The Big Brain Theory: A Review of Overgrowth Syndromes for the Neuroradiologist

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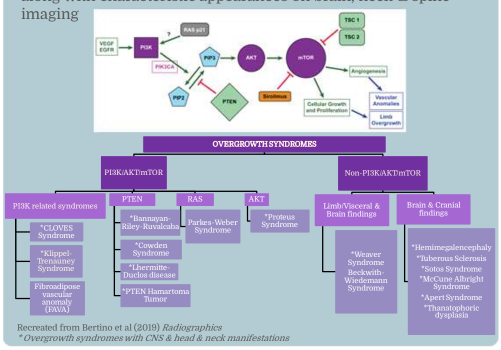
Background

Segmental overgrowth

- ◉ Phenotype confined to one or a few regions of the body
- ◉ Asymmetric growth of musculoskeletal, adipose &/or brain tissue along with focal hyperplasia of capillary, venous or lymphatic vessels & overlying skin lesions
- ◉ Occurs with mutations in receptor tyrosine kinase (RTK)–phosphatidylinositol-3-kinase (PI3K)/ protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway
- ◉ PI3K/AKT/mTOR closely related to Ras/MAPK pathway
- ◉ Non PI3K/AKT/mTOR overgrowth syndromes also exist
- ◉ Macrocephaly is a common finding in segmental overgrowth
- ◉ Head circumference > 3 SD above mean (≥99.7 percentile), is highly suspicious of PTEN Hamartoma Tumor syndrome
- ◉ This poster describes our current understanding of molecular basis & cancer predispositions of these overgrowth syndromes along with characteristic appearances on brain, neck & spine imaging



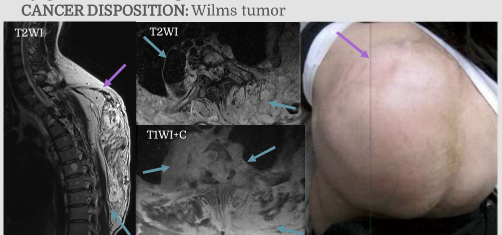
VEGF EGFR
PI3K
RAS p21
PIK3CA
PIP3
PIP2
AKT
mTOR
TSC 1
TSC 2
PTEN
Sirolimus
Angiogenesis
Cellular Growth and Proliferation
Vascular Anomalies
Limb Overgrowth
OVERGROWTH SYNDROMES
PI3K/AKT/mTOR
Non-PI3K/AKT/mTOR
PI3K related syndromes
PTEN
RAS
AKT
*CLOVES Syndrome
*Klippel-Trenauney Syndrome
Fibroadipose vascular anomaly (FAVA)
*Bannayan-Riley-Ruvalcaba
*Cowden Syndrome
*Lhermitte-Duclos disease
*PTEN Hamartoma Tumor
Parkes-Weber Syndrome
*Proteus Syndrome
Limb/Visceral & Brain findings
*Weaver Syndrome
Beckwith-Wiedemann Syndrome
Brain & Cranial findings
*Hemimegalencephaly
*Tuberous Sclerosis
*Sotos Syndrome
*McCune Albright Syndrome
*Apert Syndrome
*Thanatophoric dysplasia

Recreated from Bertino et al (2019) *Radiographics*
** Overgrowth syndromes with CNS & head & neck manifestations*

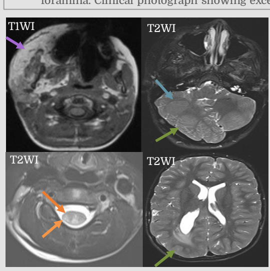
PI3K Related Syndromes (PROS)

CLOVES Syndrome

CLO: Congenital lipomatous overgrowth, V: Vascular anomalies, E:Epidermal nevi, S: Scoliosis/spinal deformities
GENETIC MUTATION: PI3KCA gene mutation on 3q26
PHENOTYPE: High or low flow vascular anomalies (lymphatic malformations are more common), lipomatous overgrowth with port wine stain over trunk & extremities; Spine: Scoliosis, spina bifida, thoracic lipomatous hyperplasia
CNS manifestations: Neuronal migration defects, hemimegalencephaly, ventriculomegaly, corpus callosal dysgenesis, tethered spinal cord & neural tube defects
CANCER DISPOSITION: Wilms tumor



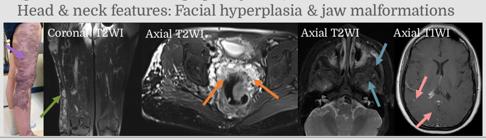
A patient with CLOVES syndrome demonstrating lipomatous overgrowth in the back with large, high flow paraspinal vascular malformation, insinuating intraspinally through neural foramina. Clinical photograph showing excessive soft-tissue growth in the back.



