Prenatal diagnosis of Klippel-Trenaunay syndrome: case report and review of literature

F. PEPE1, F.A. GULINO3, A. PRIVITERA2, F. DE LUCA2, G. LEANZA3, M. STRACQUADANIO3


F. PEPE, F.A. GULINO, A. PRIVITERA, F. DE LUCA, G. LEANZA, M. STRACQUADANIO

Klippel-Trénaunay syndrome (KTs) is a rare but well-documented congenital anomaly characterized by cutaneous capillary malformations, soft tissue or bone hypertrophy (or both) and varicose veins or venous malformations. Prognosis depends on severity, progressive nature of the malformations and associated anomalies. As it is a lifelong condition, treatment requires a multidisciplinary approach. We described a fetus in the 20th week of pregnancy who showed at ultrasound examination the presence of multiple anechoic cystic areas involving the right thigh, leg, perineum and abdomen, suggesting KT syndrome. The mother opted for interruption of pregnancy. Autopsy confirmed the diagnosis. We also provide a review of the literature, with emphasis on fetal prognosis and prenatal counselling.

KEY WORDS: Klippel-Trenaunay syndrome - Overgrowth syndrome - Fetal malformation - Limb hypertrophy - Cutaneous capillary malformation - Venous anomalies.

Introduction

Klippel-Trénaunay syndrome (KTs) (OMIM #149000), first described in 1900 by the French physicians Klippel and Trénaunay, is a complex congenital developmental disorder, originally called naevus vasculosus osteohypertrophicus, usually involving the limbs at birth or during early infancy or childhood. It occurs in 1/20,000 to 1/40,000 live births. Neither racial nor geographic predisposition nor sex predilection authors reported in literature. Clinically, it is characterized by the coexistence of a cutaneous capillary malformation ("port wine stain") on an extremity, congenital vascular abnormalities, including varicose veins and venous malformations, and skeletal or soft tissue hypertrophy (localized gigantism) occurring in the same site of the vascular malformation. These descriptions are useful to show the main features of the syndrome, and two among these three descriptions could confirm the diagnosis (1). The vascular capillary malformation may show both superficial (cutaneous) and deep (muscles and bones) components (2).

In 1907, Parkes Weber defined as hemangiectasic hypertrophy the case of a patient who also showed, in addition to the classic triad, an arteriovenous malformation of the affected limb. Since then, the term KT has often been used interchangeably with Parkes-Weber or Klippel-Trénaunay-Weber syndrome. However, it would probably better to reserve the definition of KT exclusively to the classic triad of congenital anomalies, considering Klippel-Trénaunay-Weber syndrome as a separate entity consisting of the triad of KT accompanied by a clinical apparent arteriovenous fistula. Furthermore heterozygous loss-of-function RASA1 mutations were related to patients affected by Parkes Weber syndrome (3). The distinction is important, as treatment and prognosis of these two conditions are different, due to the increased morbidity associated with arteriovenous malformations. On the other hand, hemodynamic insignificant arteriovenous malformations do not preclude a diagnosis of KT (2).

According to the associated vascular findings, KT has been classified into five levels of severity (4). Venous stasis may occur, due to valve insufficiency, varicose ve-
nous, venous malformations, obstructed venous outflow, or abnormal lymphatic drainage (5). Coexisting Sturge-Weber syndrome may also be present in some cases (6). In some paediatric cases it was also described presence of hemimegalencephaly and seizure episodes with KTs (7).

The pathogenesis is unknown. Some theories have been argued in the past, but recently it is believed that KTs is multifactorial disorder due to gene mutations causing an alteration of the tight balance between angiogenesis and vasculogenesis, which is controlled by several genes (8). This is also supported by studies reporting a higher incidence of “port wine stains” in first-degree relatives of patients with KTs (9).

Warhit et al. described this rare syndrome for the first time in the prenatal period in 1983 (10). The aim of this paper is to present a new case of prenatal diagnosis of KTS and to make a review of the literature, with emphasis on prenatal diagnosis and counselling.

Case report

A 37-year-old woman was in the course of her first pregnancy. The father’s age was 41 years. The parents were not relatives and healthy. There was neither family history of congenital malformations nor patient anamnesis of vascular disorders or drug intake. Ultrasound exam performed at 13th week showed a normal single foetus. Following a screening test (NT + free beta-hCG + PAPP-A with nuchal translucency of 3.6 mm) positive for risk of Down syndrome, amniocentesis was performed, demonstrating normal karyotype and amniotic α-fetoprotein levels.

Ultrasound exam performed at 20th week showed an adequate foetal development, but disclosed hypertrophy of the left lower limb with macroscopic alterations of leg and foot morphology. In addition, multiple anechoic cystic areas were detectable in the affected limb (thigh, calf and leg), in the pelvis, in the perineal area, and in the anterior abdominal wall, up to the umbilical cord insertion (Figures 1-5). Morphology and length of long bones were normal in both limbs. The foetal movements and amniotic fluid were normal. The other foetal organs appeared normal. Echocardiography showed normal heart with ventricular golf balls. A diagnosis of KTs was suggested. The patients opted for interruption of pregnancy. Postmortem examination (Figures 6, 7) confirmed the diagnosis. The bones of the left leg were normal in postnatal X-ray.

