

## KLIPPEL-TRENAUNAY SYNDROME WITH RARE ASSOCIATED COMPLICATIONS – A CASE REPORT

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### Abstract

Klippel-Trenaunay Syndrome (KTS) is a rare congenital malformation consisting of venous, capillary and lymphatic abnormalities, in addition to hypertrophy and overgrowth of the bony and/or soft tissue of the affected limbs. We report a unique case of KTS due to its complex association of complications (hydronephrosis, rectorrhagia and splenomegaly).

**Key words:** Klippel-Trenaunay Syndrome (KTS), hydronephrosis, rectorrhagia, splenomegaly

### Introduction

Klippel-Trenaunay Syndrome (KTS) was first described in 1900 by physicians Klippel and Trenaunay, who evidenced the constellation of three major clinical features: capillary, venous and lymphatic vascular malformations; varicose veins with an early onset; and bony and/or soft tissue hypertrophy and overgrowth [1]. One of the lower limbs is the most frequent involved site and it is usually hypertrophied [2].

Other common features of KTS include: hyperhidrosis, skin atrophy, verrucae, dermatitis, thrombophlebitis, and cellulitis [3]. Deep vein thrombosis, pulmonary embolism, gram-negative sepsis and coagulopathy are sometimes present and represent life-threatening complications [4]. While most KTS cases are sporadic, theories arguing for an autosomal dominant (AD) mode of inheritance have been formulated. It was noticed that in the case of some affected individuals, first-degree relatives presented a high incidence of capillary malformations and varicose veins [5]. KTS has been linked to two balanced reciprocal translocations, namely 46,XX,t(5;11)(q13.3;p15.1) [6] and 46,XY,t(8;14)(q22.3;q13) [7]. Moreover, a genetic predisposition for the development of KTS has been established following the discovery of a susceptibility gene for the syndrome, specifically the angiogenic factor gene VG5Q, the up-regulation of which results in increased angiogenesis [8]. As these tests are unavailable in most clinics, a diagnosis of KTS, be it idiopathic or genetic, is usually based on clinical signs, ultrasound and imagistic studies.

### Case presentation

An 8 year and 7 month old child, first newborn of healthy, nonconsanguineous parents aged 20 and 24 was referred to us. The patient's mother had an uneventful pregnancy, with no history of medication intake. However, both parents worked in a toxic environment (car cable factory) both prior and throughout pregnancy. Family history is unremarkable. Examination of the infant after birth revealed multiple diffuse cutaneous hemangiomatosis of the port-wine type (covering 60% of body surface and involving completely both legs and the left arm, and part of the gluteal region, genitalia, trunk and face); edema and hypertrophy of the above-mentioned limbs; and bilateral syndactyly of the second and third toes. Ultrasound of the abdomen showed bilateral congenital hydronephrosis (stenosis of the vesicoureteral junction on the right and stenosis of the pielo-ureteral junction on the left). Chromosomal analysis revealed the 46,XY karyotype.

Over the years, the patient underwent surgery for the following conditions: hydronephrosis (right ureterostomy at 5 months of age followed by ureter reimplantation at 10 months of age; left Hynes-Anderson pyeloplasty at 5 months of age); left inguinal hernia; congenital verrucous lesions of the endobuccal and perianal cavity; and periodontal abscess. Patient history is significant for the following: pneumocystis pneumonia; rectorrhagia; recurrent bronchiolitis; and profound venous thrombosis and thrombophlebitis (for which he is taking anticoagulant treatment).

At the moment (Figure 1) the patient presents, throughout the entire length of the lower extremities, edema and hypertrophy, with multiple dilated and tortuous venous varicosities. The left lower extremity is more severely affected than its counterpart (50 cm versus 43 cm in girth at the level of the hip and 34 cm versus 31 cm at the level of the thigh). Moreover, the left leg presents an overgrowth in length of 4 cm compared to the right leg; this difference was 2 cm two years ago. The patient's left upper extremity presents muscular hypoplasia. Doppler echography demonstrates normal arterial and venous blood flow all throughout the affected members; however, there is destruction of the venous valves and higher blood flow rate in the left leg versus the right leg.

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Port wine stains are present in the same distribution as upon birth. Abdominal ultrasound reveals second degree

hydronephrosis on the left, first degree hydronephrosis on the right and splenomegaly (14.5 cm).



Figure 1: Evidence of limb hypertrophy and hyperplasia, left lower limb overgrowth, tortuous venous varicosities, port-wine stains and syndactyly.

MRI shows multiple hemangiomas in the subcutaneous tissue all throughout the body and a scrotal lymphangioma. MRI angiography reveals normal arterial system with no evidence of AV fistulas in the lower extremities (Figure 2)

while MRI phlebography reveals dilation of the superficial venous system of the affected members and multiple varicose venous tracts in the subcutaneous tissue of the hips and calves (more severe on the left) (Figure 3).



Figure 2: MRI Angiography with no evidence of AV fistulas.



Figure 3: MRI Phlebography evidencing calves varicosity.

The patient has a normal mental development, with an IQ of 103. He was diagnosed at 3 years of age with developmental language disorder but responded very well to logopedic therapy. He attends regular school and is well integrated among his classmates, despite his inability to participate in group activities that require physical exercise. Current management of our patient includes orthopedic shoes (which are changed every 6 months), lymphatic drainage massage (2 x week), compression garments and monthly INR monitoring.

