Klippel-Trenaunay Syndrome

Contents

Klippel-Trenaunay syndrome (KTS) is primarily a rare congenital capillary-venous vascular malformation associated with altered limb bulk and/or length. In 1900, Klippel and Trenaunay first reviewed systematically a condition consisting of capillary nevus, early onset of varicosities, and hypertrophy of tissues and bones of the affected limb. These three features constitute the primary diagnostic criteria of the syndrome today. The additional name Weber is sometimes added to describe those individuals who also have clinically significant arteriovenous malformations as a component of the syndrome, an association noted by Weber in 1918. More than 1,000 cases of Klippel-Trenaunay syndrome have now been reported in the literature (Berry et al. 1998).

Synonyms and Related Disorders

Angioosteohypertrophy syndrome; Klippel-Trenaunay-Weber syndrome; Parkes-Web syndrome; *PIK3CA*-related overgrowth spectrum

Genetics/Basic Defects

1. Etiology
    1. Sporadic occurrence
    2. Somatic mutation of an as-yet-unknown gene
    3. Multifactorial inheritance
    4. Autosomal dominant inheritance with variable expression
2. Genetics of KTS (Wang 2005): three chromosomal abnormalities reported in three different KTS patients
    1. Two balanced translocations t(5;11)(q13.3;p15.1) (Tian et al. 2004)
        1. Chromosomal breakpoints involved in translocation t(5;11)(q13.3;p15.1) have been fully characterized, which has led to the identification of a susceptibility gene, *AGGF1* (previously known as *VG5Q*), for KTS

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   2. *AGGF1* is located on chromosome 5q13.3 and encodes an angiogenic factor
   3. *AGGF1* as the first susceptibility gene that confers a risk to the development of KTS and suggests that that the molecular mechanism for the pathogenesis of KTS is the "increased" angiogenesis. These results are consistent with histological studies that showed an increase in both the number and diameter of the venules in the dermis and subdermal fat of KTS tissues (Baskerville et al. 1985)
2. Translocation t(8;14)(q22.3;q13) (Wang et al. 2001) and an extra supernumerary ring chromosome 18 (Timur et al. 2004) were reported in patients with KTS
   1. Shown to arise de novo, which strongly suggests that genetic factors contribute to the pathogenesis of KTS
   2. The specific vascular gene disrupted by either 8q22.3 or 14q13 breakpoint remains to be identified
   3. The ring chromosome 18, r(18), was mostly derived from the short arm of chromosome 18, and further analyses of the genes on the r(18) may lead to the identification of a vascular gene
3. Terminal deletion 2q37.3 (by comparative genomic hybridization) reported in a patient with Klippel-Trenaunay-Weber syndrome (Puiu et al. 2013)
4. Sporadic occurrence of KTS and a mosaic pattern of KTS features may be explained by the two-hit hypothesis and the concept of paradominant inheritance proposed by Happle (1986, 1987, 1993)
   1. Germline mutations in a KTS gene (e.g., *AGGF1*) are important for development of KTS but not sufficient
   2. A "second hit," somatic mutation in the same KTS gene or in a different gene is required for the development of KTS features
5. Klippel-Trenaunay syndrome belongs to the *PIK3CA*-related overgrowth spectrum (Vahidnezhad et al. 2015)
3. Possible mechanisms/pathogenesis leading to overgrowth of the affected limb: poorly defined
   1. Two phases of manifestations
      1. Increased bulk or girth
      2. Increased length accompanied by bone enlargement
   2. Increased girth and size of bone due to venous hypertension, based on observations following hind leg deep vein ligation in dogs
   3. Atresia of the venous system leading to stasis, edema, varicosities, and ultimately to limb elongation and hypertrophy
   4. Limb enlargement seen in children following thrombosis or ligation of a deep vein postnatally
   5. Overgrowth in fetal life promoted by increased blood flow through the abnormal capillary network and cutaneous venous channels
   6. A mesodermal defect acting on angiogenesis leading to the formation of hemangiomas and varicose veins (Martin et al. 2001)
   7. A defect in the process of vessel remodeling during embryogenesis

