

Andrzej Brodkiewicz[1], Magdalena Pastuszak-Gabinowska[2], Jarosław Peregud-Pogorzelski[1], Krzysztof Łuksza[3], Mieczysław Walczak[4], Martyna Tuziak[4], Maria Giżewska[4]

INCOMPLETE EXPRESSION OF KLIPPEL-TRENAUNAY SYNDROME

NIEPEŁNA EKSPRESJA ZESPOŁU KLIPPEL-TRENAUNAY

[1]Department of Pediatrics, Hematology and Pediatric Oncology
Pomeranian Medical University, Szczecin, Poland
Head: Prof. *T. Urasiński*
[2]Department of Dermatology and Venereology,
Pomeranian Medical University, Szczecin, Poland
Head: Prof. *R. Maleszka*
[3]Aesthetic Medicine Clinic "Beauty Clinic", Poznań, Poland
Head: *K. Łuksza MD*
[4]Department of Paediatrics, Endocrinology, Diabetology,
Metabolic Diseases and Cardiology
Pomeranian Medical University, Szczecin, Poland
Head: Prof. *M. Walczak*

Abstract

Klippel-Trenaunay syndrome (KTS) is a rare, congenital vascular anomaly, defined as a triad including a port-wine stain, underlying bone and soft tissue hypertrophy and varicose veins and/or venous malformations.

***Aim:** Our aim is to present the case of a 13-year-old girl with a delayed proper diagnosis of incomplete expression of KTS presenting with a port-wine stain of her left lower extremity associated with hypertrophy of the affected limb (upon the moment of diagnosis no varicose veins were observed). The patient did not experience any pain in affected limb, nor was she diagnosed with neuropathy – both of abovementioned symptoms are often a significant issue.*

To ensure proper diagnosis, the patient underwent a broad spectrum of diagnostic tests, including physical examination with anthropometric measuring, biochemical tests as well as radiological examinations including CT scan, Doppler vein ultrasound and bone X-ray.

Based on physical examination and test results we were able to establish the diagnosis of incomplete expression of Klippel-Trenaunay syndrome.

***Summary:** The authors aim to emphasise the very rare incidence of KTS, as well as the low level of awareness on the described disease, which resulted in the significantly delayed final diagnosis in the presented case. Establishing the diagnosis of KTS before the onset of severe vascular complications, regular check-ups in the Outpatient Clinic of Haemangioma Care and compression dressing may help avoid/diminish the severity and significantly delay the development of venous failure of the affected limb.*

Key words: children, Klippel-Trenaunay syndrome, port-wine stain, extremity hypertrophy

Streszczenie

Zespół Klippel-Trenaunay (KTS) jest rzadką wrodzoną anomalią naczyniową, dla której charakterystyczna jest triada objawów: plamy typu czerwonego wina, przerosty tkanek miękkich i kości oraz malformacje naczyń żylnych i/lub żylaki.

***Celem** pracy jest zaprezentowanie przypadku 13-letniej dziewczynki z późno rozpoznanym zespołem KTS o niepełnej ekspresji. Główne objawy obejmowały plamy typu czerwonego wina oraz przerost lewej*

kończyny dolnej (w momencie rozpoznania choroby nie stwierdzono obecności malformacji naczyniowych). U pacjentki nie rozpoznano neuropatii, nie skarżyła się również na ból zmienionej chorobowo kończyny. Objawy te stanowią często duży problem u chorych z pełną ekspresją KTS.

W celu postawienia właściwego rozpoznania u dziewczynki przeprowadzono szeroko zakrojoną diagnostykę, na którą składało się badanie przedmiotowe z pomiarami antropometrycznymi, badania biochemiczne oraz obrazowe w skład których wchodziły: badanie USG metodą Dopplera, tomografia komputerowa oraz badanie rtg układu kostnego.

W oparciu o występowanie dwóch z trzech składowych zespołu u pacjentki rozpoznano niepełną ekspresję KTS – bez występowania malformacji naczyniowych oraz bez objawów bólowych i neuropatii.

