Epilepsies with Distinctive Constellations

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Discuss Two Epilepsies with Distinctive Constellations

- Early childhood onset
- Chronic, and commonly catastrophic epilepsies
- Often Multi-system involvement

Focus on Medical and Surgical Management of EPILEPSY

Sturge Weber Syndrome (SWS)
or
Encephalofacial angiomatosis

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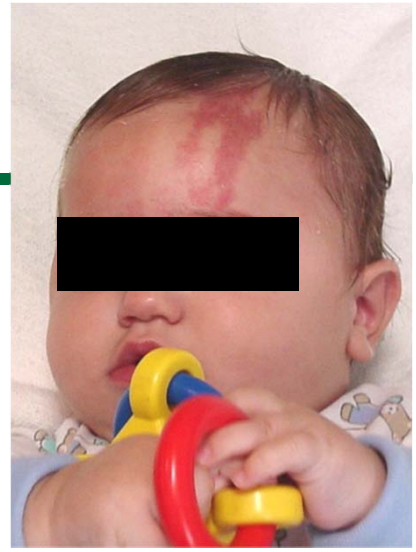
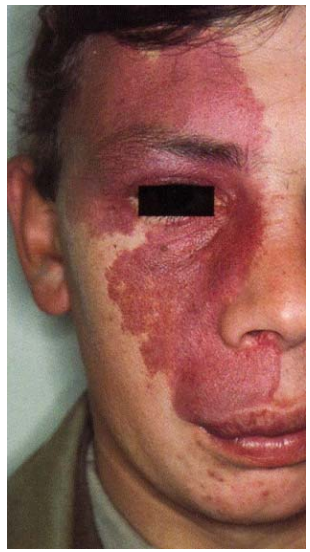
SWS: Core Clinical Features

- Sporadic condition
- Defined by cutaneous capillary malformations - Port-wine stain (PWS/nevus) in V1 territory *with or without*
  - V2, V3 or more extensive cutaneous involvement
  - *Epilepsy* with Cerebral venous malformations (leptomeningeal angiomatosis)
  - *Glaucoma* with ocular capillary venous vascular malformations





Lo W et al., Dev Med Child Neurol 2012; 54: 214

SWS: *Sporadic Condition*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sturge–Weber Syndrome and Port-Wine Stains Caused by Somatic Mutation in *GNAQ*

Matthew D. Shirley, Ph.D., Hao Tang, Ph.D., Carol J. Gallione, B.A., Joseph D. Baugher, Ph.D., Laurence P. Frelin, M.S., Bernard Cohen, M.D., Paula E. North, M.D., Ph.D., Douglas A. Marchuk, Ph.D., Anne M. Comi, M.D., and Jonathan Pevsner, Ph.D.

***GNAQ* encodes Gαq, a member of the q class of G-protein alpha subunits that mediates signals between G-protein–coupled receptors and downstream effectors**

Shirley MD et al., N Engl J Med 2013;368:1971-9

Epilepsy in SWS: Key Features

- Early childhood or infantile onset
- "Acute clusters" or "status epilepticus or EPC" with periods of quiescence
  - Triggers: infection, fever, dehydration, head bump
  - Bland seizures/subtle foot hand twitching (EPC)
  - Precious time lost to before treatment of seizure cluster/status is initiated
  - EEG: Sharp waves are often very low amplitude, in runs (PLEDs), and poor clinical - ictal EEG correlation during status

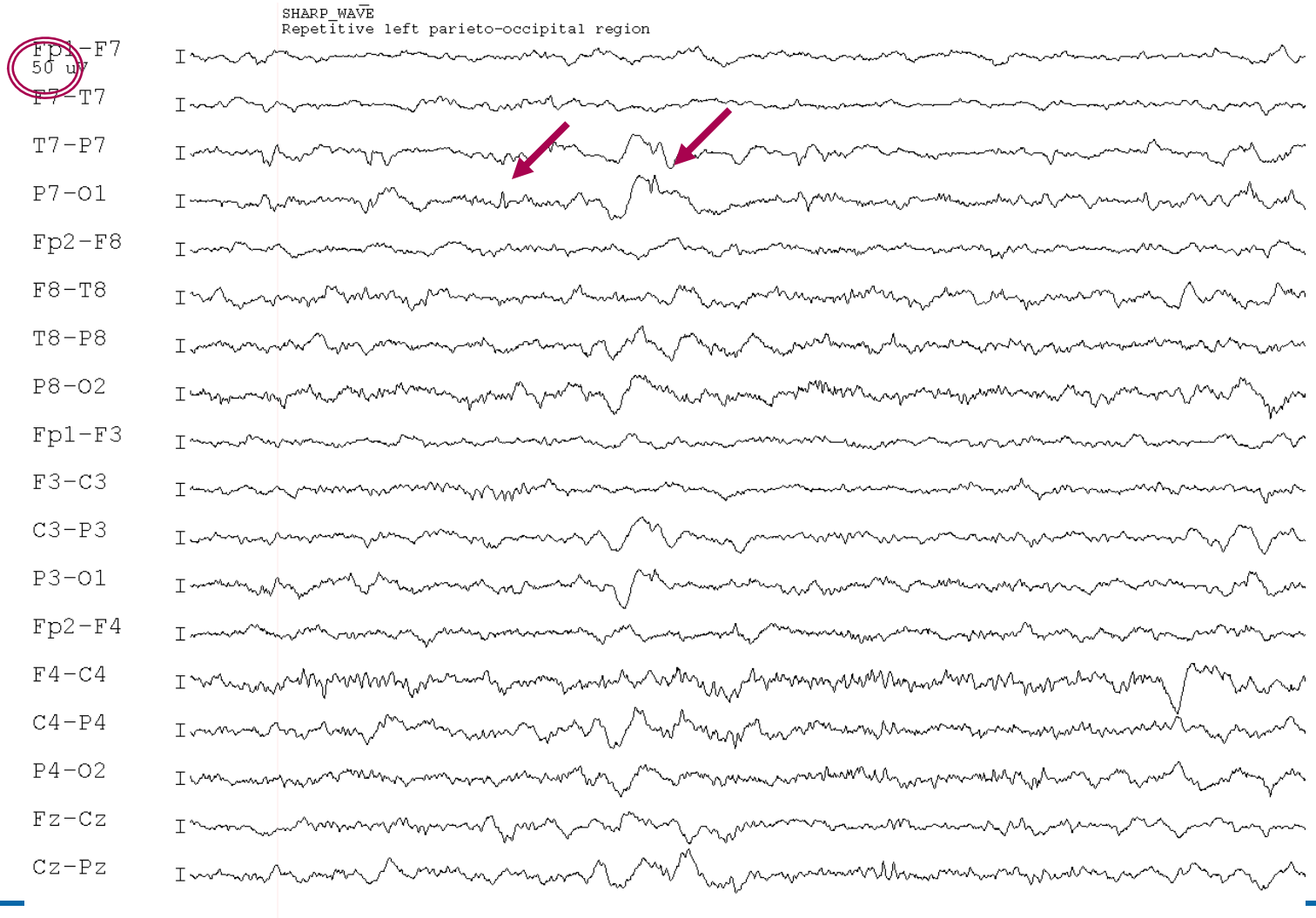
Bodensteiner J et al., Sturge Weber Syndrome textbook, 1999; Comi A. The Neurologist 2011; 17: 179

