CASE REPORT

Overgrowth syndrome in neonates: a rare case series with a review of the literature

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SUMMARY

We present here two-term neonates presenting with right lower limb hypertrophy, a port-wine stain, acral abnormalities and clubfeet. These neonates had overlapping features of Klippel Trenaunay syndrome and congenital lipomatous overgrowth, vascular malformation, epidermal nevi and scoliosis/skeletal abnormalities. Such overgrowth syndrome has not been previously described in the literature. Both the neonates are doing well and are under regular follow-up.

BACKGROUND

Klippel-Trénaunay syndrome (KTS) is a rare congenital disorder involving vascular, skeletal and dermatological systems and was originally described a century back by Klippel and Trénaunay.¹ It is primarily diagnosed clinically and is characterised by a triad of capillary, venous malformations and hypertrophy of bone or overlying soft tissue of the limbs with or without a lymphatic malformation. The presence of any of the two components confirms the diagnosis of KTS. The severity of manifestations may vary from a port-wine stain to a large venous ectasia, leading to limb deformity.² Over time, a number of phenotypically similar conditions have evolved collectively to be known as overgrowth syndrome. They have overlapping features of tissue overgrowth, including vascular abnormalities, cutaneous, subcutaneous as well as bone anomalies and can be differentiated from each other on the basis of mutational analysis of the genes involved. One such gene is PIK3CA, and disorders related to the mutation in this gene are called as PIK3CA-related overgrowth spectrum (PROS). These include megalencephaly-capillary malformation (MCAP); congenital lipomatous overgrowth, vascular malformation, epidermal nevi and scoliosis/skeletal abnormalities (CLOVES); and fibroadipose hyperplasia.³

examination, vitals were stable. Local examination revealed marked hypertrophy of right lower limb with a limb length discrepancy of 1 cm. (figure 1) A port-wine stain measuring 2 cm × 3 cm was present on the right gluteal region and was associated with skin thickening. The hypertrophied limb also showed multiple small lumps with dimpling scarring evident over the calf area. The hypertrophied area over the thigh and trunk was comparatively firmer without such soft lumps. There was bilateral congenital talipes equinovarus (CTEV), widened digit angles and hypoplastic toe nails. (figure 2) There were no other obvious congenital malformation, facial asymmetry or skeletal deformity such as scoliosis. There was one episode of blood in stools which was treated conservatively.

Patient 2

A 30-day-old male baby, born through normal vaginal delivery at term to a 29-year-old primigravida mother out of a non-consanguineous marriage, with a birth weight of 3580 g presented to out centre with hypertrophy of right lower limb extending up to trunk since birth. The antenatal period was uneventful and the antenatal scans were normal. There was no history of any drug or radiation exposure during the pregnancy. On examination, vitals were stable. Local examination revealed marked hypertrophy of right lower limb and of the right side of the trunk. (figure 3). There was bilateral CTEV, widened digit angles (figure 4) There was no other obvious congenital malformation, facial asymmetry or skeletal deformity such as scoliosis.

There were no seizures, haematuria, polydactyly, facial dysmorphism or murmur observed in either of the neonates.

Although KTS was a close differential for our patients, there are few peculiar findings which have not been reported before like bilateral CTEV, sandal gap, extensive neonatal thrombosis (patient 1), absence of port-wine stain and capillary malformation (patient 2).

INVESTIGATIONS**Patient 1**

The ultrasonogram of the hypertrophied limb displayed multiple cystic spaces in subcutaneous and superficial muscular plane suggesting a low flow (lymphatic) malformation. Mild enlargement of the right kidney with multiple linear calcifications was also reported. Contrast-enhanced CT of

CASE PRESENTATION**Patient 1**

A 17-day-old male baby, born through normal vaginal delivery at term, to a 26-year-old primigravida mother out of a non-consanguineous marriage, with a birth weight of 2580 g presented to outcentre with hypertrophy of right lower limb extending up to trunk since birth. The antenatal period was uneventful and the antenatal scans were normal. There was no history of any drug or radiation exposure during the pregnancy. On

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Figure 1 Hypertrophied right lower limb of patient 1.

the abdomen confirmed the presence of thrombus in inferior vena cava. Complete blood count, coagulation profile, renal and liver functions were normal. Protein C, protein S and homocysteine levels in the blood were within normal limits. Infantogram, cranial ultrasound and echocardiography were also reported to be normal. Colonoscopy was done as there was one episode of blood in stools and such patients are prone to have had ectasia of gut vessels. It revealed multiple abnormal vessels with sharp demarcation from the normal mucosa.