Clinical Features

1. Triad (Berry et al. 1998; Cohen 2000)
   1. Combined vascular malformations of the capillary, venous, and lymphatic types
   2. Varicosities of unusual distribution, in particular the lateral venous anomaly observed during infancy or childhood
   3. Limb enlargement
2. Cutaneous manifestations
   1. Primarily a diffuse capillary malformation
   2. Typically present on an affected limb
   3. May be present on any body part
   4. Often presenting as an irregular but relatively linear border
   5. Rarely crossing the midline when present on the trunk, sometimes exhibiting a sharp demarcation

3. Vascular malformations
    1. Typically combined with cutaneous capillary malformation
    2. Persistence of abnormal superficial veins associated with deep venous hypoplasia/duplications and abnormal venous valve formation
    3. Presence of mixed vascular malformations including capillary, venous, arterial, and lymphatic systems
    4. Classification of vascular malformations by Mulliken and Glowacki (1982)
        1. Capillary-venous malformation (CVM): typical finding
        2. CVLM (CVM + lymphatic malformation): common finding
        3. CLAVM (including arterial malformation): uncommon
    5. Congenital in nature
    6. Not responding to agents used in the treatment of hemangiomas such as prednisone or interferon-α
4. Limb hypertrophy
    1. Due to an increase in bulk of the subcutaneous tissues
    2. Bony hypertrophy
5. Sites of involvement (Mueller-Lessmann et al. 2001)
    1. Lower limb most common (about 95%)
    2. Upper limb (about 5%)
    3. Trunk only: uncommon
    4. Orofacial involvement
        1. Jaw enlargement
        2. Facial asymmetry
        3. Malocclusions
        4. Premature tooth eruption
        5. Hemangioma of the lips, tongue, and oral mucosa
6. Sex ratio: males and females affected equally
7. Complications
    1. Abnormal vasculature
        1. Thrombosis
        2. Coagulopathy
        3. Pulmonary embolism
        4. Heart failure (in the presence of significant AVM)
        5. Bleeding from abnormal vessels in gut, kidney, or genitalia
    2. Gastrointestinal varicoses
        1. Bleeding: uncommon but can be fatal (Samo et al. 2013)
        2. Pain
        3. Diarrhea
    3. Protein-losing enteropathy secondary to intestinal lymphangiectasia
    4. Infection is a particular risk for patients with abnormal lymphatic drainage. Antibiotics indicated in:
        1. Cellulitis
        2. Surgery
        3. Injury in an affected limb
    5. Pain due to venous insufficiency or lymphedema in some older children and adults
    6. Venous thromboembolism
        1. Chronic thromboembolic pulmonary hypertension
        2. Subsequent right ventricular failure
    7. Occurrence of ulceration on affected leg
    8. Rare occurrence of skin tumors on the affected limb
        1. Squamous cell carcinoma possibly secondary to a long-standing venous ulcer (De Simone et al. 2002)
        2. Basal cell carcinoma
    9. Pregnancy and KTS: known perinatal risks to both the mother and fetus (Fait et al. 1996; González-Mesa et al. 2012; Stein et al. 2006)
        1. Hemorrhage secondary to increased hemangiomas and varices
        2. Coagulopathy including deep and superficial thrombosis
        3. Acute and chronic disseminated intravascular coagulation
        4. Kasabach-Merritt syndrome (Neubert et al. 1995)
        5. Placental abnormalities
8. Four levels of severity of Klippel-Trenaunay syndrome (You et al. 1983)
    1. Venous dysplasias: phlebectasic dysplasias (Klippel-Trenaunay syndrome)
    2. Arterial dysplasias
    3. Arterial and associated venous dysplasias:
        1. Phlebarterectasia (no arteriovenous shunt)
        2. Angiodysplasias with shunt (Klippel-Trenaunay-Weber syndrome)