Epilepsy in SWS: Key Features

- "Seizures may be accompanied by unusual symptoms"
  - Extreme irritability (?migraine like headaches)
  - Ictal hemiparesis (Stroke like episodes)
  - Todd's palsy- ?weeks to months to recover
  - Stuttering progressive hemiparesis with each seizure or seizure cluster
- **Pathophysiology – Ischemia:**
  - Seizure -> ischemia -> seizure -> ischemia vicious cycle - Status Epilepticus

Bodensteiner J et al., Sturge Weber Syndrome textbook, 1999; Comi A. The Neurologist 2011; 17: 179

SWS: Interictal: Low amplitude SW



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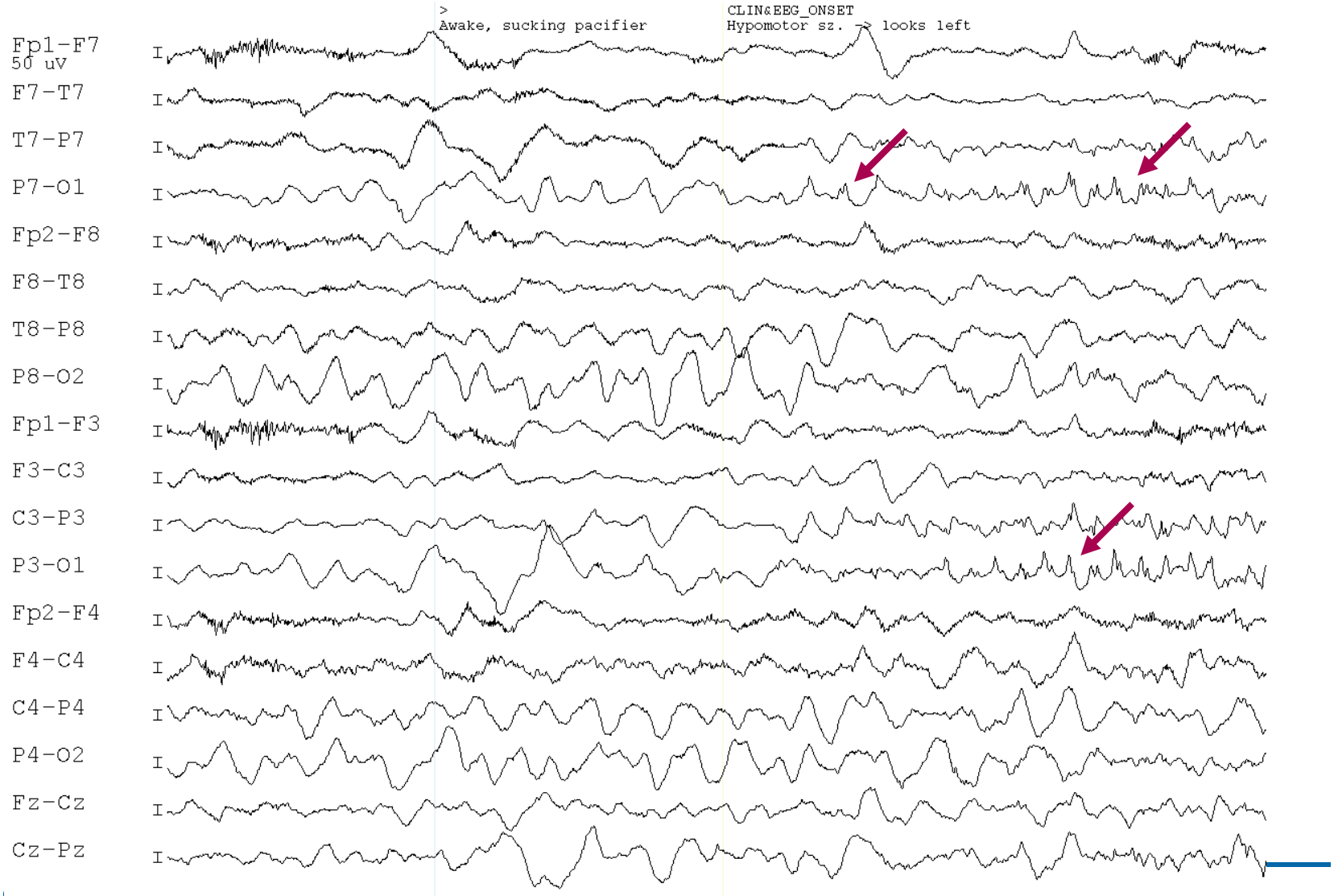
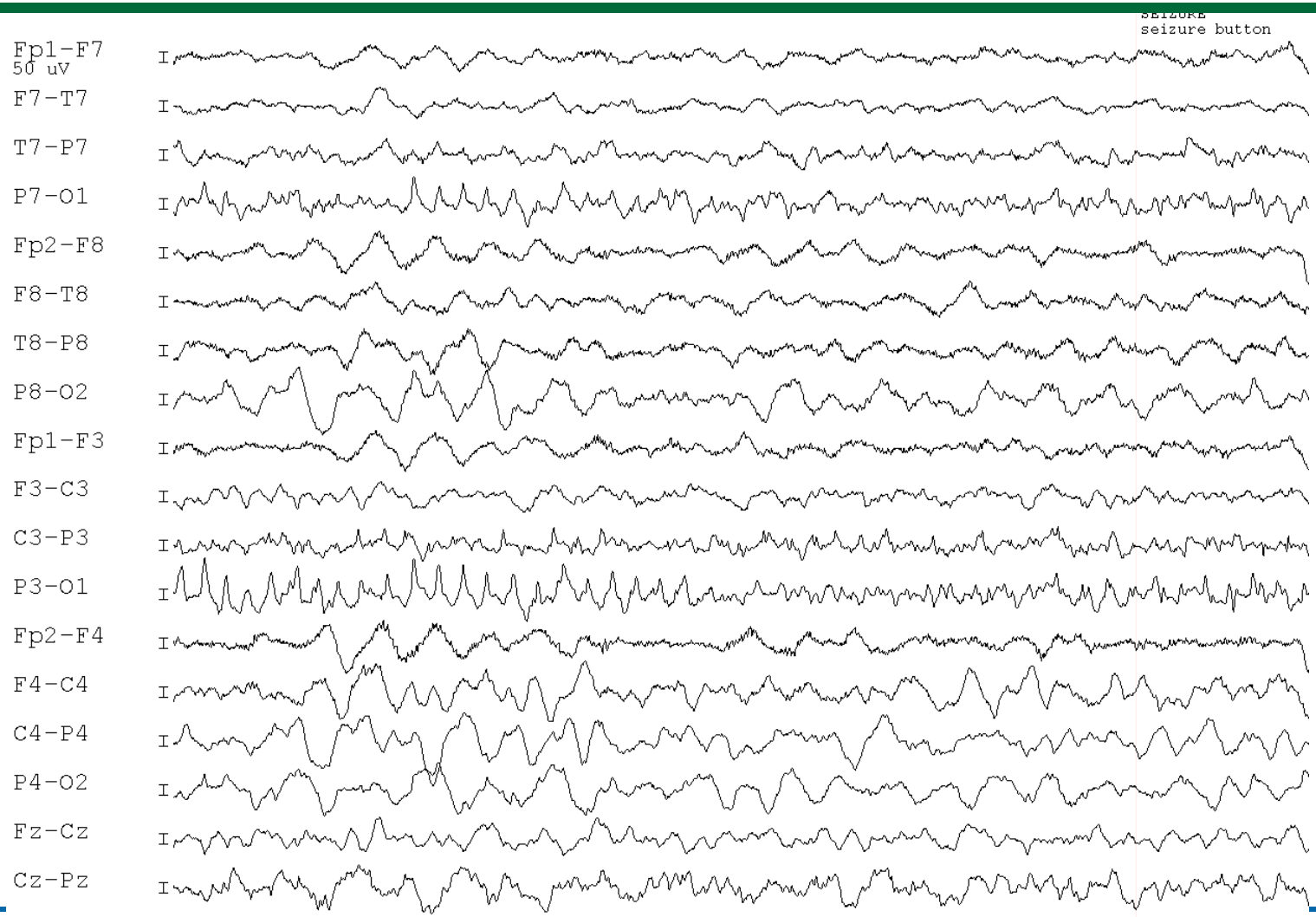
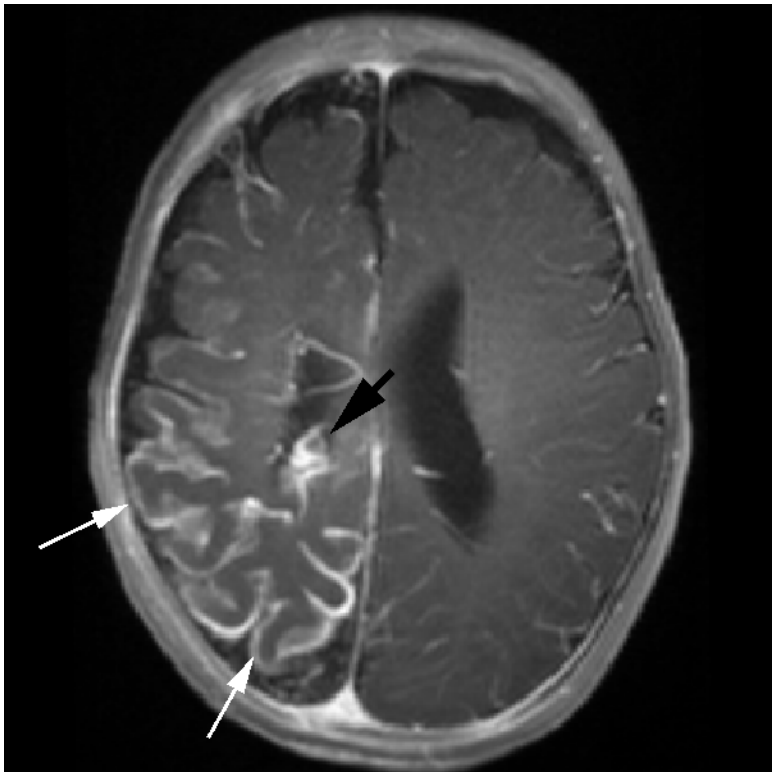
Ictal Onset: O1 - Despite Large Region of Abnormality