Patient 2

The ultrasonogram of the hypertrophied limb showed multiple cystic spaces in subcutaneous and superficial muscular plane suggesting a slow flow (lymphatic) malformation. MRI abdomen revealed lymphatic malformation in the abdomen. Doppler

Figure 2 Bilateral congenital talipes equinovarus with sandal gap of patient 1.

Figure 3 Hypertrophied right lower limb of patient 2.

studies of both the limbs and abdomen did not reveal any thrombus. Complete blood count, coagulation profile, renal and liver functions were normal. Infantogram, cranial ultrasound and echocardiography were also reported to be normal. Colonoscopy revealed multiple abnormal vessels with sharp demarcation from the normal mucosa.

Genetic studies could not be carried out because of the financial constraints.

DIFFERENTIAL DIAGNOSIS

- ▶ CLOVES.
- ▶ Diffuse capillary malformation with overgrowth (DCMO).
- ▶ Proteus syndrome.
- ▶ Beckwith- Weidemann syndrome.⁴
- ▶ Parkes Weber syndrome.

Figure 4 Right congenital talipes equinovarus with sandal gap of patient 2.

TREATMENT

Patient 1

The baby was given unfractionated heparin therapy for 3 months. Serial sclerotherapy for the lymphatic malformation over gluteal and thigh region was done because of the difficulty in the movement. Compression bandages were also used. The baby had meningitis for which he received 3 weeks of antibiotics. The other patient had no evidence of thrombosis on Doppler studies. During the follow-up, patient 1, had three episodes of cellulitis of the involved limb until 9 months of age.

OUTCOME AND FOLLOW-UP

Patient 1

At 9 months of follow-up, the baby was thriving well with a weight of 9.2 kg with no other new symptoms. Thrombus resolved completely on repeat Doppler studies at 6 months.

The second patient is also well and thriving with no complications.

DISCUSSION

Overgrowth syndromes is an umbrella term used for disorders associated with global or regional surplus growth compared with an equivalent body part or as per the age group.⁴ These include, KTS, Bannayan–Riley–Ruvalcaba, CLOVES and proteus syndromes. Another new entity PROS has been described which includes MCAP, CLOVES and fibroadipose hyperplasia.³ These syndromes often show overlapping phenotypic features. The KTS and CLOVES share a number of common clinical features like presence of capillary, venous and lymphatic malformation, neurological abnormalities like hemimegalencephaly, seizure and acral anomalies like polydactyly, syndactyly and macrodactyly. But there are some features that may suggest diagnosis of CLOVES such as presence of thoracic lipomatous hyperplasia, spinal arteriovenous malformation, corpus callosum dysgenesis, saddle gap, renal agenesis or hypoplasia, splenic haemangioma, scoliosis, pectus excavatum, hip dysplasia, facial asymmetry due to overgrowth which may later present as malocclusion.⁵ In our cases, babies had classical features of KTS along with skeletal abnormality in the form of bilateral clubfeet with interphalangeal gap. Hence, making it a unique syndrome.