CLOVES syndrome mainly affects the right face & brain. Imaging demonstrates lipomatous overgrowth of right half of face, hemimegalencephaly involving the right cerebral & cerebellar hemispheres, right half of the brainstem & spinal cord (total hemimegalencephaly) with dysplasia & nodular heterotopia. Ill-defined T2 hyperintensity within the dorsal & dorsolateral aspects of right hemicord, representing abnormal myelination or hamartomatous change.

Klippel-Trenauney Syndrome (KTS)

GENETIC MUTATION: PIK3CA mutation
PHENOTYPE: Triad of capillary malformations manifesting as port-wine stain, venous varicosities along lateral aspect of lower extremities & bone/soft tissue hypertrophy
Most frequent brain abnormalities are aneurysm, venous malformation, infarction, hemimegalencephaly & brain tumors (glioblastoma & hemangiopericytoma)
Head & neck features: Facial hyperplasia & jaw malformations



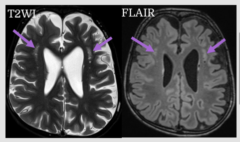
Imaging in different KTS patients, demonstrating unilateral hypertrophied limb with port-wine stain, superficial varicosities in the limb, rectal venous malformations, left sided facial hypertrophy, prominent choroid plexus & intracranial developmental venous anomalies.

PTEN Syndromes

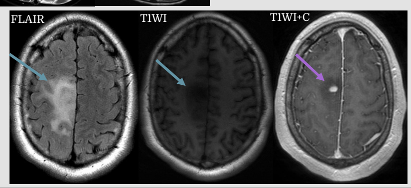
- ◉ PTEN mutations can manifest as high- or low-flow vascular anomalies
- ◉ PTEN syndrome demonstrate hamartomas & tumor growth rather than vascular anomalies compared to PROS
- ◉ PTEN Hamartoma Tumor Syndrome (PHTS) caused by germline autosomal-dominant mutations of tumor suppressor gene PTEN
- ◉ Increased risk for tumor development, with thyroid carcinoma occurring in young children

Bannayan-Riley-Ruvalcaba Syndrome

GENETIC MUTATION: PTEN gene mutation on 10q23
PHENOTYPE: Vascular anomalies: AVMs, venous malformations with lipomatous overgrowth, macrocephaly, cutaneous freckling
CANCER DISPOSITION: Colon, renal, breast, thyroid
IMAGING FINDINGS: Macrocephaly, cystic dilatation of VRS, white matter cysts with associated surrounding T2 hyperintensities



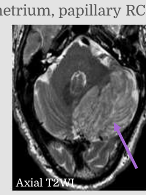
Imaging in a 11 year old with macrocephaly & PTEN mutation, demonstrating prominent perivascular spaces & surrounding FLAIR hyperintensities in bilateral frontal white matter.



26 year old male with PTEN mutation & follicular thyroid carcinoma status post thyroidectomy, presented with focal seizures. MRI shows right parasagittal frontal ill defined T2 hyperintensity with enhancing nodule. Pathology consistent with IDH mutant anaplastic astrocytoma.

Cowden Syndrome

GENETIC MUTATION: Autosomal dominant PTEN mutation
PHENOTYPE: Multiorgan hamartomas—mucocutaneous lesions, GI hamartomatous polyps, multinodular goiter, thyroid adenomas, fibrocystic changes of breast, testicular lipomatosis.
CNS manifestations: Lhermitte-Duclos disease (LDD), multiple venous anomalies, meningiomas, increased white matter signal abnormality, prominent perivascular spaces & cortical malformations
CANCER PREDISPOSITION: Breast, papillary thyroid, colon, endometrium, papillary RCC



MR imaging in a patient with Cowden syndrome demonstrates typical striated appearance of cerebellar gangliocytoma.

AKT Syndromes

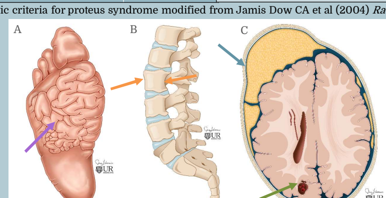
Proteus Syndrome

GENETIC MUTATION: Somatic AKT1 mutation
PHENOTYPE: Cerebriform connective tissue nevi (major diagnostic feature), epidermal nevi, overgrowth of limbs, vertebrae, skull & viscera, dysregulated adipose tissue with lipomas & regional absence of fat, low flow vascular malformations & abnormal facies including dolicocephaly, down-slanting palpebral fissure, low nasal bridge, wide nares & open mouth at rest

CATEGORY & SIGNS	RELATIVE FREQUENCY
Cerebriform connective tissue nevus	Common
Epidermal nevus	Common
Disproportionate overgrowth	Common
Dysregulated adipose tissue	Common
Vascular malformations (capillary, venous & lymphatic)	Common
Abnormal facial phenotype	Uncommon
Specific tumors before 30 yrs: Bilateral ovarian cystadenomas, Parotid monomorphic adenoma	Uncommon Uncommon

COMMON CNS RADIOLOGIC FINDINGS IN PROTEUS SYNDROME
Abnormal vertebral bodies
Scoliosis
Focal calvarial thickening
Osteoporosis or osteopenia
Asymmetric megalencephaly
White matter abnormalities
Hydrocephalus
Cavernous malformations
Spinal lipomatosis
Mastoid fluid & mucosa thickening, Paranasal sinus fluid or mucosal thickening, Abnormal middle ear

Diagnostic criteria for proteus syndrome modified from Jamis Dow CA et al (2004) *Radiographics*



(A) Cerebriform connective tissue nevus (B) Asymmetric growth, increased height & posterior scalloping of vertebral bodies (C) Expansile, fat-attenuation lesion in right frontal & parietal calvarium & cavernous malformation in right occipital lobe.

