or H1047 causes kinase activation, then leading to sporadic somatic mutations of early progenitor cells for the blood vessels and underlying bone[8]. Intra- and interpatient variability in the phenotype can be found.

The clinical manifestations of Klippel-Trenaunay Syndrome consist of 1) capillary malformations, 2) venous varicosities or venous malformations, and 3) limb hypertrophy. Arteriovenous malformation, if present, will lead to a diagnosis of Park Weber Syndrome, which requires different treatment and has a worse prognosis[6].

Capillary malformations, of typically geographic pattern, are found in 98% of patients[9]. Typically, lesions are found on the affected limb, but the involvement of the unaffected limb and trunk could be found too[2,9]. The intensity of the color of the lesions may change when the child grows up[9]. Skin breakdown, bleeding, and infection can occur upon capillary malformation.

Venous malformations and varicosities in Klippel-Trenaunay Syndrome are found in 72 to 93% of patients[2,6,9]. Varicosities result from a congenital weakness of the vascular wall or from venous hypertension[2,9-11]. The syndrome may not appear at birth and can progress at puberty. The abnormalities of superficial veins include a small ectatic vein, varicosities, venous malformations, and a persistent embryonic vein (lateral marginal vein: vein of Servelle and the sciatic vein). In some cases, the embryonic vein has no valves and often tortuous, large dysplasia occur that cause fatigue and heaviness of the affected limb[9]. An incompetent perforating vein can also be found. Various deep venous anomalies can be found, such as hypoplasia and aplasia superficial femoral and popliteal veins[9]. These may be the cause of superficial vein varicosities or venous incompetence, which increase the risk of thromboemboli and a venous ulcer[12,13]. Thrombophlebitis occurs in 45% of cases[14] and causes pain and limited limb movement. Klippel-Trenaunay Syndrome may have superficial femoral venous aneurysms that clinically present like a femoral hernia[15]. One study reported an infected giant venous malformation that caused septic shock and massive bleeding[16].

Limb hypertrophy is found in 67 to 85% of cases[2,9]. Hypertrophy may result from soft tissue or long bone overgrowth in the affected limb. Macrodactyly and polydactyly can be found too[9,17]. Limb hypertrophy may present evidently at birth. The progression of limb hypertrophy usually occurs during childhood, and the rate of progression is unpredictable[9]. There is a minimal rate of limb hypertrophy after the teenage years[18].

Lymphatic malformations are associated with Klippel–Tr□naunay Syndrome in 29 to 56% of cases[3,19]. Lymphatic malformation may be localized and cause an abnormal contour of the leg or thigh. Generalized swelling of the affected limb may result from lymphedema and can cause recurrent cellulitis and Gram negative bacteremia[19,20]. Lymphagioma circumscriptum can be found upon capillary malformation or at other sites[21]. The lesions can cause periodic bleeding, and can sometimes be life threatening[22].

Gastrointestinal tract involvement occurs in 20% of cases, mostly involving a distal colon and rectum[23]. The majority of hematochezia is self-limiting, but sometimes is massive[24,25]. The involvement of the cecum and ascending colon has been reported[26]. Urinary tract involvement can be present too, from intermittent hematuria to hemorrhagic shock[27].

Various orthopedic conditions have been reported to be associated with Klippel–Trenaunay Syndrome, including kyphoscoliosis, carpal tunnel syndrome, and sciatic

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nerve hypertrophy[28-30]. Foot ulcers can develop in the affected limb. In one study, basal cell carcinoma was reported in the foot ulcer of a patient with Klippel–Trenaunay Syndrome[31].

Other conditions associated with Klippel–Trenaunay Syndrome include ophthalmic alterations, such as glaucoma, conjunctival telangiectasia, orbital varix, and strabismus[32,33], acanthocytosis, splenic and retroperitoneal lymphatic malformation[34], ipsilateral axillary hyperhidrosis[35], localized intravascular coagulopathy[36], and an aneurysm of the abdominal aortic and inferior vena cava[37,38].

A plain film can be used to demonstrate soft tissue and bone hypertrophy. Phleboliths, which are typical findings for venous malformation, can be seen as calcification on a plain film. Radiologic measurement of the limb-length difference is more accurate than clinical measurement[11].

Color duplex ultrasound is used for the assessment and diagnosis of venous varicosities, localized venous and lymphatic malformation, venous valve incompetence, and the presence of deep vein, deep vein thrombosis, and thrombosis that cause acute pain[39,40]. Sonographic findings that are not typical for venous malformation or lymphatic malformation should alert the physician of neoplastic lesions, such as synovial sarcoma, epithelioid sarcoma, and angiomatoid fibrous histiocytoma. These tumors have a thick septa and solid vascularized component on sonographic findings[40]. Park Weber syndrome should be suspected if high flow vascular lesions are found.

Venous and lymphatic anomalies can also be assessed by computed tomography venography. Computed tomography is the imaging of choice for the detection of bone abnormalities and phleboliths. Magnetic resonance imaging (MRI) is the best imaging technique for evaluating vascular malformations extension to the adjacent structures[41]. MRI can detect muscle hypertrophy in the nearby structures, and can differentiate venous and lymphatic malformations from simulating lesions[39]. Magnetic resonance venography is the best imaging technique for detecting deep vein anomalies[39]. The concordance rate for a prenatal diagnosis of Klippel-Trenaunay Syndrome by color Doppler ultrasound and MRI is 50%[42].

Venography and lymphoscintigraphy can also be used to assess venous and lymphatic anatomy, respectively. However, deep vein of the calf and thigh may not be demonstrated on venography[3]. Near-infrared fluorescence lymphatic imaging has been used to assess the spatial and temporal resolution for contractile function[43]. Klippel–Trenaunay Syndrome with gastro-intestinal involvement may show diffuse elevated abdominal activity on Technetium-99m-labeled red blood cell imaging[44].

