Tuberous Sclerosis Complex: Clinical overview

Elizabeth A. Thiele, MD, PhD
Director, Carol and James Herscot Center for Tuberous Sclerosis Complex
Director, MGH Pediatric Epilepsy Program
Professor of Neurology, Harvard Medical School
Tuberous Sclerosis Complex

4 years old (1960)
Tuberous Sclerosis Complex

12 years
TSC: a Genetic Disorder

- Incidence of 1: 5,500  (not rare)
- Autosomal dominant disorder, although 2/3 cases appear sporadic
- 2 genes: TSC1 (hamartin) and TSC2 (tuberin)
- Identifiable TSC1 or TSC2 mutation in 85% with TSC
  - TSC2 mutations are more common (6:1)
  - TSC2 mutations have a more severe phenotype
- Wide phenotypic variability, including within families
- Gender somehow matters: e.g. LAM in women
- TSC1/TSC2 components of mTOR signaling pathway
Tuberous Sclerosis Complex: History

- **1862 (von Recklinghausen)**
  - described multiple heart tumors and hardened areas of brain in newborn who died from respiratory distress

- **1880 (Bourneville)**
  - first description of cerebral manifestations of the disease, “sclerose tubereuse”, indicating the superficial resemblance of the lesions of a potato

- **1885 (Balzer and Menetrier, independently)**
  - describe skin disease they interpreted as adenoma sebaceum
Tuberous Sclerosis Complex: History

- **1908 (Vogt)**
  - recognized the brain findings and adenoma sebaceum were manifestations of the same disease;
  - described triad of intractable epilepsy, mental retardation and adenoma sebaceum (now known to be present in less than 1/3 of patients with TSC)

- **1914**
  - first description of cognitively normal male with epilepsy and adenoma sebaceum
Tuberous Sclerosis Complex: History

- 1993  TSC2 gene discovered
- 1997  TSC1 gene discovered
- 2002  TSC1 and TSC2 proteins found to be components of mTOR signalling pathway
- 2008  Clinical trials with rapamycin (mTOR inhibitor)
- 2011  FDA approval of everolimus (mTOR inhibitor) for treatment of SGCT, renal AML in TSC
- 2015  FDA approval of rapamycin (mTOR inhibitor) for treatment of LAM
mTOR Pathway (J. Blenis, simplified)
TSC: Revised diagnostic criteria 2012

- **Multisystem involvement**
  - Brain
  - Skin
  - Heart
  - Kidney
  - Eyes
  - Lung
  - Teeth
  - Bone
  - Other

- **Definite TSC:**
  - 2 major features OR
  - 1 major feature + 2 minor features

- **Possible TSC:**
  - 1 major feature OR
  - 2 or more minor features
TSC: Revised diagnostic criteria 2012

• **Major features:**
  » facial angiofibromas (>2) or forehead plaque
  » nontraumatic ungual or periungual fibroma
  » hypomelanotic macules (3 or more)
  » shagreen patch (connective tissue nevus)
  » cortical dyplasias
    – Includes tubers and WM radial migration lines
  » subependymal nodule
  » subependymal giant cell astrocytoma
  » multiple retinal nodular hamartomas
  » cardiac rhabdomyoma, single or multiple
  » lymphangioleiomyomatosis
  » renal angiomyolipoma (3 or more)

Skin

Brain

Eye

Heart

Lung

Kidney
TSC: Revised diagnostic criteria 2012

- Minor features:
  - dental pits (>3), multiple randomly distributed
  - intraoral fibromas (2 or more)
  - nonrenal hamartomas
  - retinal achromatic patch
  - “confetti” skin lesions
  - multiple renal cysts
TSC Consensus Conference 2012
Clinical guidelines

TSC and the brain

• CNS involvement is a hallmark of the disease, and is seen in 95% of affected individuals

• Pathologic features
  » cortical tuber
  » subependymal nodule (SEN)
  » subependymal giant cell tumor (SGCT)
  AND…..
  » radial migration lines (RML)
TSC: CNS pathology
TSC CNS involvement: Cortical tubers