Non-PI3K/AKT/mTOR Overgrowth Syndrome with Limb, Visceral & Brain Findings

Weaver Syndrome

GENETIC MUTATION: EZH2 mutation
PHENOTYPE: Accelerated prenatal & postnatal growth, development delays, hypotonia, advanced bone age, dysmorphic facial features (large bi-frontal diameter, micrognathia, hypertelorism, large ears), low pitched cry, camptodactyly
CANCER PREDISPOSITION: Hematologic malignancies
IMAGING FEATURES: Dysmorphic facial features, camptodactyly, advanced bone age

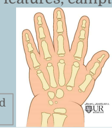
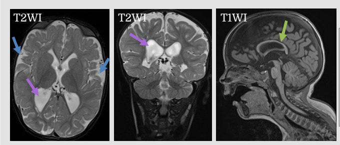


Illustration depicts a hand of an 8 month old with bone age consistent with 4 year old.

Non-PI3K/AKT/mTOR Overgrowth Syndrome with Brain & Cranial Findings

Soto Syndrome

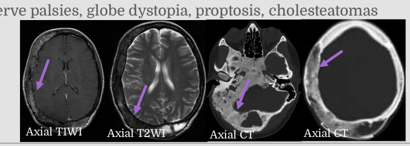
GENETIC MUTATION: Autosomal dominant syndrome NSD1 mutation on 5q35
PHENOTYPE: Increased birth weight & length (>97th percentile), large head circumference at birth, excessive growth in first years of life, craniofacial dysmorphisms (dolichocephaly, prominent forehead, hypertelorism, epicanthic folds, flat nasal bridge, down-slanting palpebral fissures, high arched palate, premature eruption of teeth & pointed chin), intellectual disability & developmental delay
CANCER DISPOSITION: Wilms tumor, neuroblastoma, gastric carcinoma, neuroectodermal & hematologic malignancies
IMAGING FINDINGS: CNS: Ventriculomegaly, increased extra-axial fluid, midline anomalies (corpus callosal dysgenesis & persistent cavum velum interpositum; Spine: kyphoscoliosis



MRI in a 16 year-old with macrocephaly & Soto syndrome demonstrating prominent ventricles, prominent extra-axial spaces & thinning of corpus callosum.

McCune Albright Syndrome

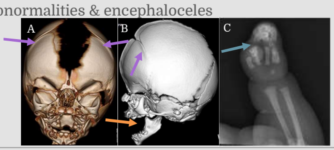
GENETIC MUTATION: Postzygotic mutations in guanine nucleotide binding protein (G protein), alpha stimulating activity polypeptide 1 (GNAS1) gene on chromosome 20
PHENOTYPE: Triad of polyostotic fibrous dysplasia, café-au-lait pigmentation & precocious puberty
CANCER DISPOSITION: Breast, thyroid, testicular & bone
IMAGING FINDINGS: Craniofacial fibrous dysplasia, cranial nerve palsies, globe dystopia, proptosis, cholesteatomas



Imaging demonstrating classic polyostotic fibrous dysplasia of the skull base & right calvarium in a patient with McCune Albright disease. The fibrous dysplasia is expansile with internal ground glass density.

Apert Syndrome

GENETIC MUTATION: FGFR2 mutation
IMAGING FEATURES: Primary malformation: Midline abnormalities, ventriculomegaly, cortical malformations, vermian hypoplasia, cerebral hemiatrophy, pyramidal tract abnormality, fused thalami, megalencephaly.
Secondary to bony malformations: Tonsillar herniation, temporal lobe abnormalities & encephaloceles



Premature closure of bilateral coronal sutures with brachycephaly & midface hypoplasia in this patient with Apert's syndrome. Hand radiograph demonstrating soft tissue & bony syndactyly.

Take Home Points

- ◉ PI3K/AKT/mTOR & non PI3K/AKT/mTOR overgrowth pathways exist & have unique genetic & phenotypic features
- ◉ PI3K/AKT/mTOR overgrowth syndromes are often associated with vascular anomalies & have distinct clinical manifestations & imaging findings, which are key for diagnosis, treatment & prognosis
- ◉ Several overgrowth syndromes are associated with cancer predisposition syndromes & imaging should be appropriately performed for early detection.

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