The treatment of Klippel–Trenaunay Syndrome is mainly nonoperative and focuses on the symptoms. A multidisciplinary team is necessary for achieving optimum treatment results. Many complications may develop when the patients grow up; then prevention of these complications is important.

Capillary malformation can be treated with a pulsed-dye laser[4]. Many treatment sessions are required to achieve optimum results. The early treatment of capillary malformation since 2-weeks old with a 595-nm pulsed-dye laser was reported with excellent results[45].

Venous malformations and varicosities may cause pain, thrombus formation with thrombophlebitis, and chronic venous ulcers. Simple pain can be managed by oral analgesic and leg elevation. External compression may decrease pain, lessen intravascular coagulation, and protect the lesions from minor trauma[46]. Endovenous laser ablation can be used to destroy venous malformation or embryonic veins[47-49]. For lateral embryonic veins that have no fascial encasement and have a very superficial location, sclerotherapy is a good option to avoid thermal skin burn by using endovenous laser abrasion[50]. A sclerosing agent, such as sodium tetradecyl sulfate, can extend to deep venous systems. Endovenous laser abrasion can be used to facilitate sclerotherapy by obliterating the outflow vein before sclerotherapy to prevent extension of the sclerosing agent[47]. Endovenous treatment with non-migration-tissue adhesive agents, such as N-butyl cyanoacrylate, was recently reported[51]. Excision of the venous malformation, venous stripping, or direct perforator ligation should be performed in selected patients, such as those with a large embryonic vein that is not suitable for a less invasive procedure or severe cosmetic or functional impairment by a mass effect[9,52]. Five years freedom of pain and freedom from the need for a secondary procedure were reported in 59% and 74% of cases, respectively[52,53]. Identification of the patency of deep vein is necessary before these surgical operations. Surgical reconstruction of the missing deep vein for improving a chronic wound in the affected limb was recently reported[12].

A limb-length difference less than 2 cm should be managed by insertion of a heel at the contralateral limb to avoid scoliosis or gait disturbance. A surgical procedure, such as osteotomy or epiphysiodesis, should be considered if the limb length difference is more than 2 cm[9,10].

Lymphatic malformation can cause a mass effect that disturbs limb function. Debulking of the lymphatic malformation can remove mass, but with the chance of recurrent pain and cellulitis[9]. The use of a fractional carbon dioxide laser for the treatment of lymphangioma circumscriptum was reported with less thermal injury to the skin[54]. Lymphedema in the affected limb can cause cellulitis and a chronic wound. Compression therapy can diminish edema, improve the cosmetic appearance, decrease the lymphatic volume, and protect against minor trauma[46,55]. Lymphaticovenular anastomosis was reported to reduce edema and recurrent cellulitis in the affected limb of Klippel–Trenaunay syndrome patients[56].

Hematochezia in Klippel–Trenaunay syndrome can originate from venous malformation in the colon and rectum. In the majority of cases, the bleeding is self-limited[26]. Chronic bleeding can cause anemia, which can be treated by oral iron supplementation[24]. More severe bleeding needs surgical resection of the involved bowel segment[23-26].

Endoscopic treatment may be useful only in cases of rare localized lesions[23,26]. Angiographic embolization is used as a bridging procedure before surgical resection to reduce intraoperative bleeding[24]. Recurrent bleeding is common if treatment is performed by selective angiography alone[23].

Enhanced mTor signaling will increase vascular endothelial growth factor expression and then angiogenesis and lymphangiogenesis[57]. Sirolimus or rapamycin is an allosteric inhibitor of mammalian Target of Rapamycin (mTOR)[58]. There are reports of bleeding cessation in Klippel–Trenaunay Syndrome after sirolimus administration[22,26].

Patients with Klippel–Trenaunay Syndrome often have pain, depression, and anxiety that affect their quality of life[59]. Awareness and appropriate psychiatric screening are important for early detection and treatment[60].

Klippel–Trenaunay Syndrome is a rare complex vascular anomaly. Symptoms usually present at birth and may progress in childhood. The nature of the disease and complications lead to the patients having a poorer quality of life and in some cases are life-threatening. Multidisciplinary treatments are required to achieve optimal outcomes.

What is already known on this topic?

Klippel–Trenaunay Syndrome is a vascular malformation associated with limb overgrowth. The clinical manifestation of Klippel–Trenaunay Syndrome consists of: 1) capillary malformations, 2) venous varicosities or venous malformations, and 3) limb hypertrophy.

What this study adds?

It reviews knowledge of the genetic associations of this syndrome, new drugs in clinical trials for the treatment of this syndrome, and new agents used as sclerosing agents.

Potential conflicts of interest

The authors declare no conflicts of interest.

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ทบทวนวรรณกรรมเรื่องกลุ่มอาการคลิปเปิ้ล ทรูนาเน่

อัครพล มุ่งนิรันดร์

กลุ่มอาการ Klippel-Trenaunay เป็นความผิดรูปแต่กำเนิดของหลอดเลือดร่วมกับมีการเติบโตผิดปกติของระยางค์ อาการหลักประกอบด้วย 1) ความผิดรูปแต่กำเนิดของหลอดเลือดฝอย 2) ความผิดรูปแต่กำเนิดของหลอดเลือดดำหรือเส้นเลือดขอด 3) การเติบโตผิดปกติของระยางค์ มีการรักษากลุ่มอาการนี้หลายวิธี บทความนี้จะทบทวนวรรณกรรมเกี่ยวกับอาการ อาการแสดง การวินิจฉัย และการรักษาสำหรับกลุ่มอาการ Klippel-Trenaunay