KTS typically affects the lower extremity unilaterally. Another differentiating feature is involvement of the genitourinary tracts and the gastrointestinal in the KTS. According to 2014, international society for the study of vascular anomalies' classification, KTS is defined as a syndrome with triad of vascular malformation (capillary and venous malformations) with limb overgrowth with or without lymphatic malformation.⁶

Capillary malformation—the port-wine stains are usually apparent at birth in 95% of the patients and mostly involve the lower hypertrophied extremity, though these changes can be noted in any location of the body. This is the most common cutaneous presentation of KTS. This malformation is usually present as a flat, red- or purple-coloured capillary haemangioma with hard, dry, thickened and hyperpigmented overlying skin. There are two types of capillary stains, the one which are well defined and are known as geographical stains are commonly associated with lymphatic malformation and other complications. The other type are ill defined and are known as segmental stains.^{7,8}

Varicose veins

Venous malformations typically become more apparent during childhood although they may be evident at birth or during infancy. The persistence of embryonic avascular venous

structures leads to varicosities of both the superficial and deep venous systems. The severity ranges from ectasia of small veins of superficial veins to aneurysmal dilatation, agenesis, hypoplasia, duplications and venous regurgitation of deep venous system.⁹

Hypertrophy

The hypertrophy is mainly due to the excessive growth of underlying soft tissue and the associated adipose tissue, although bony hypertrophy leading to difference in limb length may also be seen in a few cases. Rarely there may be wasting of the affected limb leading to reverse KTS. The other limb anomalies reported are macrodactyly, syndactyly, polydactyly, clinodactyly, camptodactyly, ectrodactyly and congenital hip dislocation.^{10–13}

The other organ system which may be affected in KTS is central nervous system (cerebral aneurysm).

Complications

1. Bleeding from rectum and bladder is a life-threatening condition seen in around 1% of patients with KTS. Oesophageal variceal bleeding is also reported in patients with KTS. Haematuria is usually recurrent and painless.²
2. Thromboembolism: KTS is associated with complications like Kassabach–Merit phenomenon and episodes of thrombophlebitis, deep vein thrombosis and/or pulmonary thromboembolism.⁶ In a study of 48 patients with KTS, nearly half had a history of superficial venous thrombosis, with eight patients having deep venous thrombosis and/or pulmonary embolism, and two had evidence of chronic pulmonary embolism.¹⁴ The dilated pelvic veins has been reported as a risk factor for pulmonary embolism.¹⁵
3. Infection: KTS patients are prone to recurrent episodes of cellulitis. Nearly 13 per cent of the patients have been reported to have cellulitis. It may or may not be due to infection, as it may be due to an inflammatory reaction to venous stasis, chronic lymphoedema, or thrombosis. New-onset erythema, pain, swelling and warmth fever are the common signs of cellulitis and should never be ignored.²
4. Pain: the prevalence of pain in KTS has been reported to be around 37 to 88 per cent. It may be due to chronic venous insufficiency, cellulitis, superficial thrombophlebitis, deep vein thrombosis, arthritis, contractures and haemarthrosis.¹⁶
5. Limb length discrepancy: this may lead to secondary scoliosis, impaired gait and pain. These functional limitation is severe when the discrepancy is 2 cm or greater. Limb overgrowth usually ceases at the end of adolescence.^{17,18}

Differential diagnosis

Diffuse capillary malformation with overgrowth

As the name suggests, patients of DCMO typically have extensive, often reticular capillary malformations, with proportionate, non-progressive overgrowth. The overgrowth may not involve the entire limb and be restricted to fingers or toes. The capillary malformations of DCMO are often patchy, more widespread and fainter in colour compared with those seen in KTS.¹⁹ DCMO lacks lymphatic malformation although one-third of these patients may have prominent varicosities.

Parkes Weber syndrome

It is characterized by capillary malformation, fast-flow arteriovenous fistulae and limb overgrowth and preferentially involves the lower extremity. However, structural venous and lymphatic malformations are usually absent, differentiating it from KTS. The Parkes Weber syndrome may further be differentiated from KTS because of its brighter pink stains with rapid capillary refill,

unusual skin warmth and excessive pain which is out of proportion for the physical findings.²⁰

Proteus syndrome

Like KTS, it is characterized by asymmetric and progressive overgrowth of soft tissue and bone, with extensive cutaneous and visceral mixed vascular malformations. However, cerebriform connective tissue nevi of the plantar feet, epidermal nevi, lipomas, café au lait spots, macrocephaly, learning difficulties, pulmonary cysts and ovarian cystadenomas are its unique features which differentiate it from KTS.²¹

