PTEN Hamartoma Tumor Syndrome (PHTS)

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Pathophysiology and Presentation

Genetic Mutation

- Mutation in the Phosphatase Tensin Homologue (PTEN) Gene [1]
    - Tumor Suppressor Gene
- Autosomal Dominant Inheritance [1]

Associated Malignancy [1]

- Breast Cancer (85%)
- Thyroid Cancer (35%)
    - Predominantly Follicular, Rarely Papillary, Never Medullary [2]
- Renal Cell Cancer (34%)
    - Predominantly Papillary [2]
- Endometrial Cancer (28%)
- Colorectal Cancer (9%)
- Melanoma (6%)

Benign Tumors [1]

- Gastrointestinal Polyps
- Lipomas
- Acral Keratosis
- Mucosal Papillomas
- Fibromas
- Benign Breast, Thyroid, and Uterine Lesions

Neurodevelopmental Associations [1]

- Macrocephaly (Large Head Size) – 94%
- Dolichocephaly (Head Longer than Wide)
- Autism
- Intellectual Disability
- Developmental Delays

Variations

Spectrum of Disorders

- PHTS Presents with a Spectrum of Disorders (Previously Believed to Be Completely Separate Conditions) [1]
  - *Cowden Syndrome*
  - *Bannayan-Riley-Ruvalcaba Syndrome (BRRS)*
  - *Proteus-Like Syndrome/SOLAMEN Syndrome*
- Traditionally Cowden Syndrome was Diagnosed in Adults and BRRS Diagnosed in Pediatrics [1]
  - Cowden Characteristics Generally Do Not Appear Later [1]

Cowden Syndrome – The Most Common PHTS [3] MN

- Major Criteria:
  - Breast Cancer
  - Endometrial Cancer (Epithelial)
  - Thyroid Cancer (Follicular)
  - Gastrointestinal Hamartomas
  - Lhermitte-Duclos Disease (Adult)
  - Macrocephaly
  - Macular Pigmentation of the Glans Penis
  - Multiple Mucocutaneous Lesions (Trichilemmomas, Acral Keratoses, Mucocutaneous Neuromas, Oral Papillomas)
- Minor Criteria:
  - Autism Spectrum Disorder
  - Colon Cancer
  - Esophageal Glycogenic Acanthosis
  - Lipomas
  - Mental Retardation
  - Renal Cell Carcinoma
  - Testicular Lipomatosis
  - Thyroid Cancer (Papillary of Follicular Variant of Papillary)
  - Thyroid Structural Lesions
  - Vascular Anomalies

Bannayan-Riley-Ruvalcaba Syndrome (BRRS) [4]

- Macrocephaly
- Hamartomatous Intestinal Polyposis
- Lipomas
- Vascular Malformations/Hemangiomas
- Pigmented Penile Macules
- Developmental Delay
- Intellectual Disability

Proteus-Like Syndrome/SOLAMEN Syndrome

- Typical Proteus Syndrome (PS) Itself is No Longer Considered to Be Due to a germline PTEN Mutation [5,6]
- Proteus-Like Syndrome is Undefined but Describes Individuals with Clinical Features of Proteus Syndrome with a PTEN Mutation that Do Not Meet the Diagnosis of PS
- Proteus Syndrome (PS) Characteristics: [7]
    - Distorting and Progressive Overgrowth of the Skeletal Architecture
    - Cerebriform Connective Tissue Nevi
    - Linear Verrucous Epidermal Nevus
    - Lipomatous Overgrowth
    - Vascular Malformations
    - Overgrowth of Other Tissues (Spleen, Liver, and Thymus)
    - Dysmorphic Facial Features
- Some Recommend the Term SOLAMEN Syndrome to Describe the Phenotypic Features of PS but with a PTEN Mutation [8]
    - Segmental Overgrowth, Lipomatosis, Arteriovenous Malformation, and Epidermal Nevus (SOLAMEN)

Other Familial Colorectal Cancer and Polyposis Syndromes

- *See Familial Colorectal Cancer and Polyposis Syndromes

Diagnosis and Management

Diagnosis

- Clinical Diagnosis of Cowden: [4]
    - Individual with Either:
        - Three Major Criteria, One Must Include Macrocephaly, Lhermitte-Duclos Disease, or GI Hamartomas
        - Two Major and Three Minor Criteria

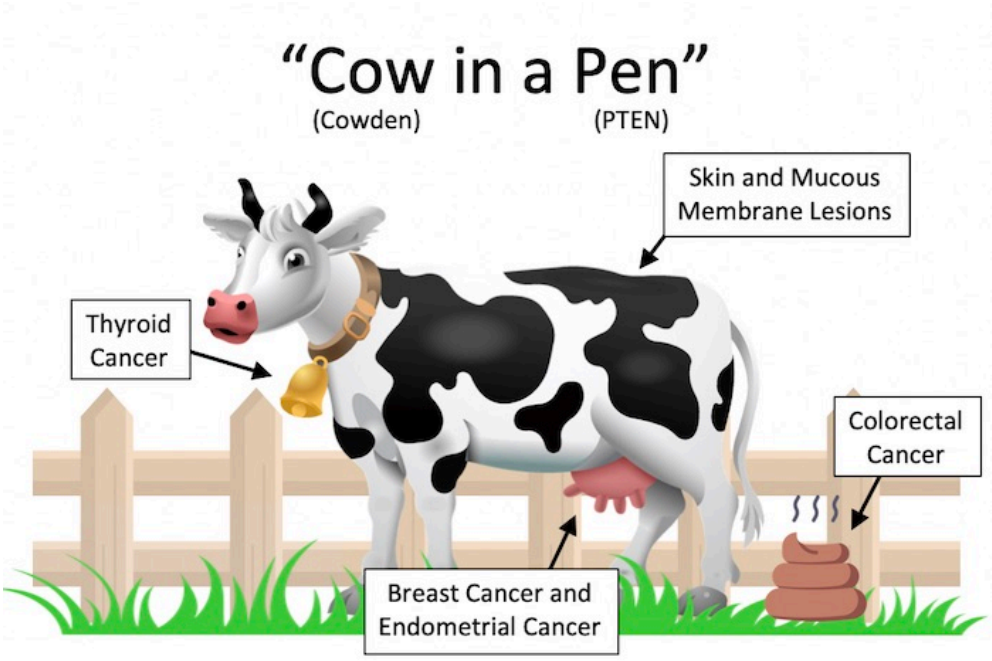
    - Family with an Individual Meeting Criteria or a PTEN Mutation
        - Any Two Major Criteria
        - One Major and Two Minor Criteria
        - Three Minor Criteria
- Clinical Diagnosis of Bannayan-Riley-Ruvalcaba Syndrome is Poorly Established
- Diagnosis Confirmed by Genetic Testing

Screening/Surveillance [9-11]

- Physical Exam at Diagnosis
    - Include Dermatologic, Neurological, and Cognitive Exams
- Thyroid US Annually, Starting at Age 18
    - Consider Baseline Ultrasound at Age 15
- Breast MRI or Mammography Annually, Starting at Age 30
- Transvaginal Ultrasound Annually, Starting at Age 30-35
    - Also Consider Endometrial Biopsy
    - Utility of Endometrial Cancer Surveillance is Debated
- Colonoscopy Every 5 Years, Starting at Age 35
- Renal US Every 2 Years, Starting at Age 40

Mnemonics

Cowden Syndrome Associations [12]



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