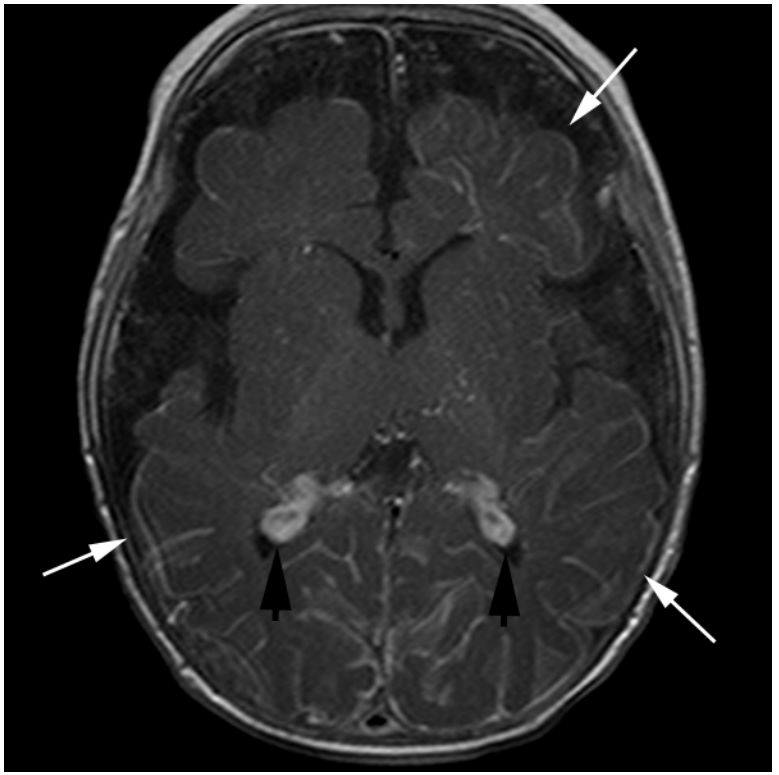
Ictus + 7s: Secondary Generalization Uncommon



