Klippel Trenaunay Syndrome, Inverse Klippel Trenaunay Syndrome: Hypertrophy of Lower Limbs and Atrophy of the Upper Limbs and Facial Muscles: Case Report and Literature Review

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Abstract

Introduction: Klippel Trenaunay Syndrome (KTS) is a rare, congenital malformation. Several theories have been postulated to describe its pathogenesis. However, the exact etiology is not known. It’s characterized by a triad of (1) haemangioma due to capillary malformation, (2) bone and soft tissue hypertrophy, and (3) varicose veins. Interestingly, lipoatrophy rather than hypertrophy of the involved limbs had been described in some cases. The clinical presentation of this syndrome is variable ranging from minimal disease to severe presentation such as significant cosmetic disfiguring, life threatening bleeding and embolism. The KTS is classified according to severity. This is important step in away to educate patients, to predict prognosis and to set treatments, especially in severe cases. Physicians should not only be attentive to the physical aspects but also to the psychological and social aspects of KTS.

Case presentation: A 16-year-old boy presented with multiple port-wine stain type vascular anomalies and varicose veins. Also, there was a marked deforming enlargement of his right foot, right knee and number of his left toes with, striking gigantism of both lower limbs. This is consistent with clinical presentation of KTS. Furthermore, there were additional features matching myotonic dystrophy outlook; face showed a remarkable lipodystropy with bilateral upper limbs wasting and atrophy. This could represent the Inverse- Klippel Trenaunay Syndrome. According to our knowledge, this had never been reported to be associated with Klippel Trenaunay Syndrome.

Conclusion: Klippel Trenaunay and Inverse Klippel Trenaunay Syndrome can be seen in the same patient.

Keywords: Klippel Trenaunay syndrome; Inverse Klippel Trenaunay syndrome; Myotonic dystrophy; Aterio-venous malformation; Varicosities; Port wine haemangiomia; Limbs hypertrophy

Abbreviations: KTS: Klippel Trenaunay Syndrome

Introduction

Klippel Trenaunay Syndrome is a rare mesodermal abnormality. It has three major features: 1) vascular naevus, 2) hypertrophy of soft tissue and bony overgrowth, and 3) varicose veins. It has a wide spectrum of presentation, from truncular involvement to extratruncular and from infiltrating to limited form of presentation [1-5].

Klippel Trenaunay Syndrome must be differentiated from the Parkes-Weber syndrome [6]. Both are characterized by overgrowth limbs. Both share similar clinical features, but represent separate clinical entities with different pathogenesis and natural history. While the key vascular components of Klippel Trenaunay Syndrome is capillary-lymphatic-venous malformation [7], the Parkes-Weber syndrome comprises a congenital persistence of multiple microscopic arterovenous fistulas and varicosities [8]. However, the management and prognosis of these two syndromes are distinctly different.

The diagnosis of KTS is merely clinical and the treatment is conservative unless complications occur [3]. We are presenting a case of classical KTS with elements of hypotrophy resembling myotonic dystrophy features with brief review of KTS literatures.

Case Report

A 16-year-old male patient presented on September, 2011 to the emergency room with 2 weeks history of increasing fatigue to the extent that he can’t carry out his usual daily activities. He described a persistence pain and swelling of his left lower limb which has been progressively increasing with walking and standing. The swelling doesn’t subside by lifting of the limbs or lying down straight on his bed. It was accompanied by continuous blood oozing from an ulcer on the medial lower part of the left shin. He gave a history of enlarged right knee and foot and his left leg since birth, which increased with time as he grows up. The patient did not have paresthesia. There was no history for haematuria or rectal bleeding. In systemic review there were no respiratory, cardiovascular or gastroenterology symptoms and no neurological complains. Parent and siblings are normal.