4. Mixed angiodysplasias: a typical Klippel-Trenaunay syndrome
9. Diagnostic criteria: Presence of two of the three following cardinal features is sufficient to make a diagnosis (Jacob et al. 1998)
   1. Capillary malformations (98%)
   2. Venous malformations or varicose veins (72%)
   3. Hypertrophy of the affected tissues (67%)
10. Diagnostic criteria and proposed definition: two major features at least one from congenital vascular malformations, which should always include either capillary malformations or venous malformations and at least one from disturbed growth (bi or bii) (Oduber et al. 2008)
    1. Congenital vascular malformations
       1. Capillary malformations (CMs). This includes port-wine stains
       2. Venous malformations (VMs): This includes hypoplasia or aplasia of veins, persistence of fetal veins, varicosities, hypertrophy, tortuosity, and valvular malformations
       3. Arteriovenous malformations (AVMs): This includes only very small AVMs or arteriovenous fistulas (AVF)
       4. Lymphatic malformations (LM): This includes any LM
       5. Localization
          1. CM can be located anywhere on the body, although location in the face is exceedingly rare
          2. AVM, VM, and LM are mainly located on the extremities and adjacent parts of the trunk (pelvis, shoulder) but in expressed forms of KTS also elsewhere (bladder, rectum, lower GI tract, penis, uterine, vulva, vagina, liver, kidneys, lung, spine)
          3. AVM, VM, and LM are not located in the face or brain
    2. Disturbed growth
       1. Disturbed growth of bone in the length or girth
       2. Disturbed growth of soft tissue in the length or girth
       3. The disturbed growth includes:
          1. Hypertrophy (frequent) of a small body part (isolated finger, macrodactyly) or larger body part (total limb, half of the total body)
          2. Hypotrophy (infrequent) of a small or larger body part
       4. Can be present both on the same site as the vascular malformation(s) (frequent) and at another site (infrequent)
11. Four commonly held conceptions about Klippel-Trenaunay syndrome challenged
    1. Renaming Klippel-Trenaunay-Weber syndrome by addition of arteriovenous fistulas (Meier 2009)
       1. Significant arteriovenous communications not observed in Klippel-Trenaunay syndrome in large surgical series
       2. Parkes Weber syndrome
       3. Parkes Weber syndrome (PWS)
          1. Characterized by enlarged arteries and veins, capillary or venous malformations and enlargement of a limb
          2. Closely associated with and similar to Klippel-Trenaunay syndrome, except that high-flow arteriovenous malformation (AVM) (resulting in high-output heart failure) occurs in association with a cutaneous capillary malformation (increased chance of skin ulcerations) and skeletal or soft tissue hypertrophy with increased limb-length discrepancies (Ziyeh et al. 2004; Sunderkrishman 2015)
          3. Lymphatic malformations found in Klippel-Trenaunay syndrome not observed in Parkes Weber syndrome
    2. Overlap with Sturge-Weber syndrome
       1. Characteristics of Sturge-Weber syndrome: craniofacial angiomatosis, port-wine nevus, and cerebral calcification
       2. Overgrowth in Sturge-Weber syndrome tends to be minor and is always secondary to the vascular anomaly. In contrast,

overgrowth in Klippel-Trenaunay syndrome is striking
3. Presence of a bleeding diathesis of the Kasabach-Merritt type
    1. Kasabach-Merritt syndrome erroneously applied to patients with extensive venous or lymphaticovenous malformations who develop a localized intravascular coagulopathy in which the platelet count is minimally depressed (varying from 50,000 to 150,000/mm^3)
    2. Profound thrombocytopenia in true Kasabach-Merritt phenomenon (varying from 3,000 to 60,000/mm^3)
    3. Klippel-Trenaunay-Weber syndrome with Kasabach-Merritt coagulopathy and hydronephrosis (Bhat et al. 2015)
        1. Rare
        2. Mortality: high with development of Kasabach-Merritt syndrome
4. Familial aggregation with various genetic interpretations
    1. Inadequate documentation of cases
    2. Over interpretation of minor manifestations in relatives, including "nevus flammeus," hemangiomas, and varicosities (common manifestations in general populations)
    3. Klippel-Trenaunay syndrome defined as a capillary malformation with or without "hemihypertrophy" without mentioning of lymphatic malformations, lateral venous anomaly, lymphatic vesicles, or venous flares within the capillary malformation, or macrodactyly
5. Klippel-Trenaunay syndrome, Parkes Weber syndrome, and Sturge-Weber syndrome
    1. Each occurring sporadically
    2. Each considered separate entity because clinical manifestations and types of complications are different

