Tuberous Sclerosis: New Treatment Strategies for an Old Disease

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Objectives

- History and Diagnostic Criteria for Tuberous Sclerosis
- Current management of common disease manifestations
- New and emerging therapies

"Sclérose tubéreuse des circonvolutions cérébrales".

Désiré-Magloire Bourneville
1881

Vogt’s Triad

- Epilepsy
- Idiocy
- Adenoma Sebaceum

Tuberous Sclerosis Complex

- Less than 1/3 have all three classic symptoms of Vogt’s Triad
- 35% of patients with TSC have normal intelligence
- Incidence of TSC much higher than previously appreciated
- New Diagnostic Criteria for TSC

Clinical Manifestations of TSC

Brain: cortical tubers, subependymal nodules (SENs), subependymal giant cell astrocytomas (SEGA)s
Eye: retinal hamartomas
Heart: cardiac rhabdomyomas
Kidney: benign angiomyolipomas, cysts, malignant angiomyolipomas, renal cell carcinoma
Lung: lymphangioleiomyomatosis (LAM), multifocal micronodular pneumocyte hyperplasia
Skin: hypomelanotic macules, shagreen patches, periangual or subungual fibromas, facial angiofibromas
Behavior: mental retardation, autism, bipolar disorder

Pan et al, Trends Cell Biol. 2004
Facial Angiofibroma

Hypopigmental Macule and Shagreen Patch

Periungual Fibroma

Retinal Hamartoma

Cardiac Rhabdomyoma

Lymphangioleiomyomatosis (LAM)
Renal Angiomyolipoma (AML)

Cortical Tuber

Subependymal Nodules

Subependymal Giant Cell Astrocytoma (SEGA)

Acute Hydrocephalus with SEGA

Dental Pits and Gingival Fibromas
Retinal Achromic Patch

Connective Tissue Hamartoma

Bone Cyst

Liver Angiomyolipoma

Uterine PEComa

Clinical Diagnostic Criteria

Major features

1. Cortical tubers
2. Subependymal nodules (SENs)
3. Subependymal giant cell astrocytomas (SEGA)
4. Hypomelanotic macules (3 or more)
5. Sturge-Weber (congenital angiomatous proliferation or occlusive venous disease)
6. Facial angiofibromas or forehead plaque
7. Multiple retinal nodular hamartomas
8. Nodular fibromas or periungual fibromas
9. Cardiac rhabdomyomas, single or multiple
10. Pulmonary lymphangioleiomyomatosis and/or renal angiomyolipomas

Minor features

1. Multiple, randomly distributed pits in dental enamel
2. Hamartomatous rectal polyps
3. Bone cysts
4. Cerebral white matter radial migration lines
5. Gingival fibromas
6. Neuronal hamartomas
7. Retinal achromatosis patches
8. "Confetti" skin lesions
9. Multiple renal cysts

<table>
<thead>
<tr>
<th>Definite</th>
<th>Probable</th>
<th>Possible</th>
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<tbody>
<tr>
<td>MAJOR: 2</td>
<td>1</td>
<td>1</td>
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<tr>
<td>MINOR: 2</td>
<td>-</td>
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</table>
Genetics of TSC

Autosomal Dominant
Near 100% Penetration
Variable Expression

TSC1 (15-20%)
TSC2 (60-70%)
PKD1
NMI (10-15%)

Clinical Management of TSC

Dermatological Management

• Laser ablation of facial angiofibromas
  • Differing techniques and laser types
  • Cosmetic or symptomatic treatment
  • Variable response
  • Transient effect (6m-3 years)

Dermatological Management

• Hypopigmented Macules, Shagreen Patches, and Facial plaques require no specific treatment

• Ungal fibromas removed by surgical excision when symptomatic (bleeding, causing pain)
  • Tend to recur over time
  • May also be removed due to cosmetic concerns

Cardiac Management

• Rhabdomyomas are benign growths
• Transthoracic ECHO at birth or time of diagnosis
• Baseline ECG to evaluate for conduction defects

• F/U evaluations and interventions dependent on severity and course
  • Most no hemodynamic interference and spontaneously resolve. Annual ECHO until resolve, then only as needed.
  • Repeat ECG only required if prior abnormal, clinical concern for arrhythmia, or treatment with medications associated with significant risk for such

