Unilateral leg swelling in a newborn

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A female neonate was born with asymmetric lower limbs, the right leg appearing enlarged, with thickened, reddish-purple skin and ectasic superficial reticulum (figure 1A,B). Limb pulses were present and symmetrical. The girl's family history and prenatal scans were unremarkable. Laboratory findings were within the normal range, except for a mild thrombocytopenia (90 000/μL), which spontaneously resolved during the next few days. A leg X-ray and the Doppler analysis ruled out the presence of calcifications and venous varices, respectively. Ultrasound showed significant skin thickening, with marked dermal hypertrophy and hyperechogenicity. Magnetic resonance showed circumferential thickening of the derma, with mild hypertrophy of some perforating vessels (figure 2). A biopsy of the right thigh showed capillary malformations on histology.

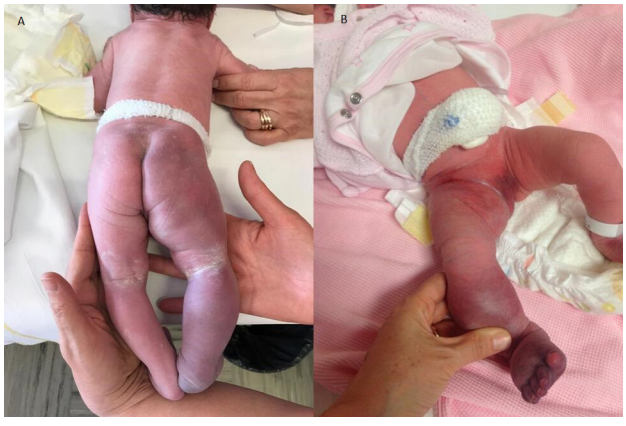

Figure 1 (A, B) Hypertrophy of the right lower limb, with large capillary malformation extending to the gluteus and the external genitalia.

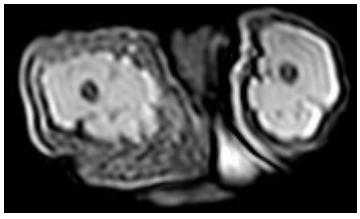

Figure 2 Axial THRIVE magnetic resonance scan of the thighs' proximal third, showing circumferential dermal thickening and inhomogeneity of the right leg's subcutaneous tissue.

QUESTIONS

1. Based on the clinical picture and investigations results, which is the most likely diagnosis?
   A. Beckwith-Wiedemann
   B. CLOVES syndrome
   C. Klippel-Trenaunay syndrome
   D. Kaposiform hemangioendothelioma
2. How can the diagnosis be confirmed?
   A. CT with PET
   B. Lymphoscintigraphy
   C. Genetic testing
   D. None of the above, the diagnosis is clinical
3. What is the mainstay of management?
   A. Conservative with follow-up
   B. Pharmacotherapy
   C. Sclerotherapy
   D. Surgery
4. Which of the following complications can occur?
   A. Scoliosis
   B. Glaucoma
   C. Urinary and gastrointestinal bleeding
   D. All of the above

Answers can be found on page 272.

Table 1 Genetic overgrowth syndromes[8]

Genetic syndromes	Clinical features	Frequency
Beckwith-Wiedemann syndrome (BWS)	Neonatal macrosomia, hemihyperplasia, macroglossia, ear lobe creases and helical pits, omphalocele/umbilical hernia, hypoglycemia, visceromegaly, hypotonia	1/13 700
Perlman syndrome	Neonatal macrosomia, macrocephaly, facies (prominent forehead, hypertelorism, broad flat nasal bridge, ante-verted upper lip, high-arched palate, micrognathia, low-set dysplastic ears), nephromegaly, ascites, hypotonia, developmental delay	<1/1 000 000 to 30 cases reported in the literature
Simpson–Golabi–Behmel syndrome (SGBS)	Neonatal macrosomia, macrocephaly, coarse facial features, supernumerary nipples, broad hands, index nail hypoplasia, syndactyly, polydactyly, diaphragmatic hernia, omphalocele, hypoglycemia, visceromegaly, hypotonia, speech delay	<1/1 000 000 to 100 cases reported in the literature
Sotos syndrome	Neonatal macrosomia, macrocephaly, advanced bone age, facial gestalt (long thin face, high hairline, broad forehead, hypertelorism, pointed chin, high-arched palate), hypotonia, hypoglycemia, learning disability	1/10 000
Weaver syndrome	Facial gestalt (broad forehead, hypertelorism, almond-shaped palpebral fissures, long philtrum, small chin, retrognathia), overgrowth with advanced bone age, camptodactyly, fetal finger pads, wrinkled skin, neurodevelopmental delay	<1/1 000 000
PIK3CA-related overgrowth spectrum (PROS): Isolated macrodactyly, Fibroadipose Overgrowth (FAO), Hemihyperplasia multiple Lipomatosis (HHML), Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, Scoliosis, skeletal/spinal anomalies, seizures (CLOVES), Megalencephaly-Capillary malformation (MCAP)	Unilateral asymmetric congenital and progressive overgrowth of the subcutaneous tissue, possible skeletal overgrowth, and lipoatrophy of areas not affected by overgrowth	<1/1 000 000
Proteus syndrome	Macrocephaly, progressive asymmetric overgrowth of soft tissue and bone, extensive cutaneous and visceral vascular malformations, cerebriform connective tissue nevi of the plantar feet, epidermal nevi, lipomas, café au lait spots, learning difficulties	<1/1 000 000
PTEN hamartoma tumour syndrome (PHTS)	Macrosomia, macrocephaly, pigmented skin, penile freckles, lipomas, oral papillomas, intestinal hamartomas, hypotonia, neurodevelopmental delay	Unknown (rare)
Klippel-Trenaunay syndrome (KTS)	Vascular malformation (capillary and venous, sometimes lymphatic, present at birth in 95% of cases) and corresponding limb overgrowth	<1/1 000 000
Parkes-Weber syndrome (PWS)	Fast-flow arterio-venous fistulae with rapid capillary refill, skin warmth and limb overgrowth, without structural venous and lymphatic malformations	Unknown (rare)