Congenital lipomatous overgrowth, vascular malformation, epidermal nevi and scoliosis/skeletal abnormalities

The characteristic features of CLOVES include facial asymmetry (due to abnormal fat deposits and overgrowth of the orbit, maxilla and/or mandible), lipomatous masses (behave more like tumours and, thus, are inclined to enlarge and recur after resection) macrodactyly, typically involving the third toe or third finger, talipes and neural tube defect. Renal hypoplasia is also frequently seen with sandal gap deformity of toe. Capillary malformations and slow-flow malformations (lymphatic, venous, and capillary) are common while arteriovenous fistula are rare. The acral abnormalities are also common and broad, spade-like hands with ulnar deviation of the digits, symmetrical overgrowth of one or more digits with laxity of collateral ligaments, most commonly the thumb metacarpophalangeal and interphalangeal joints. Other features include leg length discrepancy, chondromalacia patellae, dislocated knees, scoliosis and wide triangular feet.^{22–23}

Recent advances

Sirolimus: it is a mammalian target of rapamycin (mTOR) inhibitor and thus inhibits cell proliferation and angiogenesis. mTOR, is a serine/threonine-specific protein kinase that belongs to the family of phosphatidylinositol-3 kinase (PI3K) related kinases (PIKKs). mTOR regulates cellular metabolism, growth, and proliferation by forming and signaling through two protein complexes. Recently it has emerged as a potential therapeutic option for complex venous-lymphatic malformations such as KTS. In a study of 61 patients, including 13 with mixed capillary-venous-lymphatic malformations, treated with 12 consecutive 28-day courses of sirolimus. Eighty five per cent of those who completed full course of treatment had a partial response to sirolimus and reported improvement in quality of life and function. However bone marrow toxicity was observed in 27 per cent of these patients. Other reported side effects include mucositis, headache, hyperlipidaemia, transaminitis, myelosuppression and infection.^{24–26}

Capillary and lymphatic malformations may be treated with laser therapy if they bleed or are crusted. There are two types of laser available, pulsed dye laser is effective in lightening capillary malformations, whereas ablative CO₂ lasers are used to control leakage and bleeding from lymphatic vesicles.

The management of KTS is mainly conservative, involving multidisciplinary approach and regular follow-up. Compression therapy is pivotal in the management, along with care of the local site. This includes avoiding trauma and infection in the affected limb. Vascular surgeries are usually not recommended because of high recurrence rate. However, ultrasound-guided foam sclerotherapy or steam vein sclerotherapy followed by foam sclerotherapy may be used. The advantages of performing this procedure are minimal pain and less invasion.²⁷ KTS has

a favourable prognosis in most of the babies but complications like deep vein thrombosis, pulmonary thromboembolism, Kasabach–Meritt syndrome, life-threatening haematochezia, renal haemangioma complicating as perirenal haematoma requiring nephrectomy may occur. Approximately, 10% of children with KTS develop deep vein thrombosis, especially in postoperative period.²⁸ The presence of large venous channels also increases the risk of thrombosis. Until now, the case reports of thromboembolism in paediatric population are confined to older age group (ie, preadolescent group). Management options include parenteral anticoagulants and fibrinolytic therapy. Furthermore, there have been previous reports of CLOVE syndrome in neonates diagnosed on the basis of clinical features but all of them had no frank manifestations which could complicate the diagnosis.^{29–35} Until now no single case in neonatal period has been published where there are overlapping of features of KTS and CLOVES.

Learning points

- ▶ Overgrowth syndrome is a group of various syndromes with various differentiating features.
- ▶ Infants with overgrowth syndrome need to be evaluated for complications like vascular malformations, thrombosis, sepsis and bleeding.
- ▶ Klippel–Trénaunay syndrome is the the most common overgrowth syndrome.
- ▶ Treatment is mainly supportive and involves a multidisciplinary approach.

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