***Podsumowanie:** Autorzy pragną zwrócić uwagę na bardzo rzadkie występowanie i niewielką wiedzę na temat tego zespołu, co w przypadku prezentowanej pacjentki było przyczyną późnego postawienia rozpoznania. Wczesne rozpoznanie, regularne wizyty w Poradni Leczenia Naczyniaków oraz terapia uciskowa mogą znacznie zmniejszyć dolegliwości i opóźnić w czasie pojawienie się niewydolności żylnej w dotkniętych chorobą kończynach.*

Słowa kluczowe: dzieci, zespól Klippel-Trenaunay, plama typu czerwonego wina, przerost kończyn

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INTRODUCTION

Klippel-Trenaunay syndrome (KTS) (Online Mendelian Inheritance in Man, OMIM – 149000) is a rare, congenital developmental disorder first described in 1900 by two French physicians: Maurice Klippel and Paul Trenaunay (1-6).

Although its exact etiology is unknown, there are many hypotheses regarding the cause of the disease, most based on the probability of mesodermal abnormality during fetal development due to mutated angiogenetic factors (1-6). In this complex process, the different vascular endothelial growth factors (VEGFs) are critical regulators (2). Vascular endothelial growth factors bind to receptor tyrosine kinases (VEGF-R1 and VEGF-R2) and modulate endothelial proliferation and vessel tube formation – an action that is influenced greatly by an antagonist, angiopoetin-2. It is likely that in KTS there is an alteration in vascular remodeling, perhaps at the level of altered angiopoetin-2 antagonism (2). Alterations in the RASA 1 (chromosome 5q), VG50 gene (chromosome 5) and balanced translocation in chromosomes 8q22.3 and 14q13 may also cause vascular malformations observed in KTS (2, 5, 6). It has also been suggested that KTS could result from the action of a mosaic gene abnormality that is lethal to the gamete when present in all cells of the embryo (2).

Klippel-Trenaunay syndrome belongs to the group of combined vascular malformations and has a wide spectrum of presentation. The classic triad of symptoms used to diagnose KTS is: a capillary malformation (port wine stain), a longer and larger extremity as a result of soft tissue and bone hypertrophy and atypical, mostly lateral, superficial varicosity (1-7). Rare cases may present with a shorter and smaller limb instead of overgrowth (2). Patients with at least two of the three cardinal features have been classified as having an incomplete form of KTS (2, 5). Diagnostic test in KTS should focus on the evaluation of the type, extent and severity of the malformation, and on confirming the absence of any clinical significant arteriovenous shunting (2, 4).

A magnetic resonance scan (MR), MR angiography, a computed tomography scan (CT), high quality three-dimensional CD venography, Doppler ultrasonography, contrast venography (contrast arteriography is seldom used) and plain X-rays have multiple advantages in patients with KTS (2).

The management of KTS has been mainly conservative including e.g. compression therapy (mainstay of therapy), massage treatment or intermittent pneumatic compression therapy. Surgery, laser therapy, scleroteraphy and embolotherapy have also been employed (1, 2, 4). Since KTS affects multiple organs, a multidisciplinary approach to the management of this complex malformation is clearly warranted. Prognosis may be very serious (1, 2).

AIM

We present the case of a 13-year-old girl referred to the Department of Pediatrics, Hematology and Pediatric Oncology, Pomeranian Medical University, Szczecin, Poland, due to numerous flat hemangiomas located in the lower left extremity and left gluteal area. Past history: the child of young, healthy, unrelated parents, born on term, Ist pregnancy, Ist delivery, with the birth weight 3400 g and APGAR score 10. Family history was insignificant as far as genetic disorders were concerned.

A single lesion 2 x 3 cm in the lateral aspect of the left lower leg was noted during the neonatal period. New port-wine stains emerged in the same location during the forthcoming years. Starting from the first month of life the girl has been consulted by a neonatologist, numerous pediatricians and surgeons that diagnosed these lesions as pigmentous nevi or hemangiomas, neglecting the symptoms.

At the age of 12 the child was referred to a vascular surgeon due to the exacerbation of the disease within the last 2 years (more new port-wine stains emerged, previously noted stains enlarged). The vascular surgeon made an initial diagnosis of KTS and referred the patient to the Department of Pediatrics, Pediatric Hematology and Oncology, Pomeranian Medical University, Szczecin.