ANSWERS TO THE QUESTIONS ON PAGE 271

Answer to question 1: C

The association of soft-tissue hypertrophy and ipsilateral vascular malformation suggested a Klippel-Trenaunay syndrome (KTS). Beckwith-Wiedemann syndrome appeared unlikely due to the localised nature of the hypertrophy and the absence of macroglossia, hypotonia, hypoglycemia, as well as abdominal abnormalities.[1] CLOVES (Congenital Lipomatous Overgrowth with Vascular, Epidermal and Skeletal anomalies) syndrome generally includes a degree of lipomatosis, which was missing here. The mild thrombocytopenia evoked our consideration of a Kasabach-Merrit phenomenon, associated with kaposiform hemangioendothelioma. This concern prompted a skin biopsy, which ruled out this possibility as well. Table 1 summarises the main neonatal overgrowth syndromes.

Answer to question 2: D

The diagnosis of KTS is clinical and relies on the presence of at least two of the following: soft tissues or osseous localised hypertrophy, capillary malformation and venous varices. The lower extremities are most frequently involved, and the capillary malformation is usually present at birth. Neither PET CT nor scintigraphy assists the diagnosis.

KTS is currently considered a sporadic disease without a clear inheritance pattern. Due to the possible clinical and genetic overlap with the PIK3CA spectrum disorders, a biopsy in search of somatic mutations is sometimes performed.[2]

Answer to question 3: A

The management of KTS is mainly conservative. Therapeutic attempts with sirolimus have shown variable

success.[3] The skin overlying the vascular abnormality tends to display slow wound healing and a higher risk of thrombophlebitis and infections due to venous stasis. This diagnosis can be clarified by the appearance of venous varices, which emerge in almost all patients on learning to walk. Drainage of the lower limb can be helped through compressive bandages, with surgery reserved for the most severe cases, mostly in adults. Investigation of acute pain in the affected limb is merited, due to the risk of deep venous thrombosis and pulmonary embolism, especially postoperatively.[4]

Answer to question 4: D

The management of patients with KTS should be multidisciplinary, given the broad spectrum of possible complications. Hypertrophy of a lower limb can lead to impaired gait and secondary scoliosis, requiring orthopaedic follow-up. Periocular localisations of the vascular malformation can degenerate into ipsilateral glaucoma, thus scheduled ophthalmological evaluations should be considered. Urinary and gastrointestinal bleeding, although rare, can represent life-threatening conditions.[5] These complications explain a higher frequency and degree of pain symptoms in these children.[6] The long-term prognosis is favourable overall, although some degree of functional impairment in daily activities can occur into adulthood, with psychosocial well-being generally preserved.[7]

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Contributors LCW and MS drafted the manuscript; FMM edited the radiological aspects of the case; IB and EB supervised the work; FMR edited the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Cortellazzo Wiel L, Berti I, Starc M, *et al*. *Arch Dis Child Educ Pract Ed* 2022;**107**:271–273.

Received 11 August 2020
Accepted 25 October 2020
Published Online First 18 November 2020

Arch Dis Child Educ Pract Ed 2022;**107**:271–273. doi:10.1136/archdischild-2020-320450

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