CHAPTER 23

Overgrowth syndromes

PROTEUS SYNDROME

Epidemiology
<1/1,000,000.

Age of onset
Usually postnatal onset.

Cutaneous findings
• Cerebriform or nodular gross thickening of the palms and soles (Figures 23.1 and 23.2)
• Linear verrucous epidermal nevi (distributed along Blaschko's lines) (Figure 23.3)
• Hamartomatous masses of subcutaneous tissue consisting of adipose tissue or various combinations of adipose and lymphatic–angiomatous tissue (Figure 23.4)
• Vascular malformations (capillary, venous or lymphatic)
• Café-au-lait macules
• Hypopigmented spots

**Extracutaneous findings**

• Progressive and asymmetric macrodactyly (Figure 23.5)
• Macrocephaly and skull exostosis
• Body hemihypertrophy (Figure 23.4)
• Scoliosis and spinal canal stenosis
• Bullous lung abnormalities
• Ocular manifestations (strabismus, high myopia, retinal pigmentary anomalies, and epibulbar dermoids)
• Usually normal mental function, but central nervous system abnormalities are possible (intellectual disability, seizures, hemimegalencephaly, hydrocephalus, and other brain malformations)
• Renal/urologic findings (renal asymmetry, renal cysts, hydroureters, hydronephrosis)
• Reported but uncommon neoplasms include monomorphic adenoma of the parotid gland, cystadenomas of the ovary, testicular tumors, meningiomas, and mesothelioma

**Laboratory findings**

Radiography shows bone and soft-tissue hypertrophies.

**Genetics and pathogenesis**

• The disease is inherited in an autosomal dominant manner.
• Some individuals with Proteus syndrome were found to have germline PTEN mutations.
• Paradominant inheritance is possible (see Chapter 25).
• A mosaic somatic mutation of the AKT1 gene has been identified in more than 90% of individuals meeting the diagnostic criteria.
• Since PTEN down-regulates AKT1 by decreasing phosphorylation, the finding of an activating AKT1 mutation in Proteus syndrome corroborates that Proteus syndrome is a PTEN-pathwayopathy.

**Differential diagnosis**

• Neurofibromatosis type 1
• Klippel–Trénaunay–Weber syndrome
• Maffucci syndrome
• CLOVES syndrome
• Hemihyperplasia–lipomatosis syndrome
• Beckwith-Wiedemann syndrome

**Course and prognosis**

The disease is slowly progressive and dependent on the extent and severity of extracutaneous lesions. About 20% of patients with Proteus syndrome have premature deaths. Deep Vein Thrombosis is common.

**Follow-up and therapy**

• Great variability between extremely severe forms and milder forms
• Propensity for neoplastic changes
• Surgical approach for gigantism and asymmetry
• Antithrombotic prophylaxis should be considered when undergoing a surgical procedure
• Pulmonary cystic lesions should be carefully monitored

Bibliography


CLOVES SYNDROME

Synonyms
Congenital lipomatous asymmetric overgrowth of the trunk, lymphatic, capillary, venous, and combined-type vascular malformations, epidermal nevi, skeletal, and spinal anomalies.

Age of onset
At birth.

Cutaneous findings
• Epidermal nevi
• Complex congenital overgrowth of lipomatous tissues (typically manifesting as a truncal lipomatous mass) (Figure 23.6)
• Combined lymphatic and vascular malformations (Figure 23.7)
• Deeply grooved plantar thickening, not consistent with a cerebriform connective tissue nevus

Extracutaneous findings
• Skeletal anomalies include scoliosis, wide hands and feet, macrodactyly, and prominent sandal-gap toes (Figure 23.8).
• Renal agenesis/hypoplasia.
• Splenic lesions.

![Figure 23.6](image-url)  CLOVES syndrome.
Neurological findings: Neural tube defects, tethered cord, megalencephaly/hemimegalencephaly, Chiari malformation and polymicrogyria.

Seizures.

Tumors reported in CLOVES syndrome include chorangioma, extradural spinal tumor, hemangioma, and multiple angiomatosis.

Genetics and pathogenesis

Heterozygous (somatic mosaic) mutations of PIK3CA are causative.

Differential diagnosis

- Proteus syndrome
- Klippel–Trénaunay syndrome

Follow-up and therapy

Monitoring for paraspinal high-flow lesions with spinal cord ischemia, central phlebectasias and thromboembolism.

Bibliography


BECKWITH–WIEDEMANN SYNDROME (BWS)

Epidemiology
1:13,700.

Age of onset
At birth.