12. Cutaneous vascular anomalies in the neonatal period (Hook 2013)
    1. Nevus simplex
    2. Port-wine stain
    3. Vascular malformation syndromes with overgrowth
        1. Sturge-Weber syndrome
        2. Klippel-Trenaunay syndrome
        3. Parkes Weber syndrome
        4. Capillary malformation-macrocephaly syndrome
        5. Proteus syndrome
        6. Beckwith-Wiedemann syndrome
    4. Cutis marmorata telangiectatica congenita
    5. Capillary malformation-arteriovenous malformation syndrome
    6. Blue-rubber-bleb nevus syndrome
    7. Vascular tumors
    8. Infantile hemangioma
    9. Congenital hemangioma
    10. Tufted angioma
    11. Kaposiform hemangioendothelioma

Diagnostic Investigations

1. Color duplex ultrasonography (Berry et al. 1998)
    1. AV malformation
    2. Deep venous hypoplasia (a decrease in caliber of at least 50% of a vein along its length)
    3. Venous duplication
    4. Variable varicosities
2. Radiography
    1. Enlargement of the limb bones
    2. Yearly to monitor evidence of leg length discrepancy
3. Noninvasive imaging and endoscopy for severe gastrointestinal bleeding
4. Lymphoscintigraphy using radionuclide tracers
    1. Indication: edema or a girth discrepancy more than 4 cm
    2. No uptake of tracer along major lymphatics of the affected limb during repeated scans over at least a 1-h period
5. MRI
    1. Pelvis: to look for vascular malformations involving the kidneys, bladder, or intestines
    2. MRI with gadolinium to distinguish lymphatic from venous malformations
    3. Magnetic resonance venogram or phlebography/venography to document the

lateral venous anomaly and any abnormalities that may be present in the deep veins of the leg
4. Able to demonstrate arteriovenous fistulas in Parkes Weber syndrome
5. Diffuse venous malformation of the uterus in a pregnant woman with Klippel-Trénaunay syndrome diagnosed by DCE-MRI (dynamic contrast-enhanced MRI) (Yara et al. 2016)

6. Angiography (Sunderkrishman 2015)
   1. Arteriography: primarily indicated when spinal cord or brain involvement is suspected
   2. Venography: rarely indicated

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: not increased
   2. Patient's offspring: not increased (doubtful that autosomal dominant inheritance exists)
2. Prenatal diagnosis
   1. 2D/3D ultrasonography (Paladini et al. 1998; Roberts et al. 1999; Cakiroglu et al. 2013)
      1. Asymmetric limb hypertrophy associated with cutaneous or subcutaneous multiloculated cystic or multicystic lesions. Color Doppler examination reveals the presence of persistent embryonic lateral marginal veins
      2. Limb edema
      3. Cardiac failure ranging from isolated cardiomegaly to severe hydrops
      4. Prenatal sonographic diagnosis of Klippel-Trenaunay-Weber syndrome with cardiac failure (Zoppi et al. 2001)
      5. Prenatal ultrasound diagnosis of Klippel-Trenaunay-Weber syndrome with Kasabach-Merritt syndrome which caused acute hemolytic anemia, leading to high-output cardiac failure and fetal hydrops, in utero (Tanaka et al. 2015)
   2. MRI
      1. Limb hypertrophy
      2. Multiple subcutaneous and internal hemangiomas
      3. Good definition of soft tissue lesions
      4. Identify vascular malformations and their extent
      5. Presence of low signal indicating flow voids, hemosiderin deposits, or calcification indicative of vascular malformations
3. Management (James et al. 1999; Gloviczki and Driscoll 2007; Sharma et al. 2015; Sunderkrishman 2015)
   1. Normally conservative
   2. Elastic garment or compression bandage: beneficial in managing both lymphedema and chronic venous insufficiency
   3. Physical therapy using massage treatment and intermittent pneumatic compression therapy
   4. Local wound care, compression dressings, special orthopedic footwear, and lifestyle modification
   5. Prednisolone
      1. Used to treat coagulopathy
      2. Decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reducing capillary permeability
   6. Psychological support: participate in the activities of a support group
   7. Stripping of superficial varicose veins
   8. Successful pulmonary thromboendarterectomy in a patient with Klippel-Trenaunay syndrome (Walder et al. 2000)
   9. Pulsed dye laser treatment for superficial hemangioma component (Jih 2003)
   10. Sclerotherapy and embolotherapy
   11. Reduction of significant arteriovenous malformations
   12. Rare reconstructive surgery at sites of deep venous obstruction
   13. Orthopedic procedures for overgrowth
      1. Epiphysiodesis: to prevent (stop) overgrowing of limb and correction of bone deformity
      2. Excision of soft tissue hypertrophy
   14. Use of thromboembolic prophylaxis with low-molecular-weight heparin is generally recommended, mainly in the postpartum (Güngor Gündoğan and Jacquemyn 2010; González-Mesa et al. 2012)