Figure 1 a, b - Dysmorphic and enlarged left thigh with anechoic area (a) and foot with soft tissues hypertrophy (b, arrow).
Figure 2 - Scan of both legs: difference in circumference with multiple anechoic areas is evident in one leg.

Figure 3 - Multiple anechoic areas in the thigh and leg.
Figure 4 - Anechoic area near to foetal bladder extending to the pelvis and the abdominal wall, up to the umbilical cord insertion.

Figure 5 - Abnormal left foot morphology with marked soft tissue hypertrophy.
Prenatal diagnosis of Klippel-Trenaunay syndrome

Figure 6 - Clinical features of the aborted foetus.

Figure 7 - Clinical features of the aborted foetus.
Discussion

KTs is the prototype of disorders characterized by non-cranial Vascular Malformations and a Dysregulated Growth (VM-DG). Most cases of KTs are sporadic, but familiar cases have been described (11) and, occasionally, cases have been consistent with autosomal dominant inheritance (12). The aetiology is unknown, but polygenic para-dominant inheritance involving mutations or polymorphisms in two or more genes simultaneously, of which one (or more) involved in (lymph)angiogenesis (such as VG5Q gene on chromosome 5) (13) and others in growth regulation, has been proposed. An imprinting disturbance may also be involved (14). This provides an explanation for the variability of the VM-DG syndrome through the numerous possible combinations of the involved mutated genes.

KTs is a lifelong condition that may require different treatments by a multidisciplinary team based on patients’ individual presentation. Prognosis is dependent by severity, progressive nature of the malformations and associated anomalies. Patients with Parkes-Weber syndrome have similar presentation as those with KTs and could often be indistinguishable on physical examinations. However, advanced imaging has made the differentiation between high- and low-flow arteriovenous malformations (AVMs). Low flow AVMs are shown in KTs and have relatively low morbidity, whereas high flow AVMs are more appropriately assigned as Parkes-Weber syndrome. Differentiation is important because high-flow AVMs can cause serious clinical consequences (such as high-output heart failure), more prominent skin manifestations with an increase chance of skin ulcerations, and increased limb-length discrepancies (15).

All paediatric or adult patients have significant morbidity (16, 17). The diagnosis could be done when at least two of the three classic features are present (17). Major findings of KTs include capillary malformations (port wine stains), varicose veins, and bone and soft tissue hypertrophy. The leg is the most commonly affected site, usually with unilateral involvement respecting the midline. In a series of 252 patients, 63% of patients had all three features and 37% had two of the three features (12). Minor findings are visceral vascular malformations involving brain (18), liver, spleen, intestine, kidney, bladder, spine (19) and uterus (20), intestinal lymphangiectasia, lymphedema, asymmetric facial hypertrophy, cataracts, glaucoma, micro or macrocephaly, seizures or mental retardation, polydactyly, syndactyly or macrodactyly. Limb hypertrophy can lead to unsteady gait as a result of leg length discrepancy, but the progression of limb length discrepancy is not uniform nor predictable (16). Involvement of the gastrointestinal tract may be more common in KTs than previously believed, occurring in up to 20% of patients, and it may go unrecognized in patients without overt syndrome.

Possible complications include thrombophlebitis, susceptibility to infection and cellulitis, and bleeding. The most common site of bleeding are the distal colon and rectum, but haematuria or life-threatening menorrhagia may also occur in case of genitourinary involvement. Rapidly enlarging cavernous haemangiomas may sometimes develop in the first year of life, producing high-output congestive heart failure or a consumptive coagulopathy due to intra-lesional fibrinolysis (Kasabach-Merritt syndrome). Congestive heart failure and progressive pulmonary insufficiency may also occur as result of repeated pulmonary emboli (21). When arteriovenous malformations are present (Parkes-Weber syndrome), high-output congestive heart failure is very likely. Parkes-Weber syndrome has also a poor prognosis for limb viability (22).

Classification according to severity is also essential (4) in order to educate patients, predict prognosis and set an appropriate treatment. Fifty percent of patients with KTs could be treated medically, whereas the remainder require surgical intervention. Patients with functional limbs, small edema (or absence of it), bleeding, ulcerations or pain can be managed conservatively, focusing on symptomatic relief. Pulsed dye laser may be used with excellent clinical results in the management of cutaneous capillary malformations (4). This fact may be important in patients with facial port-wine stains, although has been observed spontaneous involution of the cutaneous capillary malformations. Elevation, elastic compression stockings, or intermittent pneumatic compression pumps are frequently used for patients with edema or varicosities of the extremities. Compression stockings are recommended for virtually all patients with KTs, especially when they begin to walk. Compression therapy, however, has no effects on the ultimate size of the limb.