Brain MRI findings



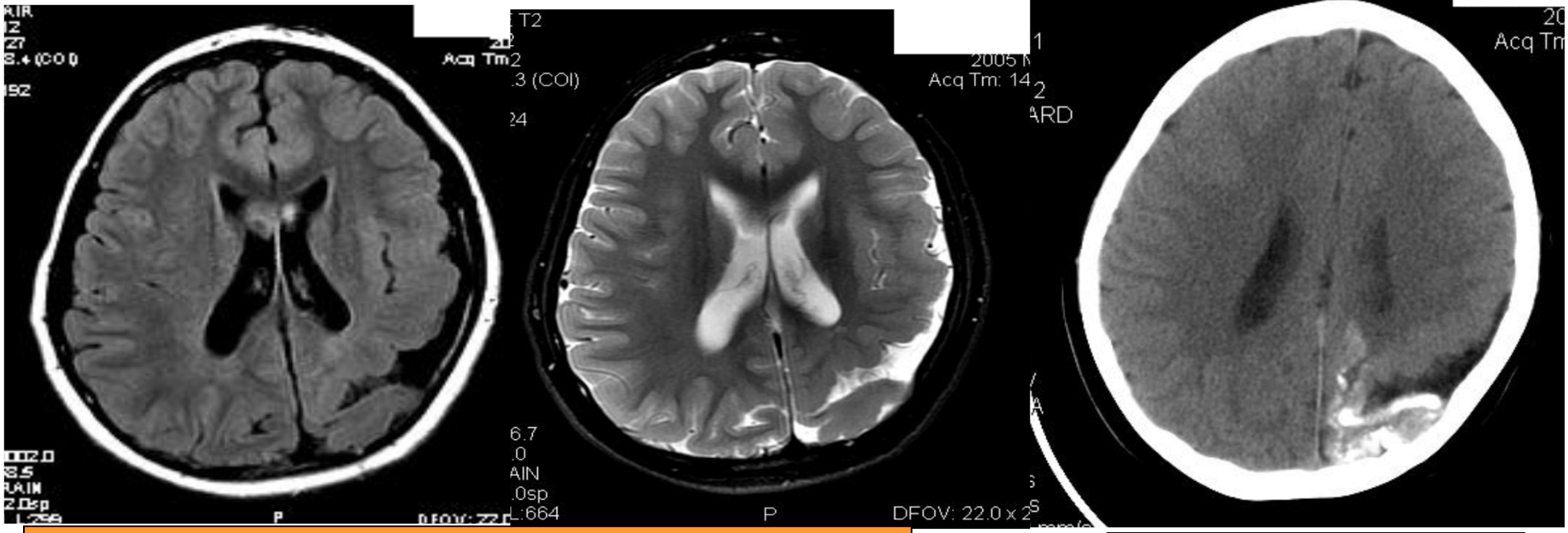
Unilateral



Bilateral

Gupta A, Prayson R, Reid J, Pictoral Atlas, Textbook of Epilepsy, Lippincott Williams Wilkins 2010

Non-GAD MRI: Diagnosis can be Missed without Proper Study



Mimics MCD, cleft or even subtle/no finding in newborn

Intra-cortical Ca++ is late

Recommended: SWI sequences, GAD use, High res sequences for deep medullary veins

SWS: Medical Treatment of Epilepsy

- Partial or broad spectrum AEDs
  - Aggressive treatment is advocated
- Treatment of coexisting eye disease
  - Critical for epilepsy surgery candidacy
- Early recognition/ anticipation of status epilepticus – Treat, as if imminent….
- Hydration during illnesses and fevers
- Aspirin is generally recommended
- Early consideration for epilepsy surgery often based on VEEG and MRI only

(Luat A et al., Ped Neurol 2019; Arzimanoglou AA et al., Neurology 2000; 55: 1472; Bourgeois M et al., J Neurosurg 2007: 106: 20; Maton B et al., 2010)

SPECT in SWS - ?Progression

- **SPECT:**
  - **Interictal: Decline in cerebral perfusion from being generous in infancy to deficient by 1-2 years of age**
    - **Venous stasis -> reduced arterial perfusion -> chronic ishemia** (Pinton F et al., J Neurol Neurosurg Psychiatr 1997)
  - **Ictal: "Reduced hyperperfusion" at origin and absolute reduction to ischemic levels in adjacent or remote areas**
    - **Abnormal vascular response to seizures -> further ischemic injury with status or clusters??** (Namer IJ et al., Clin Nuc Med 2005; 30: 39; Aylett SE et al., Dev Med Child Neurol 1999; 41: 480)

PET in SWS - ?Progression

- **Stable PET disease**
  - stable or improving regional hypo-metabolism
- **Severe PET disease - extensive hypo- (or hyper-) metabolism**
  - PET abnormalities often extend beyond the structural T1 MRI abnormalities
  - Major metabolic progression occurs by age 4 and is related to seizures
- **Contralateral PET metabolism (normal side)**
  - High – preserved IQ, evidence of reorganization
  - Low – correlates with low IQ and hence proponents of radical aggressive surgery even in patients without intractable epilepsy ?

Lee JS et al., Neurology 2001; 57: 189; Juhasz C et al., Eur J Pediatr Neurol 2007; 11: 277; Juhasz C et al., Am J of Neuroradiol 2007; 28: 900