Physical examination demonstrates a teenager that’s not in distress. His vital signs were stable. Abdominal examination was normal apart from a large spleen. His rectal examination showed no blood. Lower limbs examination showed massive enlargement of his right foot and knee with significant hypertrophy of several toes in his left foot (3rd, 4th and 5th toes) (Figures 1A-1C). Oozing of blood was noticed from an ulcer, which was situated over the medial aspect of the left shin, with evidence of cellulitis (Figure 2). Skin examination showed multiple well-demarcated, vascular areas on the trunk and upper lateral left thigh (port wine stain), which were not painful or tender. Multiple ulcers: Case Report and Literature Review. J Clin Exp Dermatol Res 2013, 4:1
varicose veins were present over the medial aspect of his leg and over the trunk anteriorly and posteriorly (Figure 3). Patient’s face showed gross lipodystrophy, wasting of sternomastoid muscles and upper arms muscles, bilaterally (figure 4A-4D). There was no motor weakness despite the noticeable muscular atrophy. Neurological examination showed no cranial nerves abnormalities. There was no scoliosis, skeletal or spinal anomalies.

Laboratory investigations revealed very low hemoglobin of 3.8 g/dl (normal range 13.5-18 g/dl), low haematocrit of 13.1% (normal range 38.8-50%), low mean cell volume of 56.8 fl (normal value 76-96 fl), Low mean cell hemoglobin of 16.4 pg (normal value 27-32 pg), and low mean cell hemoglobin concentration of 29.0 g/dl (normal range 30-36 g/dl). There was a profound iron deficiency with an iron level of 23 mcg/dl (normal value 6-170 mcg/dl). Other laboratory results including electrolytes, liver function, renal function, and coagulation parameters were normal. Urine analysis showed no haematuria and stool showed no occult blood. Musculoskeletal x-rays revealed no distorting bony overgrowth (hyperostosis).
On the basis of the above triad of port wine stain, limb hypertrophy and varicosity diagnosis of Klippel Trenaunay Syndrome was made. The patient was treated conservatively by elastic compression stockings, systemic antibiotic, daily dressing of an ulcer region and blood transfusion. With this conservative treatment his bleeding ulcer diminished spontaneously, his blood level increased and his ulcer started to heal. Patient was giving an appointment to the surgical outpatient clinic for regular dressing of his ulcer and has been advised to keep his limb elevated whenever possible.

Discussion

The constellation of soft-tissue hypertrophy, varicose veins and a cutaneous hemangiomatous lesion is characteristic of Klippel Trenaunay Syndrome.

The history of the patient revealed a marked interval progression of soft-tissue hypertrophy which occurred with his growth. The patient and his parent stated that the sizes of his limbs were growing excessively with time, a feature that is reported in KTS.

Gingivitis is a result of bone elongation or circumferential soft-tissue hypertrophy [9]. Girls are more affected than boys. The left side is more involved than the right. This preferential of left side involvement suggests some mechanical factor responsible [10]. The condition may involve half of the body and give rise to true hemi-hypertrophy (bilateral and contra lateral involvement occurs). Gigantism of the whole limb may be produced or hypertrophy may be confined to part of the extremity [10]. In this patient, the gigantism involved different parts of both lower limbs with more prominent hypertrophy changes in the right lower limb (right knee and right foot). Left leg showed less hypertrophy changes that confined to the lower end of the left leg and the third, fourth and fifth left toe.

Danarti et al. reported that Klippel Trenaunay Syndrome is defined by a coexistence of nevus flammeus and overgrowth of one or more limbs [4]. They reported that, deficient growth of an affected limb may likewise be noted. Hence, a term inverse Klippel Trenaunay Syndrome has been proposed by them. They collected from the literatures a number of cases of Klippel Trenaunay Syndrome associated with deficient growth such as shortening or hypoplastic muscle mass of the affected extremity. They proposed that some patients may carry compound heterozygotes ‘plus’ and a ‘minus’ allele at the responsible gene locus, and the post zygotic recombination may give rise to two different cell clones that are homoygous for either allele [4].

Features of Klippel Trenaunay Syndrome have been reported in myotonic dystrophy patient [11]. Myotonic dystrophy: an autosomal dominant disorder, is the commonest muscular dystrophy in adults [12]. The clinical severity and age of presentation are extremely variable [12]. The mean age at onset of myotonic dystrophy lies between 20 and 25 years [13]. Absence of clinical myotonia in the adult myotonic dystrophy patients varies from 10% in one study to 45.8% in another study [14]. Our patients showed external features of myotonic dystrophy: facial muscle lipodystrophy and wasting of the neck sternomastoid and upper limbs muscles.