Surgical intervention is controversial and often unnecessary or contraindicated. It requires adequate preoperative examination, carefully weighing potential risks and benefits. Usually, a disproportion of leg length projected to exceed 2.0 cm is a clear indication for orthopaedic surgery. However, only 11% of patients have hy-
pertrophy severe enough to warrant epiphysiodesis, and amputation of a grossly hypertrophied, poorly functioning digit is rarely necessary.

Finally, it has to be considered that this disease bears considerable emotional and social distress, significantly affecting quality of life (QoL). Therefore, especially in cases of severe KT's, physicians should not only be attentive to its physical aspects, but also to its psychological and social drawbacks (24).

In this case-report KT's was detected by ultrasound examination during the 20th week of pregnancy. Ultrasound prenatal diagnosis is rarely reported in literature, but possible since the second trimester (14-15th weeks) of pregnancy. The appearance is a soft tissue mass of an extremity, usually affecting the adjacent trunk. Other findings may include ascites, abdominal hemangiomatous masses, hepatomegaly and hydrops from high-output cardiac failure. Roberts et al. (25) reported a case of prenatal KT's presenting with a complex thoracic multicystic mass associated with progressive unilateral lower limb enlargement. Seoud et al. (26) described a large complex mass with pulsating channels over the anterior fetal chest wall. In an infant with KT's, Mor et al. (27) observed foetal hydrops (edema of the limbs, ascites, and palpable liver); the infant lost 520 g of weight in the first 6 days of life without medication. Christenson et al. (28) made the prenatal diagnosis of KT's complicated by foetal congestive heart failure. The postnatal course was complicated by Kasabach-Merritt syndrome; neonatal cardiopulmonary resuscitation and limb amputation were required. Sahinoglu et al. (29) described a case of prenatal sonographic diagnosis of KT's associated with a spherical, low echogenic mass without any active blood flow located in the umbilical cord. Assimakopoulos et al. (30) reported a clinical case of a foetus with KT's with abdominal hemangiomia appearing on ultrasound examination as intestinal obstruction. Chen et al. (31) described an affected foetus with ascites and second trimester abnormal maternal serum screening in addition to limb hypertrophy and subcutaneous cystic lesions. Coombs et al. (32) described an affected fetus with lower limb venous hypoplasia. 

Trombocytopenia due platelet consumption within the hemangiomia and high-output cardiac failure may complicate the outcome in utero (33). Cerebral atrophy has been reported in a minority of cases, presumably due to diversion of blood to the vascular anomaly (34). Colour flow Doppler studies in some conditions have usually yielded negative results (35).

Three dimensional ultrasound and prenatal magnetic resonance imaging (MRI) may also be used to better demonstrate the mass according to the findings of both modalities, with limb hypertrophy, and multiple hemangiomia, both subcutaneously and internally (36-39).

Peng et al. (40) reviewed outcomes of 21 cases of KT's involving foetal thigh. Among the 21 cases, 28.57% of foetuses showed an isolated thigh lesion, and the other ones had extensive lesions involving pelvis, abdomen, retroperitoneum, or thorax. Prenatal manifestations varied, and included hypoechoic cystic mass with limb asymmetry (95.23%), polyhydramnios (38.09%), cardiomegaly (19.4%), thick placenta (9.52%), non-immune foetal hydrops (9.52%), and oligohydramnios (4.76%). Ten cases (47.62%) underwent to termination of pregnancy, and for those who continued pregnancy, the rate of complications with Kasabach-Merritt syndrome was 36%; neonatal mortality rate was 45%.

In conclusion, the prenatal diagnosis of KT's is well described in the literature as the evidence of limb hypertrophy associated with subcutaneous cystic lesions. Not immune foetal hydrops, ascites, polyhydramnios, cardiac failure, macrosomia, macrocrania, ventriculomegaly, hepatomegaly may be present.

In KT's cases, prenatal counselling is very important, particularly when the lesions are severe with massive diffusion of the disease, as the prognosis is dependent on severity of the malformations and associated anomalies. Prognosis is poor in the presence of extensive lesions, hydrops, and the coexistence of arteriovenous malformations (Parkes-Weber syndrome) due to the high risk of perinatal cardiac failure and Kasabach-Merritt syndrome.

In our clinical case-report the foetus showed typical ultrasound features of KT's, with an evident modification of leg morphology, and an extensive pelvic and abdominal involvement. In addition, abnormal first trimester maternal serum screening for Down syndrome, as already reported by Coombs et al. (32), and cardiac golf ball, were present. Cardiac golf ball has no anatomical and prognostic implication for the foetus and it is a casual association. To our knowledge, this is the first case of KT's with false positive screening for Down syndrome. To explain increased muchar translucency may be suggested a possible alteration in the connective tissue of foetal nape, but this association may also be casual.

**Authors' contribution**

FP performed fetal ultrasound examination and wrote the first draft; all Authors revised the manuscript and approved the final version.

**Conflict of interest**

The Authors declare that they have no conflict of interest.
References

Prenatal diagnosis of Klippel-Trénaunay syndrome