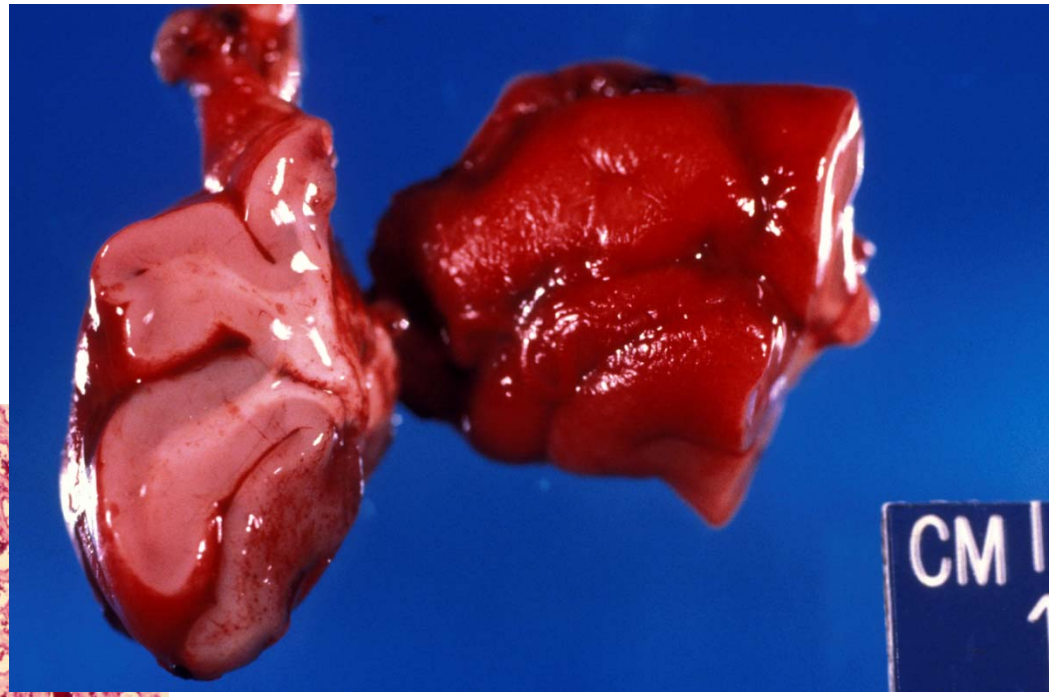
Epilepsy Surgery: Lacks Consensus

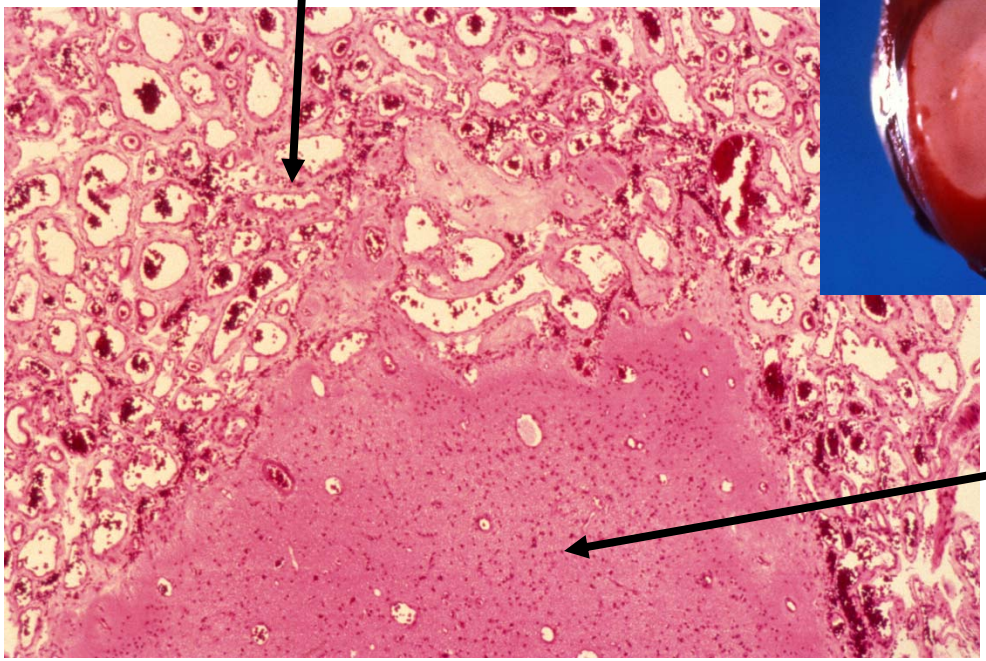
- **Studies not comparable & small**
  - **Some advocate early hemispherectomy in all SWS**
  - **Invasive studies are not practical**
- **Non hemiparetic group:**
  - **Visually guided complete resection of the pial angioma under ECOG guidance and Central sulcus mapping (SSEP and cortical stimulation)**
- **Hemiparetic group:**
  - **Functionally complete hemispherectomy may be appropriate in selected children with severe hemispheric disease with FIXED visual and motor deficits**

(Luat A et al., Ped Neurol 2019; Arzimanoglou AA et al., Neurology 2000; 55: 1472; Bourgeois M et al., J Neurosurg 2007: 106: 20; Maton B et al., 2010)

Pathology

Leptomeningeal vascular malformation





Gliosis, neuronal loss, Ca++, Leptomeningeal capillary angiomas, hemorrhages, venous stasis

Gupta A, Prayson R, Reid J, Pictoral Atlas, Textbook of Epilepsy, LWW 2010

Tuberous Sclerosis Complex (TSC)

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TSC Presents In Infancy With Seizures And Skin Findings