Cutaneous findings
- Hemangiomas
- Macroglossia, which can lead to difficulties in feeding, speech and, less frequently, sleep apnea (Figure 23.10)
- Posterior helical pits

Extracutaneous findings
- Increased rate of growth during the latter half of pregnancy and in the first few years of life (Figure 23.11)
- Prematurity
- Neonatal hypoglycemia
- Hemihyperplasia
- Abdominal wall defects (omphalocele, umbilical hernia and diastasis recti) (Figure 23.12)
- Visceromegaly
- Unilateral or bilateral renal anomalies may include primary malformations, renal medullary dysplasia, nephrocalcinosis, and nephrolithiasis
- Cardiac malformations
- Prominent eyes with infraorbital creases, midfacial hypoplasia, full lower face with a prominent mandible and anterior earlobe creases

Laboratory findings
- Advanced bone age
- Neonatal hypoglycemia

Genetics and pathogenesis
- BWS is caused by various epigenetic and/or genetic alterations that dysregulate imprinted genes on chromosome 11p15.5. Molecular subgroups are associated with different recurrence risks and different clinical findings (e.g., tumor risks).
Somatic mosaicism accounts for some of the BWS-associated clinical variability. BWS usually occurs sporadically (85%), but familial transmission occurs in 5% of cases.

**Differential diagnosis**
- Maternal diabetes mellitus
- Simpson–Golabi–Behmel syndrome
- Costello's syndrome
- Perlman's syndrome
- Sotos syndrome
- Mucopolysaccaridosis type VI (Maroteaux–Lamy syndrome)
- Mosaicism for trisomy 8

**Course and prognosis**
- Predisposition to embryonal malignancies that often occur in the first 8–10 years of life with very few being reported beyond this age; most common are Wilms tumors and hepatoblastomas. Other embryonal tumors include rhabdomyosarcomas, adrenocortical carcinomas and neuroblastomas.
- Individuals with uniparental paternal disomy (UPD) of 11p15.5 or gain of methylation at the imprinting center for domain 1 (IC1) carry the highest risk of developing Wilms tumors or hepatoblastomas.

**Follow-up and therapy**
- Abdominal ultrasounds are used to assess the kidneys, liver, pancreas, and adrenal glands every 3/4 months in the first 8–10 years of life.
- α-fetoprotein can be measured periodically to the age of 4 years for the early detection of hepatoblastomas.

**Bibliography**


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**CLAPO SYNDROME**

**Synonyms**
Capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry, and partial/generalized overgrowth.

**Epidemiology**
This disease is very rare: six cases have been reported in the literature.

**Age of onset**
At birth.

**Cutaneous findings**
- Capillary malformations of the lower lip (port-wine stain, nevus flammeus or vascular marks) with a midline and symmetrical pattern (Figures 23.13 and 23.14)

**Follow-up**
- Abdominal ultrasounds are used to assess the kidneys, liver, pancreas, and adrenal glands every 3/4 months in the first 8–10 years of life.
- α-fetoprotein can be measured periodically to the age of 4 years for the early detection of hepatoblastomas.

**Bibliography**


• Port-wine macrocheilia
• Lymphatic malformations of the face and neck
• Bleeding, infection, swelling, and vesicle formation malocclusion

Extracutaneous findings
• Overgrown and large-for-gestational-age infants
• Asymmetry of the face and limbs (Figure 23.14)
• Partial or generalized overgrowth
• Facial dysmorphism in one patient

Course and prognosis
• Bleeding, infection, swelling, and vesicle formation of the affected skin
• Malocclusion
• Normal development and mental status
• No increased risk of tumors

Laboratory findings
• Normal karyotypes
• Neither internal nor visceral abnormalities were observed
• No vascular etiology for partial overgrowth and disproportion of limbs

Genetics and pathogenesis
• Inheritance of this syndrome/association is not known. No recurrence of the disorder was observed in six siblings of all six families.
• There is a slight female preponderance.
• Somatic mosaicism is a theoretical possibility due to patchy vascular markings of the skin and asymmetric overgrowth.

Differential diagnosis
• BWS
• PTEN hamartomas syndrome
• Macrocephaly–capillary malformations syndrome
• Klippel–Trenaunay syndrome
• Proteus syndrome
• Kaposiform hemangioendothelioma
• Tufted angioma

Follow-up and therapy
• Surgical resection of lymphatic malformations
• OK-432 sclerotherapy
• CO₂ laser photocoagulation

Bibliography

KLIPPEL–TRÉNAUNAY SYNDROME
See Chapter 18.

MACROCEPHALY–CAPILLARY MALFORMATION SYNDROME
See Chapter 18.