Ophthalmologic Management

• Baseline evaluation at birth or diagnosis

• Vision screening/slit lamp examination every 1-2 years through childhood
**Dental Management**
- No specific treatment – good hygiene and preventative dentistry is general rule
- Dental pits generally not problematic and do not require specific treatment
- Gingival fibromas can be excised if causing bleeding, discomfort, or cosmetic concerns

**Infantile Spasms in TSC**
- Infantile Spasms
  - Neurological hallmark of TSC – presenting sign of tuberous sclerosis in 10-15% affected individuals
  - Start usually by 1 year of age in 75% of children (can be in 1st month of life)
  - Earlier onset = worse prognosis
    - Developmental delay
    - Intractable partial epilepsy

**Infantile Spasms in TSC**
- Classic Hypsarrhythmia

**Infantile Spasms in TSC**
- Hemi-Hypsarrhythmia

**Infantile Spasms**
- (Saybril) is treatment of choice despite associated adverse effect on peripheral vision – As high as 95% response rate
- Steroids are second line treatment (ACTH or oral prednisone)
- Valproate, Topamax, Clonazepam minimally effective as single agents but may have beneficial adjunctive use

**Epilepsy in TSC**
- 70-80% patients with TSC experience seizures
- Virtually all seizure types have been reported (simple partial, complex partial, generalized tonic-clonic, absence)
- Medically refractory epilepsy is common, despite even polytherapy with antiepileptic drugs
- Epileptic surgery can be very beneficial in TSC patients with medically-refractory epilepsy
Pharmacologic Management of Seizures in TSC

<table>
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<th>Drug name</th>
<th>Start dose (mg)</th>
<th>Tapered daily dose (mg)</th>
<th>Consequence</th>
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<tbody>
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<td>Levetiracetam</td>
<td>500-1000 mg</td>
<td>250-500 mg</td>
<td>Taper slowly</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>50-100 mg</td>
<td>5-10 mg</td>
<td>Use with caution</td>
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<tr>
<td>Carbamazepine</td>
<td>150-300 mg</td>
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<tr>
<td>Phenytoin</td>
<td>100 mg</td>
<td>10 mg</td>
<td>Use with caution</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>500-1000 mg</td>
<td>250-500 mg</td>
<td>Use with caution</td>
</tr>
</tbody>
</table>

Management of Autism/Behavior in TSC

- 2/3 patients have Learning Difficulties and/or Mental Retardation
- 1/3 patients have Autism or Autistic Behaviors
- Significant Mood/Behavioral Difficulties and Sleep Problems

Management of Neurobehavior in TSC

- Serial Monitoring for SEGA
  - MRI + contrast at least every 1-2 years

Traditional Surgical Resection of SEGA

Stereotactic Angioplasty Balloon Technique

- MRI + contrast at least every 1-2 years
**Diagnosis and Management of Renal AML**
- Renal US or MRI Abdomen every 1-2 years
- Surgical Biopsy and excision is to be avoided if possible
- Vascular embolization or cryotherapy is treatment of choice
- Monitoring of renal function and management of comorbidities essential (Hypertension, Diabetes)

**Diagnosis and Management of LAM**
- Baseline high-resolution chest CT in post-pubertal females
- Baseline pulmonary function tests
- High suspicion if pneumothorax, chylothorax, or persistent respiratory difficulties
- Avoid Estrogen therapies

**Novel Molecular-based TSC Therapy**

**TSC1/TSC2 and mTORC1**

**Rapamycin and Everolimus (RAD001)**

**Rapalog inhibition of mTORC1**
**Rapamycin for the Treatment of SEGA**

Franz et al. Annals Neurol. 2006

**Rapamycin for treatment of AML**


**Rapamycin effect on LAM**


**Everolimus Effect on SEGA in TSC**


**RAD001 effect on SEGA volume**

**MR Spectroscopy of SEGA**

NAA = N-Acetylaspartate
Cr = Creatine
Cho = Choline
ml = myoinositol
Summary

- Tuberous Sclerosis is a multiorgan disorder with variable penetrance and severity
- Molecular-based therapies for treatment of major clinical morbidities of TSC are in development

2nd Annual TSC Summer Camp
August 6-9, 2009
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