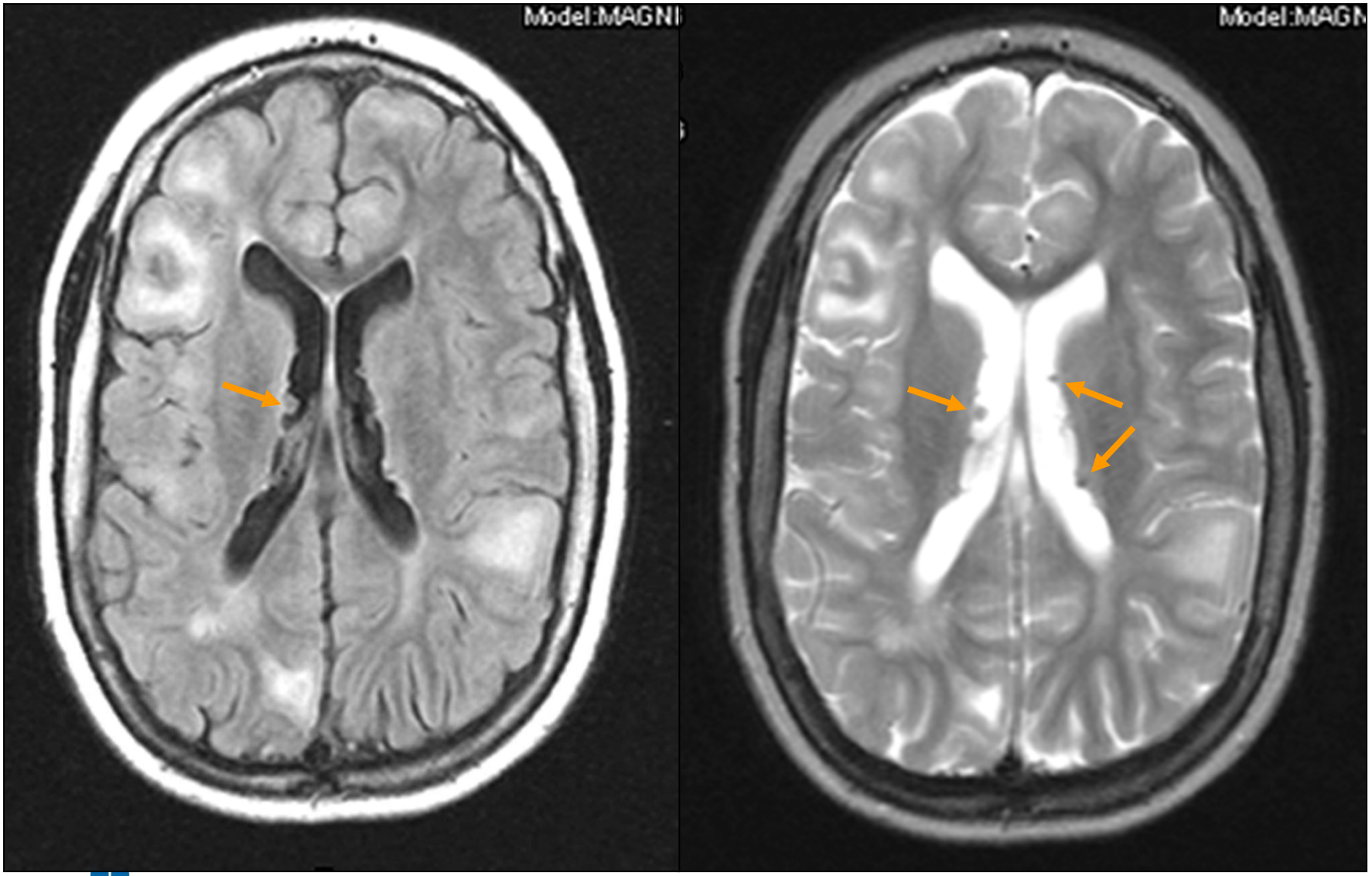
- Classical presentation
  - Infantile spasms in a healthy child, 1-6 months
  - ~ 30% of all spasm cases in US and Europe
  - Majority have seizures < 2 years of age
- Examination reveals 3 or more hypopigmented macules in >90%
- Other findings are discovered on brain MRI, cardiac ECHO, renal ultrasound, dilated eye exam, and family history

Crino PB et al., NEJM 2006; 355: 1345; Curatolo et al., Lancet 2008; 372: 657

TSC May Present Later In Life

- Seizures may begin later in life
  - Often patient has mild to moderate cognitive issues, autism, personality trait/disorder, ADHD
- Cognitive and Psychiatric disorders are common
  - Autism, low IQ, other diagnoses
- Incidental finding, diagnosis without symptoms

Brain Manifestations of TSC



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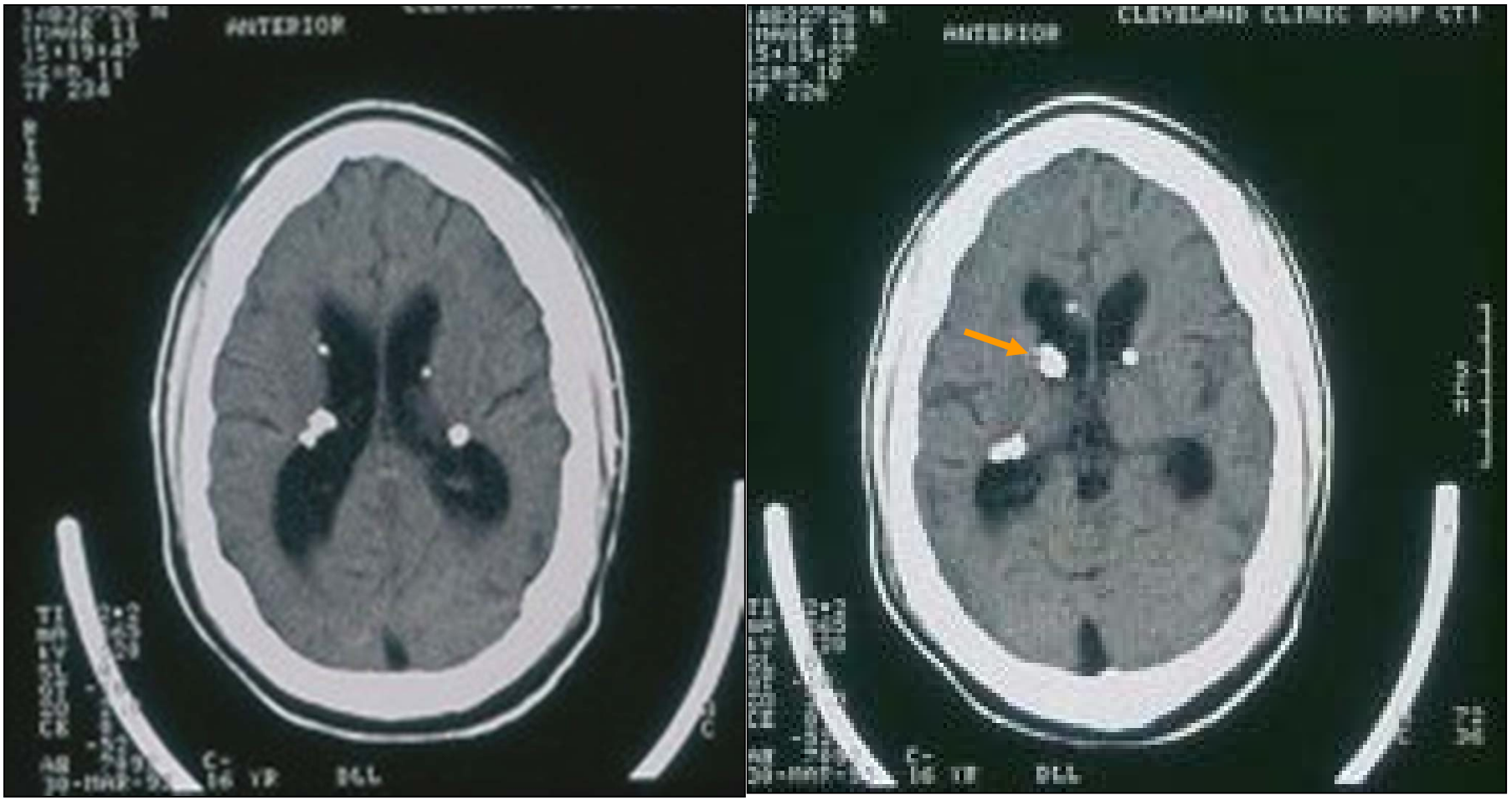
Crino PB et al., NEJM 2006; 355: 1345; Curatolo et al., Lancet 2008; 372: 657