- Located at the gray white junction
- Vary widely in size and distribution
- Histology:
  - Marked distortion of cortical lamination
  - Dysplastic, hypomyelinated aggregates of abnormal glial and neural elements
  - Glial derived cells and astrocytes predominate
  - Giant cells: enlarged, bizarre-appearing neurons or large cells with both neuronal and glial characteristics
  - Neurons lack axons and normal dendrites (but stain for neuronal markers)
TSC: Cortical tuber
TSC CNS involvement: Subependymal nodules

- Located around wall of lateral ventricle
- Most commonly occur at caudothalamic groove in the vicinity of the Foramen of Monro
- Either discrete or roughly confluent areas of firm, hypertrophic tissue (a.k.a. candle gutterings)
- **Histology**: Consist of astrocytes arising from the subependymal zone and protruding into the ventricle. They calcify by puberty.
- Generally asymptomatic, but can develop into SGCT in 5-10% of cases
TSC CNS involvement: Subependymal giant cell tumor

- Median age at presentation: 9 years (1-21 yr)
- Derived from subependymal nodules in lateral ventricular walls
- **Symptoms** consequent to increased intracranial pressure (headache, vomiting, papilledema), or increased seizure activity
- **Treatment**: surgical, or mTOR inhibitor if surgery not possible
- 1/3 of patients will develop SGCT in other hemisphere (?)
- **PRESENTATION MAY BE SUBTLE!!!!**

- (aka Subependymal giant cell astrocytoma = SEGA)
TSC CNS involvement: Subependymal giant cell tumor

SGCT growing into the 3rd ventricle
The brain in TSC: Radial migration lines
TSC: Neurology

- CNS involvement is a hallmark of the disease, and is seen in 95% of affected individuals

- Pathologic features
  - cortical tuber
  - subependymal nodule (SEN)
  - subependymal giant cell astrocytoma (SEGA)

- Clinical features
  - epilepsy
  - mental retardation / cognitive impairment
  - autism
  - sleep disorders
Expanding the TSC neurologic phenotype: epilepsy “update”

- 85% of individuals with TSC develop epilepsy
  - 70% with seizure onset 1st year of life
  - 1/3 develop infantile spasms
    - 1/3 of those with normal cognitive outcome
    - Vigabatrin particularly effective—FIRST LINE TREATMENT
  - 2/3 develop medically refractory or intractable epilepsy

Muzykewicz et al, Epilepsia 2009, Chu Shore et al, Epilepsia 2010
Expanding the TSC neurologic phenotype: epilepsy “update”

- 85% of individuals with TSC develop epilepsy
  - >1/3 experience long-term remission
    - 40% off treatment
  - Clobazam, lacosamide perhaps particularly effective
  - Dietary therapies (classic ketogenic diet, low glycemic index treatment) often very effective
  - Vagus nerve stimulator can be effective
  - Epilepsy surgery plays important role in treatment
  - And what about medical marijuana?

Muzykewicz et al, Epilepsia 2009, Chu Shore et al, Epilepsia 2010
Geffrey et al, Epil Res 2015
Tuberous Sclerosis Complex: What we need to know

- Why seizures?
- Are tubers epileptogenic, or irritating to neighboring neurons?
- Are all tubers created equal? Are some more epileptogenic than others?
- Is epileptogenicity related to diffuse and/or more subtle cortical or subcortical abnormalities?
- Are particular individuals with TSC at risk for seizures?
Managing epilepsy in TSC: What we don’t know, but would like to:

• What causes epilepsy in TSC?
• Can intractable epilepsy be predicted?
• Is there a role for prophylactic management?
• Why are infantile spasms SO common?
• Why do some children with TSC and IS have good neurocognitive outcome?
• What is relationship between epilepsy and autism?
Cognitive profiles in TSC

- 107 of 208 patients seen had neuropsychological testing at MGH
  » Demographics of “study group” similar to overall clinic group, except that study group had younger age, IS more common