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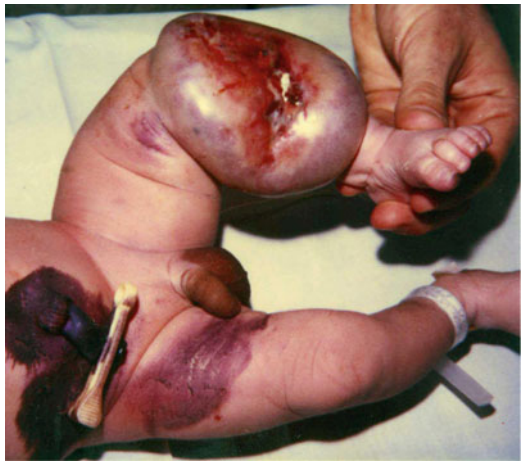

Fig. 1 A newborn with Klippel-Trenaunay syndrome showing overgrowth of left leg with vascular malformation

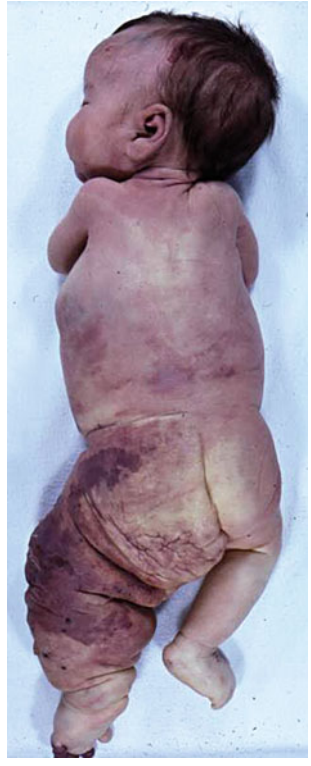

Fig. 2 A neonate with Klippel-Trenaunay syndrome showing left leg overgrowth with vascular malformation

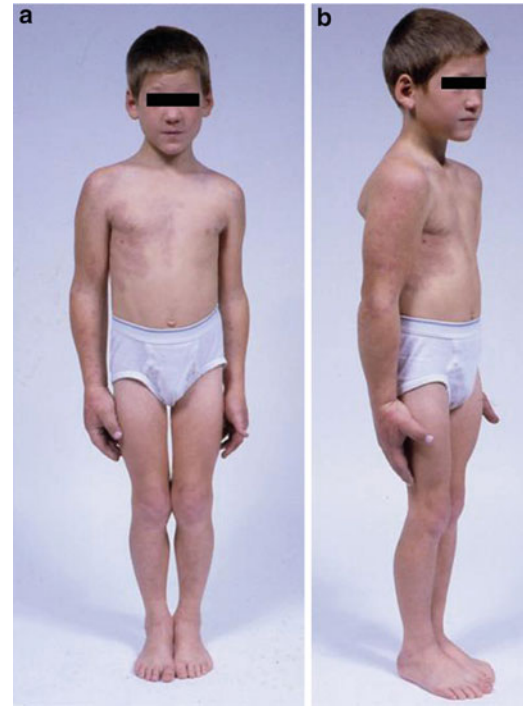

Fig. 3 (**a**, **b**) A boy with Klippel-Trenaunay syndrome showing overgrowth of the right arm and leg with vascular malformation (**a**, **b**)