On admission physical examination revealed numerous port wine stains (from 2 x 2 cm to 10 x 15 cm) located in the lateral aspect of the left lower leg and left buttock (fig. 1, 2). The discoloration blanched on pressure. There was a notable abrupt termination of the skin discoloration at the midline appreciated physically by a distinct sharp linear border. There was no evidence of varicosities. Arterial pulses were palpable and intact, without detectable bruits, thrills or pulsating vessels. A moderate discrepancy was observed between circumference of left the lower extremity (at thigh and lower leg) when compared to the right lower extremity. At thigh level the difference was 11 mm, at lower leg level – 10 mm. The lengths of the lower extremities were equal.

Laboratory studies: serine/arginine rich proteins (SR), complete blood count (CBC), platelet count, liver and kidney function tests, serum electrolytes, activated partial thromboplastin time (APTT), international normalized ratio (INR), fibrinogen, D-dimers and urinalysis proved to be normal. Abdominal and left lower extremity Doppler ultrasound and Angio-CT showed no anomalies. Bones show no abnormalities in X-ray examination.

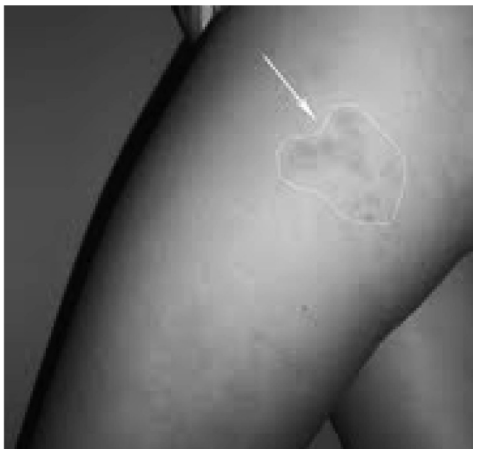

Fig. 1. Numerous port wine stains (from 2 x 2 cm to 5 x 6 cm) located in the lateral aspect of the left upper leg.

Ryc. 1. Liczne plamy typu czerwonego wina (od 2 x 2 cm do 5 x 6 cm) zlokalizowane na bocznej przestrzeni uda.

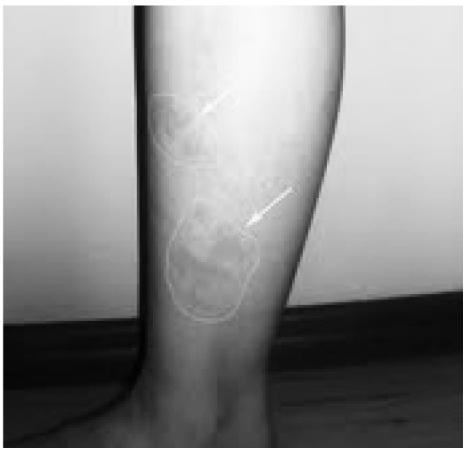

Fig. 2. Numerous port wine stains (from 2 x 2 cm to 3 x 5 cm) located in the lateral aspect of the left lower leg.

Ryc. 2. Liczne plamy typu czerwonego wina (od 2 x 2 cm do 3 x 5 cm) zlokalizowane na bocznej powierzchni lewego podudzia.

On the basis of physical examination (port-wine stains and left limb hypertrophy) the diagnosis of incomplete expression of KTS was established. The patient did not suffer from pain or neuropathy - those symptoms are often problematic for affected individuals and urge them to seek medical help. Treatment included compression therapy (compression garments). Currently the child's condition is followed by the Outpatient Clinic of Haemangioma Care.

DISCUSSION

The prevalence of KTS in children ranges from 1 per 20 000 to 1 per 40 000 in the general population (5, 8). Between the years 1990 and 2009 only two patients with KTS, including the one currently described, were diagnosed in the region of Western Pomerania, Poland and treated in Paediatric Departments in Szczecin. The extremely low number of KTS patients who have been hospitalised, may be the result of low prevalence of KTS and/or lack of proper diagnosis of KTS.

Klippel-Trenaunay syndrome affects both sexes equally; however, some authors described a higher prevalence of the disease in males (5, 8, 9).