- IQ/DQ scores approximated a bimodal distribution with means of 93 ($\pm$ 16) and 44 ($\pm$ 25)
  » Roughly 50:50 split between two modes

Winterkorn et al, Neurology 2006
Cognitive profiles in TSC
Significant variables in outcome

• Higher IQ/DQ:
  » Older age at seizure onset
    – Of patients with seizure onset >2.5 years (n=18), none with IQ/DQ<70
  » Familial TSC
    – Although also higher TSC1, lower frequency of IS and refractory seizures

• Lower IQ/DQ:
  » Current seizure activity
  » Refractory seizures and mixed seizure types
  » TSC2 mutation
Autism in TSC

• Herscot Center retrospective study; single neuropsychologist evaluation

• 41/103 (40%) with ASD

• Those with ASD:
  » Significantly more likely to have TSC2 mutation
  » Significantly more likely to have h/o IS, refractory epilepsy
  » Significantly lower IQ (51 vs 81)
  » Not more likely to be male
  » Not significant difference in TSC related brain involvement

Numis et al, Neurology 2011
Herscot Center for TSC: Mental health issues

- **66% have at least one psychiatric symptom**
  - 37% have greater than one symptom
  - Most common: mood disorders, anxiety, ADHD, aggressive, disruptive behaviors

- **Adults with TSC at much greater risk of psychiatric disorders than general population (SCL-90)**
  - Main difficulties: interpersonal sensitivity, social alienation, depression, cognitive performance

- **Self injurious behavior in 10%**
  - Highly associated with TSC2 mutation, history of IS, sz, cognitive impairment and autism

Muzykewicz et al, Epilepsy Behav. 2007
Pulsifer et al, Epilepsy Behav, 2007
Staley et al, Epilepsy Behav, 2008
Expanding the TSC neurologic phenotype: Mental health issues

- **Post traumatic stress reactions not uncommon in TSC**
  - Often occur following “mild” stressors
  - Can significantly impact individual’s ability to function
  - Typically respond to SSRI, ? Role for beta blockers?

  *Boronat et al, Ann Clin Psychiatry 2013*

- **Anxiety almost universal**
  - Obsessive, frequently centered around specific things
  - Extremely underappreciated, underdiagnosed, undertreated

- **TSC individuals can be “savants”**
  - US Presidents, Spanish, puzzles, numbers and more
The Neurology of TSC: Epilepsy, Cognition, and Behavior

What are the relationships between

- Tubers
- Seizures
- Interictal discharges
- Genotype
- Role of haploinsufficiency?

- Cognition
- Behavioral / psychological issues
- Autism
TSC: and what is the role for mTOR inhibitors?

- **Published clinical trials:**
  - Rapamycin in treatment of renal AML, LAM
  - Everolimus (Affinitor) in treatment of renal AML, SGCT
  - Everolimus in treatment of refractory epilepsy (EXIST 3)

- **Ongoing clinical trials:**
  - Topical rapamycin for facial angiofibroma
  - Everolimus in treatment of LAM
  - Rapamycin plus chloroquine in treatment of LAM
  - Everolimus in treatment of intellectual disability
TSC: and what is the role for mTOR inhibitors?

- **Lessons learned from trials, clinical use:**
  - mTOR inhibitors lead to a reduction in size of TSC related tumors, slowed progression of LAM, possible efficacy in epilepsy
  - So far, no data on role in treating cognition
  - Overall well tolerated, but are significant side effects
  - Discontinuation of treatment results in regrowth of tumors
    - acceleration of growth?
    - Therefore, longterm treatment required
TSC: and what is the role for mTOR inhibitors?

• So for which TSC patients should an mTOR inhibitor be considered?
  » Those with inoperable SGCT
  » Those with significant renal AML who are not ideal embolization candidates
  » Those with moderate-severe LAM

• And are there other effective treatments?
TSC: And what else?