Subependymal Nodules are often Calcified



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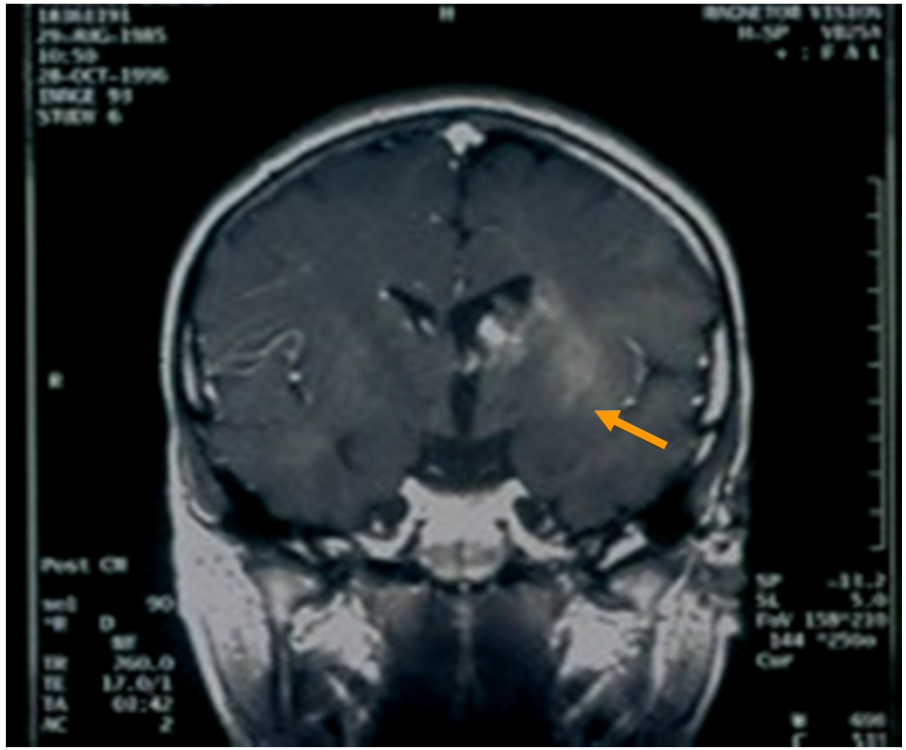
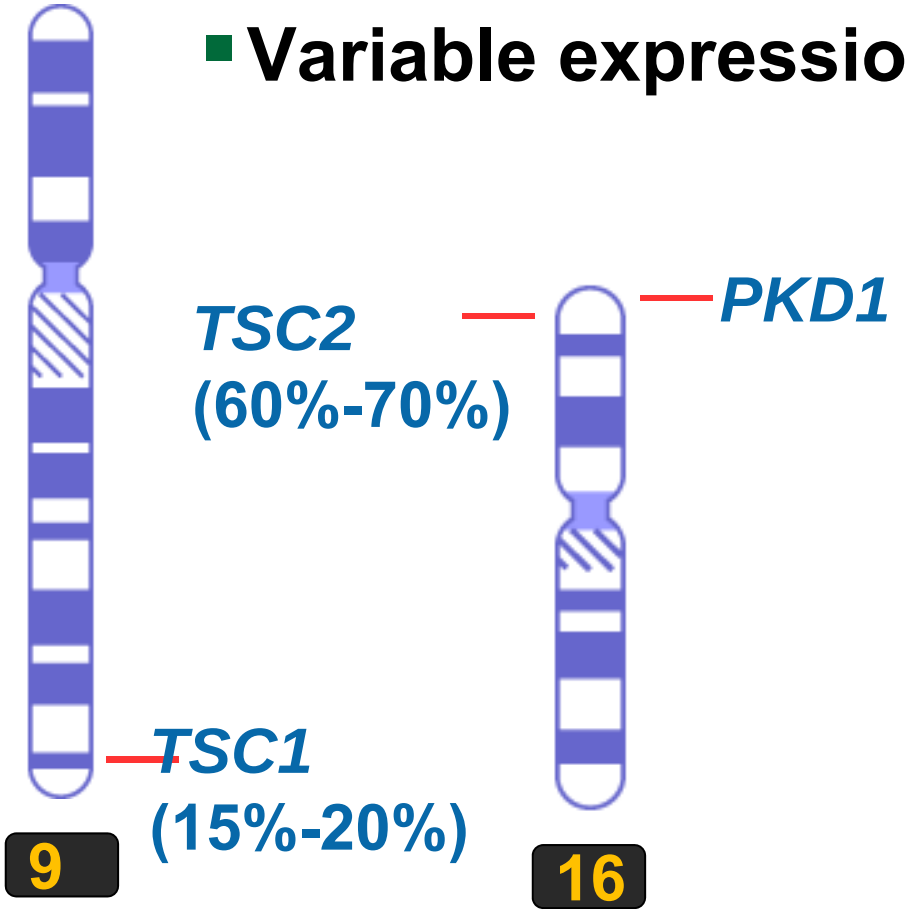
Crino PB et al., NEJM 2006; 355: 1345; Curatolo et al., Lancet 2008; 372: 657

Giant Cell Astrocytoma may occur in ~10-20% TSC patients



Genetics of TSC

- Autosomal dominant
- Variable expression



- ~ 6% with TSC mutations may not fulfill clinical criteria
- ~10% patients meeting clinical criteria have no identified TSC mutation/deletion