Clinical presentation of patients with KTS ranges from mild forms of port wine stains causing only cosmetic deformity to severe disability associated with varicose veins, massive limb overgrowths and life-threatening thromboembolism or bleeding (usually from venous malformations) (1, 2, 4, 5). The lesions are usually found only in one, most frequently, lower limb. This is consistent with our findings. In our patient the lesions were located only within the left lower limb and left buttock. According to Redondo et al, port wine stains are reported to be present in approximately 98% of the individuals affected, and in the majority of cases are already present after birth (10). The abovementioned anomalies are usually red (purple) and flat, with an irregular margin and a clear, sharp border which rarely crosses the midline. They may or may not blanch on pressure (1, 5, 11). The latter is also consistent with our findings. In our patient a single port wine stain was noted after birth, later in life new stains have emerged and those already present have changed in shape and size. All the lesions presented as red wine stains (the color turned intense red after bathing or physical exercise). The stains faded transiently after the application of local pressure (that was a typical symptom of haemangioma). They did not cross the midline.

According to Redondo et al. KTS may be unilateral in 85% of the patients, bilateral in 12.5% and crossed-bilateral in 2.5% with both upper and lower limb involvements in 10% of patients (10). Hypertrophy of the limb is observed in 67% of all the patients (1, 10). The lesions in our patient affected only the left side of the body (lower left limb and left buttock). Hypertrophy of soft tissues along the whole affected limb without discrepancy in limb lengths was noted. The bone CT scan was normal. Physical examination and imaging of the affected limb (angio-CT, Doppler ultrasound) revealed no varicose veins or arterio-venous shunts. On the basis of two (port wine stains and limb hypertrophy) out of three typical symptoms the diagnosis of incomplete form of KTS was established. It should be emphasised that in the patient described, discreet symptoms suggestive of

KTS developed immediately after birth. This is consistent with the findings described by other authors. According to Glowiczki et al., at least one feature characteristic of KTS is seen at birth in more than 90% of patients (2).

Despite the increased number of port wine stains (along with changing shapes and sizes) the symptoms were undervalued and qualified as pigment lesions that did not require diagnosis or treatment.

The limb circumferences were measured for the first time at the age of 13, thus it was difficult to establish the moment when lower left limb hypertrophy started to develop, as even now it is hard to note the abovementioned disproportion.

It seems likely that the rare prevalence of KTS in the Polish population may have contributed to the delay in diagnosis. Klippel-Trenaunay syndrome with complex expression should be distinguished especially from Parker-Weber syndrome (high-shunt arteriovenous malformation) and Proteus syndrome, Maffucci, Bannayan – Riley Ruvalcabe since management and prognosis of these diseases are distinctly different (1, 2, 4, 5, 7).

Several treatment modalities have been proposed for the management of KTS affected individuals. Only multidisciplinary approach to treatment and prevention of possible complications provide optimal care for KTS patients (1, 2, 4). Depending on the age of the affected individuals and the severity of clinical symptoms, the diagnostic team should include a pediatrician or internist, orthopedist, vascular or plastic surgeon, radiologist and physical therapy physician (2). Compression is the hallmark of conservative treatment. Laser, sclerotheraphy (with alcohol or foam), endovenous thermal ablation, surgical stripping and phlebectomy can also be used (2, 4). According to Capraro et al. approximately 25% of patients will approach doctors for cosmetic reasons (1).

SUMMARY

The described patient presented only with cosmetic lesions and was qualified for pediatric care in the Department of Pediatrics, Hematology and Pediatric Oncology and surgical care in the Outpatient Department of Haemangioma Care. The treatment included compression dressing (compression tights). As it was mentioned before a multidisciplinary approach of this subject ensures the best results of therapy.

The authors aim to emphasise that the very rare incidence of KTS, combined with the level of awareness of the described disease resulted in the significantly delayed final diagnosis in the presented case. Establishing the diagnosis of KTS before the development of severe vascular complications in this case, regular visits in the Outpatient Department of Haemangioma Care and compression dressing may help avoid/diminish the severity and significantly delay venous failure of the affected limb.

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Address for correspondence:
Andrzej Brodkiewicz
Department of Pediatrics, Hematology and Pediatric Oncology,

Address for correspondence:
Andrzej Brodkiewicz
Department of Pediatrics, Hematology
and Pediatric Onkology

Pomeranian Medical University
71-344 Szczecin, 1, Unii Lubelskiej St., Poland
Mobile: +48 601-798-066