To our knowledge, this is the first case having bilateral wasting of both upper limbs and having a myotonic dystrophy like face with presence of a typical features of Klippel Trenaunay Syndrome. Apart from the outlook of myotonic dystrophy, the patient has no other feature of myotonic dystrophy. Our patient may be having a combined Klippel Trenaunay-inverse Klippel Trenaunay Syndrome or he has an incomplete presentation of myotonic dystrophy and KTS.

Literatures Review

Historic overview

Long time ago, Virchow and both Hebra and Kaposi described the condition as elephantiasis telangectodes [10]. In 1900, the famous paper of two French physicians "Maurice Klippel and Paul Trenaunay" about angiodysplastic disorder came out. Where they described two patients with haemangiomatous lesions of the skin associated with asymmetric soft tissue and bone hypertrophy, and coined the term “naevus variqueux osteohypertrophique” [15]. This mesodermal abnormality syndrome characterized by clinical trial of (1) port-wine stain due to capillary malformation, (2) bone and soft tissue hypertrophy; and (3) varicose veins.

Etiology

The precise etiology is unknown. The KTS syndrome is generally thought to occur sporadically [16]. However, in some cases, clinical manifestations of the syndrome have been found in family members, suggesting an autosomal dominant inheritance [16]. The presumed pathogenetic pathway is that of mesodermal developmental derangement, leading to maintenance of microscopic arteriovenous communications in the limb bud, with consequent development of the naevas, superficial varices, and limb hypertrophy [17]. Several hypotheses regarding cause and pathogenesis in KTS exist, but none explains the full characteristics of KTS. Hypotheses include an alteration in vascular remodeling, perhaps at the level of altered angiopoietin-2 antagonism [18]. Servelle’s theory stated that there is a primary obstruction of the venous system resulting in venous hypertension and thus development of abnormal venous pathways and tissue overgrowth [19]. Also, maintenance of microscopic arteriovenous communication in the limb bud vein had been proposed [17]. Others suggested alteration of the balance between angiogenesis and vasculogenesis, a process that is controlled by numerous genes [20].

Clinical presentation

The classic clinical triad includes venous varices, cutaneous capillary malformations, and tissue hypertrophy that usually involve the extremities. On the other hand, in some subsets of patients only 2 of the 3 classic findings are present [21]. The clinical presentation of KTS is variable [22]. It ranges from port wine stain and few varicose veins causing cosmetic deformity to severe disability associated with massive limb overgrowths, chronic pain syndrome, skin infections and arthritis [23]. Thrombo-embolism and life-threatening pelvic or recurrent rectal bleeding as a result of venous malformations had been reported [24].

Deep venous system anomalies are reported to be present in 8% to 18% of patients with KTS [25]. However, others reported prominent superficial varicose veins are present in a majority of patients with Klippel Trenaunay Syndrome [9,26]. In over two-thirds of patients, a characteristic incompetent lateral venous channel arises near the ankle and extends a variable distance up the extremity to the infrainguinal or pelvic deep venous system [27]. This venous malformation frequently present as persistent embryonic veins, of which the lateral marginal vein (the vein of Servelle) has been the most typical finding, which found in 68-80% of patients [28].

Deep vein anomalies range from venous hypoplasia to frank aneurysm and valve hypoplasia to avulsion. The prevalence of deep venous aplasia or hypoplasia, as detected with venographic techniques (ascending venography and varicography), ranges from 18% [27] to
Lymphatic malformations have also been common in up to 70% of cases [1], that include primary lymphedaema, cystic hygroma or lymphangiectasia associated with reflux of chyle [29]. Varicose veins and venous malformations can involve abdominal and pelvic organs. Rarely, patients with KTS can have intraosseous vascular malformations [1]. Genitourinary system involvement includes the penis, scrotum, vagina, vulva, and bladder. Bleeding from the vascular malformations can present as haematomata, haematuria, rectal bleeding, intracerebral or intraspinal haemorrhage. Cha et al. reported that GI tract involvement may be more common in KTS than previously believed because most of cases remain unrecognized without overt symptoms [30].