**Discussions**

KTS affects males and females in an equal proportion, irrespective of their ethnic background [2, 9]. Its features

usually develop slowly during childhood and are fully present at birth in rare cases only. However, capillary malformations are seen at birth in 98% of cases [9]. Both upper and lower extremity involvement is present in about 10% of patients [3]. For the 1956 – 1981 period, KTS limb involvement in Mayo Clinic patients was unilateral in 85%, bilateral in 12.5%, and crossed-bilateral in only 2.5% [3]. Our patient’s involvement of both lower and the left upper extremity represents a rare case of KTS.

In a study conducted by Jacob et al [10] on 246 patients, the frequency of KTS clinical features include: port-wine stains in 98% of patients, varicosities and/or venous malformations in 72% and limb hypertrophy in 67%, all of which are present in our patient. The frequently

increased limb girth in KTS is mainly due to lymphedema and soft-tissue hypertrophy [9]. Hemangiomas in KTS may be limited to the skin or may extend into the subcutaneous tissue [11], as in the present case. Syndactyly, which characterizes the child, is a common finding in KTS [9]. The muscular hypoplasia seen in the patient's left arm is a relatively rare finding in KTS and is thought to be related to the existence of intramuscular lesions [12].

Several theories have been formulated to explain the osseous growth that is seen in an overwhelming majority of KTS patients. One theory argues that it could be attributed to venous hypertension [13]. Another suggests that it could be the result of a genetic defect that leads to both vessel malformations and excess limb circumference and length [9]. A third theory proposes that a mesodermal defect during fetal development results in delayed regression of the embryonic vascular reticular network in the developing limb, which leads to increased blood flow (within normal limits, however), higher bone growth rates, venous abnormalities and cutaneous nevus development [14]. Our patient's case supports the last theory listed, as Doppler echocardiography demonstrates normal but higher blood flow in the more effected extremity versus its less affected counterpart.

On a group of 40 patients with KTS, Głowiczki et al [3] found that the average difference in length between the affected and non-affected lower extremity was 2.39 cm, with only two patients experiencing an accentuation of more than 1 cm in this difference over a two year period. The 4 cm length discrepancy between the patient's legs and the 2 cm lengthening difference he experienced over the past two years account for an unusual case of KTS.

Common complaints of patients with KTS, which have been experienced by our patient as well, include: pain, swelling, bleeding, superficial thrombophlebitis, cellulitis, heaviness and weakness in the affected limbs [9, 11]. In addressing these problems, therapeutic approach of KTS is usually conservative – compression garments; pain management; anticoagulant therapy when there is

predisposition to thrombosis; prophylactic antibiotic therapy in recurrent cellulitis; lymphatic drainage in cases of significant edema; and rigorous hygiene of affected limbs to prevent infection and cellulitis [3,9,11].

The case we present is particularly interesting as the patient has a history of hydronephrosis, splenomegaly and rectorrhagia, all of which have rarely been individually reported in association with KTS, and, to our knowledge, never together. Splenomegaly in KTS has been linked to high venous pressure due to splenic vein stenosis [15] and/or splenic hemangioma/lymphangioma [16]. Some cases of rectorrhagia are though to occur as a result of the hypogastric vein being overloaded by the posterolateral veins of the affected extremity, which impedes proper pelvic drainage and leads to dilatation of hemorrhoidal veins and rectal bleeding [3].

Major differentials for KTS include Parkes Weber syndrome (PWS), Servelle-Martorell syndrome (SMS) and Proteus syndrome (PS). As demonstrated by arteriography, in KTS, contrary to PWS, there is absence of arteriovenous (AV) fistulae, especially at the epiphyseal plate, and there is usually no bone anomaly other than its hypertrophy [3]. SMS can be excluded on the account that, while it represents an association of capillary stains, dilated superficial veins and limb circumferential hypertrophy, it is characterized by undergrowth and not overgrowth of the affected limb, as intraosseous vascular malformations result in cortical bone and spongiosa destruction, leading to bony hypoplasia [4, 17]. In our case, MRI reveals a normal bone structure (Figure 4). The diagnosis of PS can be eliminated because, while patients with PS can experience the capillary, venous and lymphatic malformations of KTS, the most common manifestation of PS is a connective tissue nevus clinically apparent as cerebriform thickening of the palms and soles, which does not characterize our patient; moreover, linear verrucous epidermal nevi and brain structural malformations, which are common in PS, are not seen in our patient either [4].

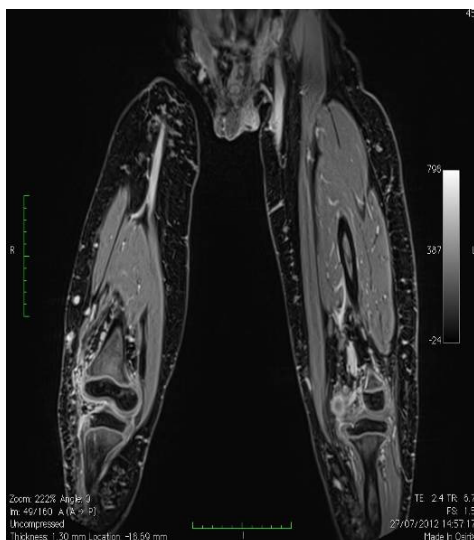


Figure 4. MRI showing normal bone structure.

**Conclusion**

Hydronephrosis, rectorrhagia and splenomegaly have rarely been associated with KTS. To our knowledge in the English literature, this is the first reported case of a patient with KTS who is affected by all three conditions. That, in addition to the unusual three limb involvement, makes our

patient's case noteworthy to report on. As none of the newly-developed genetic testing that could indicate KTS is available in our clinic, we are unable to argue whether the patient's unique condition is sporadic or whether it arose due to a genetic predisposition. The uniqueness of the case makes genetic testing highly advisable.

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