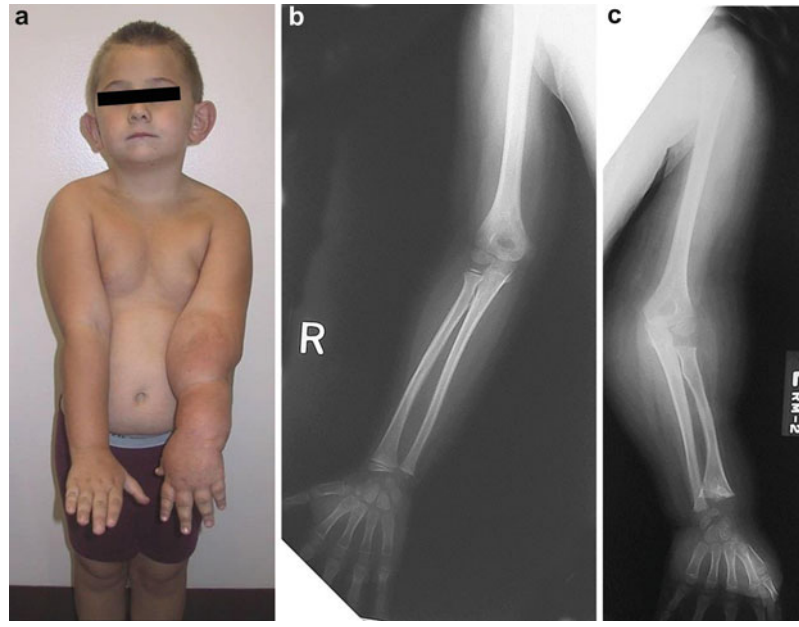

Fig. 4 (**a**–**c**) A 6-year-old boy with Klippel-Trenaunay syndrome showing overgrowth of left arm associated with vascular malformation (**a**), illustrated by radiographs (**b**, **c**)