Although Klippel Trenaunay Syndrome generally involves only one of the lower extremities, bilateral involvement, upper extremity involvement, single limb involvement (in 80-85% of cases) or extension into the trunk may occur [9]. The lower limb is the site of malformation in approximately 95% of patients [18,31]. The bony abnormalities may affect all bones in an extremity or limited to one or two bones. The enlargement of the extremity consists of bone elongation or circumferential soft-tissue growth of the affected limb [9,27]. Hypertrophy is caused by local hyperemia and secondary venous stasis [32] which are attributed to arteriovenous shunting and venous anomaly [33].

Bone and soft tissue hypertrophy may be evident at birth or may become evident as the patient grows [34]. The cutaneous vascular lesion is generally a capillary malformation and usually involves the enlarged limb, although involvement of the whole side of the body or of the contralateral limb may be seen [9,27]. In addition, other bone deformities can be seen such as macroductly, syndactyly, split hand deformity, phalangeal agenesis and hip joint dislocation [35]. Soft tissue hypertrophy may be limited to alocalized mass on the back or chest, or it can be diffuse involving an entire arm or leg [29].

The capillary hemangioma or port-wine stain usually presents first [31]. This hemangioma has a distinct, linear border that respects the midline and is often increase on the lateral aspect of the limb. It is typically of the nevus flammeus type, but cavernous hemangiomas with port wine stain or lymphangiomata may also occur [31]. Hemangioma depth is variable. It may be limited to the skin or extend deeper to subcutaneous tissue, muscle, bone, and visceral organs, which may lead to internal hemorrhage that may manifest as haematuria or haematochezia. Large cutaneous lesions may sequester platelets leading to Kasabach-Merritt syndrome, a type of consumptive coagulopathy [36]. Interestingly, cases of epidermal haemangioma and angiomylipoma have been reported to occur at the same segmental level as cutaneous haemangioma in KTS syndrome [37].

Complications

Klippel Trenaunay Syndrome is associated with both local and systemic complications. Local complications include Extremity pain, stasis dermatitis, cellulitis, ulceration and spontaneous cutaneous hemorrhage. Chronic venous insufficiency, coagulopathy, thrombosis or thrombophlebitis are commonly encountered in KTS [9,27,32]. Gangrene can occur as a result of thrombophlebitis. Other systemic complications include consumptive coagulopathy and congestive cardiac failure. Coexisting ipsilateral angiomasits may be exemplified by neurovascular anomalies such as cerebral arteriovenous fistulae [38], and spinal cord arteriovenous malformations [39]. Abdominal viscera can be affected by ipsilateral angiomasits that involve the colon [34], and the urinary tract [40] with resulting rectal bleeding and haematuria. Intrathoracic manifestations include increased liability to pulmonary embolism [27], pulmonary vein varicosities [33] and lymphangiectatic sclerosis, that give rise to pleural and pericardial effusions [41]. Renal system involvement might occur with a renovascular hypertension [42]. Clinical sequelae of the lymphatic component of the syndrome include lymphangitis, cutaneous lymphatic vesicles, lymphorrhoea, or mass effect from macrocystic portions of lymphatic malformations [43].

Diagnosis

Diagnosis is essentially a clinical one. Proper physical examinations of the limbs and other part of the body are important. Work-up of the lesion may involve noninvasive imaging like Doppler ultrasound scanning of the venous system of the leg to establish patency, incompetence, thrombosis, arteriovenous shunting and malformations and hypoplasia anomalies. Clinical examination and ultrasound can rule out diagnosis of KTS [44]. Other non invasive techniques include standard radiography to measure limb length, and magnetic resonance imaging (MRI) to look for bone, fat, muscle hypertrophy and lymphodema can be utilized. Contrast venography and computed tomography scans can be used to evaluate deep venous system and collateral, especially when ablation of dilated superficial embryonic vein is under consideration [3]. Finally, lymphoscintigraphy can be used to evaluate the lymphatic system.

Management

Although most patients do well without treatment, management of this syndrome includes careful diagnosis, prevention and treatment of complications [45]. There are some absolute indications of treatment such as haemorrhage, infections, acute thromboembolism and refractory ulcers. Generally, the management of this syndrome can be divided into medical and surgical interventions [32]. Multidisciplinary management approach for KTS is warranted [3]. The paediatrician, internist, phlebologist, orthopaedic, plastic and vascular surgeons, interventional radiologist, cardiologist, vascular internist and a physical therapy physician can all be involved in KTS patient’s management [1].