• “Living with TSC is like walking in a minefield”

• “We are just always waiting for the sky to fall, or for the other shoe to drop”
Kayleigh, a 3 year old girl with TSC
   » Cardiac rhabdomyoma, seizures, autism, SEGA

Margaret, a 10 year old girl with TSC
   » Seizures, learning problems, SEGA, kidney AML, pancreatic neuroendocrine tumor

Paul, a 36 year old man with TSC
   » Heart surgery as infant and now with pacemaker, refractory seizures s/p surgery, anxiety, significant facial angiofibroma, significant kidney AML, pulmonary LAM
Can TSC teach us about other things? an ideal model

- Epilepsy
- Autism
- Mental health
- Normal growth, differentiation and development
- Abnormal growth, including malignancies
TSC: Where do we go from here, and what do we need to know?

- What are variables determining epilepsy, autism, behavioral issues and ID, and how can we control them?
- How and why does gender matter?
- What can the various organ involvement further teach us?
- What other medications or treatment can be as if not more effective than the mTOR inhibitors?
- Etc, etc, etc……
Living with TSC

Raising awareness and providing education for people living with Tuberous Sclerosis Complex, their families, providers, and others.

TSC FAMILY STORIES

Jacob  Michael  Danica  Troy  Laurie  Brad  Steve

TUBEROUS SCLEROSIS COMPLEX

- About TSC
- Diagnosis
- Cause
- Treatment

HOW TSC AFFECTS THE BODY

- Brain: Anatomy  Seizures  Learning  Mental Health
- Heart
- Skin
- Kidney
- Lung
- Eye
- Other

COMPREHENSIVE CARE

- Medical Care
- Genetic Counseling
- Research
- Talking About TSC
- TSC Support

INTERACTIVE TIMELINE

A quick guide to the clinical features of TSC through life stages

You will need QuickTime or Windows Media Player, and Flash to view the video and animations on this site.

This is a multi-media resource from the Carol & James Herscot Center for Children and Adults with Tuberous Sclerosis Complex at Massachusetts General Hospital, Boston, Massachusetts.

Produced by WGBH Educational Foundation.
©2006 The General Hospital Corporation

Technical Help | Feedback | Credits | Order CD
Tuberous Sclerosis Complex
Genes, Clinical Features, and Therapeutics

Edited by
David J. Kwiatkowski,
Vicky Holets Whittemore,
and Elizabeth A. Thiele

WILEY-BLACKWELL
The Carol and James Herscot Center for Tuberous Sclerosis Complex

• Clinical specialty care for CHILDREN

Neurology: Elizabeth A. Thiele, MD, PhD
Neurosurgery: Tina Duhaime MD
Emad Eskandar, MD
William Butler, MD
Neuroradiology: Paul Caruso, MD
Neuropsychology: Margaret Pulsifer, PhD
Amy Morgan, PhD
Dermatology: Joop Grevelink, MD
Nephrology: Elahna Paul, MD, PhD
Cardiology: Ana Maria Rosales, MD
Psychiatry: Larry Selter, MD
The Carol and James Herscot Center for Tuberous Sclerosis Complex

- Clinical specialty care for ADULTS

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurology</td>
<td>Elizabeth A. Thiele, MD, PhD</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>Emad Eskandar, MD</td>
</tr>
<tr>
<td></td>
<td>William Butler, MD</td>
</tr>
<tr>
<td>Neuroradiology</td>
<td>Paul Caruso, MD</td>
</tr>
<tr>
<td>Neuropsychology</td>
<td>Margaret Pulsifer, PhD</td>
</tr>
<tr>
<td>Cardiology</td>
<td>Ignacio Inglessis, MD</td>
</tr>
<tr>
<td>Dermatology</td>
<td>Joop Grevelink, MD</td>
</tr>
<tr>
<td>Nephrology</td>
<td>Elahna Paul, MD PhD</td>
</tr>
<tr>
<td>Urology</td>
<td>Adam Feldman, MD</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>Larry Selter, MD</td>
</tr>
<tr>
<td>Pancreatic surgery</td>
<td>Cristina Ferrone, MD</td>
</tr>
</tbody>
</table>