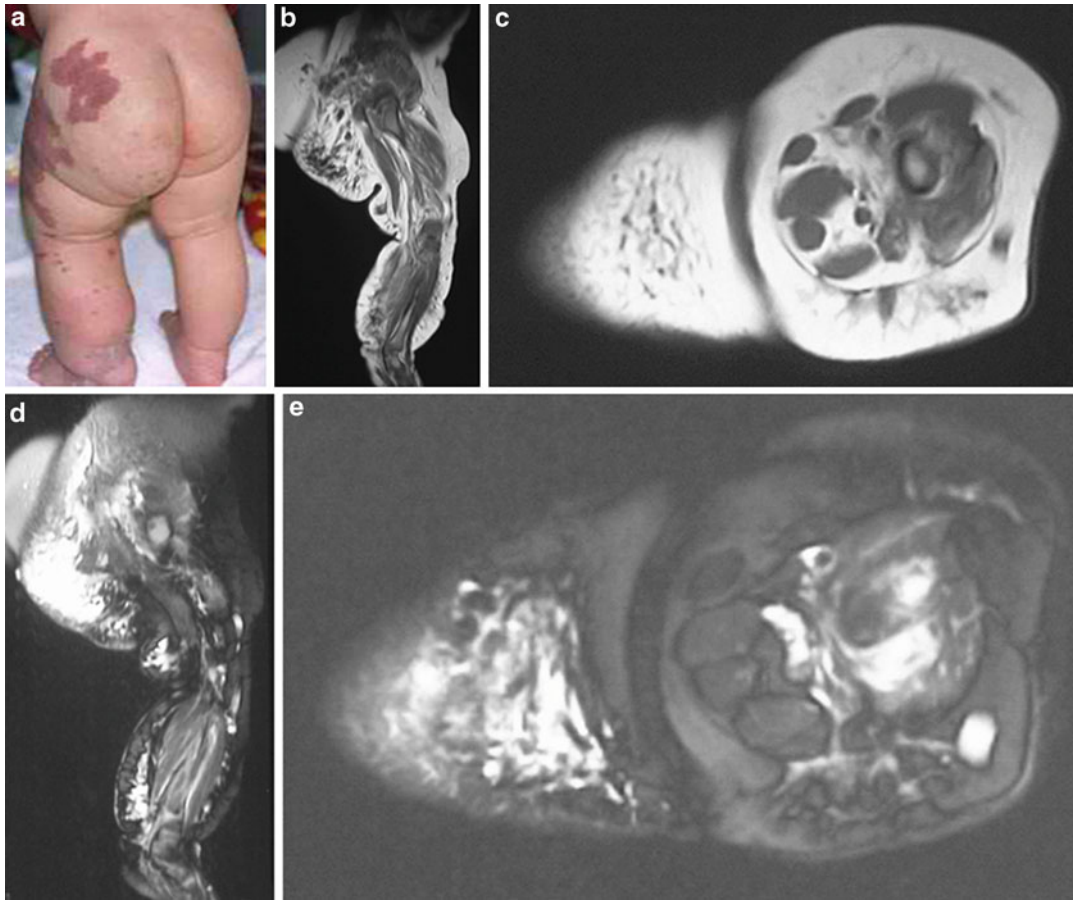

Fig. 5 A 1-year-old infant with Klippel-Trenaunay syndrome showing asymmetric lower extremities with hypertrophic left lower extremity associated with vascular malformation (**a**). T1-enhanced MRI (**b**, **c**) and T2-enhanced MRI (**d**, **e**) images at thigh level show cystic and vascular lesions, indicated by high signals suggesting lymphangiomas and hemangiomas

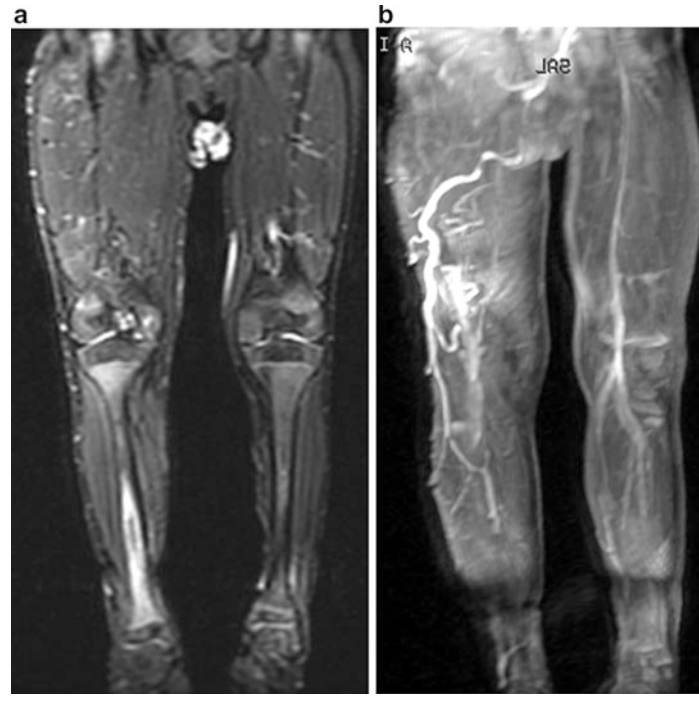

Fig. 6 (**a**, **b**) A 2-year-old boy with a history of Klippel-Trenaunay syndrome. MR image of the bilateral lower extremities demonstrates that the right lower extremity is larger than the left, with greater muscle mass in both legs and larger circumference (**a**). There is a length discrepancy in legs. A tortuous abnormal venous system is identified within the superficial fat along the posterior lateral aspect of the leg, which is seen draining through the gluteal and perineal regions into the pelvis (**b**). The deep venous system on the right is smaller than that on the left, although it is seen in its entirety (Courtesy of Dr. Grace Guo)