Management is largely conservative and the extent of diagnostic evaluation is determined by the planned treatment. Stockings or pneumatic compression is the hallmark of conservative management. It’s indicated for chronic venous insufficiency, lymphedema, recurrent cellulitis, and recurrent bleeding. Percutaneous sclerosis of localized venous malformations or superficial venous varicosities may be indicated in some patients [46]. Patient with severe chronic venous insufficiency, disturbing cosmetic appearance, and complications of haemangiomai, may benefit from surgical treatment. Techniques for ablation of superficial veins and malformations are individualized and may include sclerotherapy with alcohol or foam, that showed a good success but can cause nerve injury and cutaneous damage [47]. Foam sclerotherapy, with sodium tetra decyl sulphate and polidocanol, has been shown to be of a low risk and effective treatment for superficial venous disease [48,49]. Patient’s cosmetic satisfaction with multiple session foam sclerotherapy has been reported in about 71.5% of treated patients [50]. Others treatment approaches includes endovenous thermal ablation, surgical stripping and phlebectomy. Local wound care, compression dressings, special orthopaedic footwear and lifestyle modification may also be required to manage activities of daily living and improve the function of the limb [51]. An amputation may be required for bone overgrowth with non-healing de-cubitus ulcers, for recurrent bleeding from haemangiomas or when the large size of the
limb had interfered with the daily activities [32]. Care must be taken because the condition of patients with Klippel-Trenaunay Syndrome may worsen if intervention is performed on dilated superficial collateral veins associated with deep vein hypoplasia. Imaging before vascular interventions must confirm venous anatomy and deep venous drainage [26].

Regarding limb hypertrophy, heel inserts are generally sufficient for limb discrepancies of 1.5 cm or less. For greater discrepancies, orthopedic surgery may be considered. For overgrowth of one limb epiphyseodesis and for severe arthritis total knee arthroplasty has shown good results. [23]. In addition, excision of soft-tissue hypertrophy and epiphyseodesis can be used to control leg length discrepancy [26-28].

Vascular abnormalities are congenital and thus do not respond to agents used in the treatment of haemangiomas, such as prednisone and interferon-α [32]. Nowadays, pulsed-dye laser treatments can lighten the superficial haemangioma component [52]. However, the deeper vascular malformations are often inadequately treated. Their large size is also a factor that hinders rate of clearing with laser treatment. Second-generation pulsed-dye lasers have long pulsed widths, which, along with the dynamic cooling device, allows for safe use at higher frequencies and greater clinical improvement. Also, the treating clinician may consider the use of laser treatments with the 595-nm V-beam long-pulsed-dye laser for a better clinical improvement of the skin lesions [32].

Cellulitis and thrombophlebitis can be managed with analgesics, antibiotics, and corticosteroids. In patients with a history of recurrent cellulitis, intermittent or prophylactic antibiotics may be considered [1].

Anticoagulant therapy is indicated in acute thrombosis and prophylactically prior to surgical procedures [22]. Intraoperative use of tourniquet will decrease bleeding and selective use of an inferior vena cava filter will prevent pulmonary embolism [3].

Gastrointestinal and urogenital involvement is not low as was previously thought and may be seen in about 20 % of cases [27,53,54]. Persistent haematochezia, haematuria, and vaginal and oesophageal bleeding are considered indications for surgical intervention. Those patients usually require endoscopic cauterization, but sometimes refractory bleeding may require colonic resections [55,56]. Finally, microsurgery, endovascular embolization, and, more recently, stereotactic radiosurgery are used for the treatment of the spinal vascular malformation [21].

Conclusion
It is important to recognize that Klippel-Trenaunay Syndrome is a unique that requires a comprehensive multidisciplinary management approach for a better patient care. Lifelong clinical follow-up is mandatory in such patient as the natural history of the various organs involvement is one of progressive deterioration.

Consent
Written informed consent was obtained from the patient and his family for publication of this case report and any accompanying images.

Authors' Contributions
HS wrote the manuscript and compiled the figures. AI edited the manuscript. All authors analyzed and interpreted the patient data. All authors read and approved the final manuscript.

References