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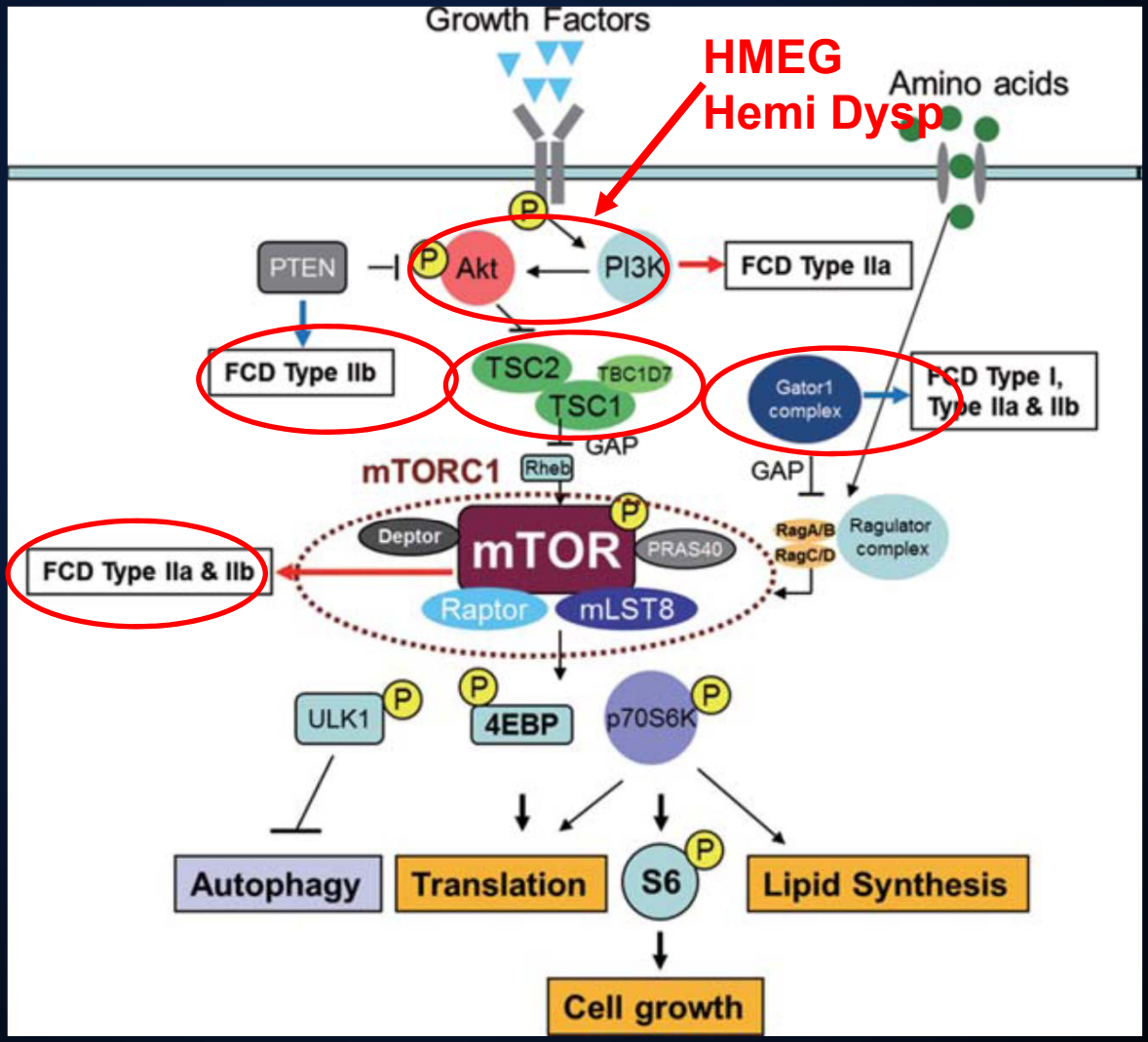
Adapted from Genetics Home Reference website. http://ghr.nlm.nih.gov. Orlova. *Ann N Y Acad Sci*. 2010;1184:87; Qin. *Hum Genet*. 2010;127:573.

TSC is one of the mTORopathies with Refractory Focal Epilepsies



Nakashima et al., ANN NEUROL 2015;78:375–386

ELSEVIER

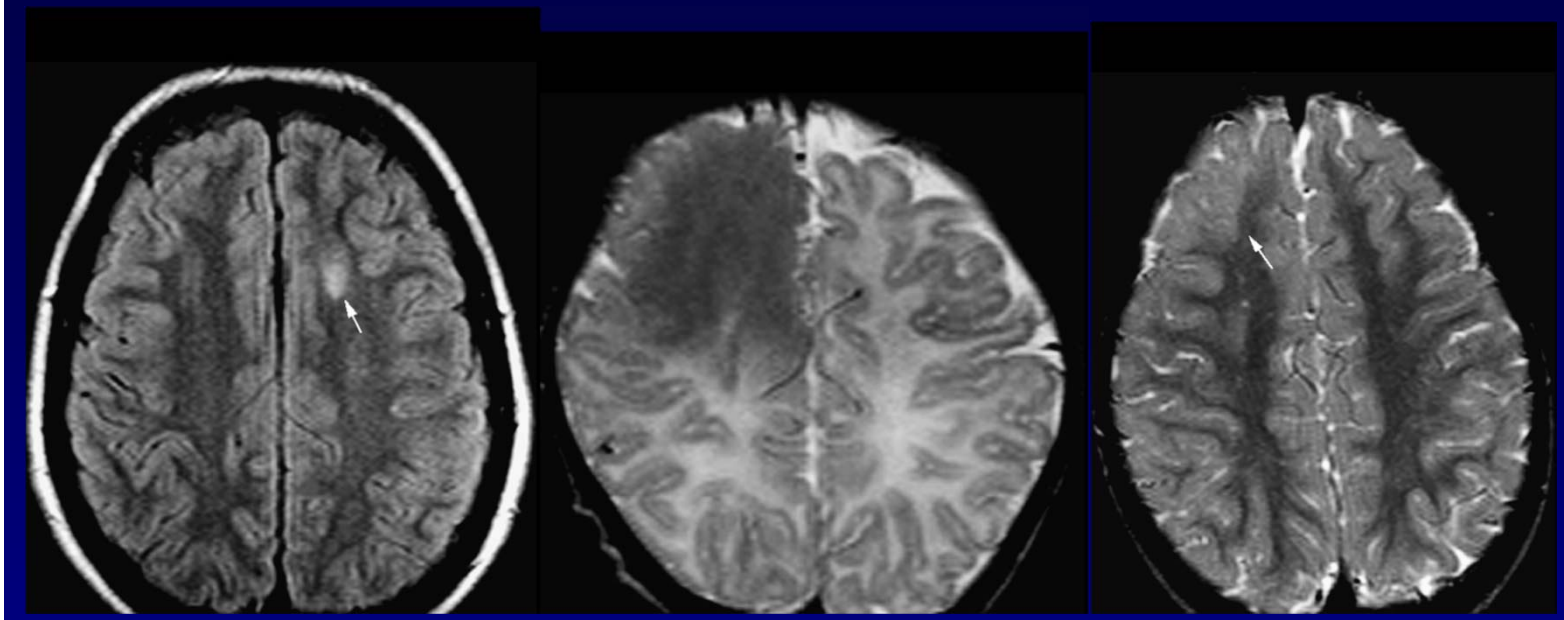
Tuberous Sclerosis Complex With a Single Brain Lesion on MRI Mimicking Focal Cortical Dysplasia

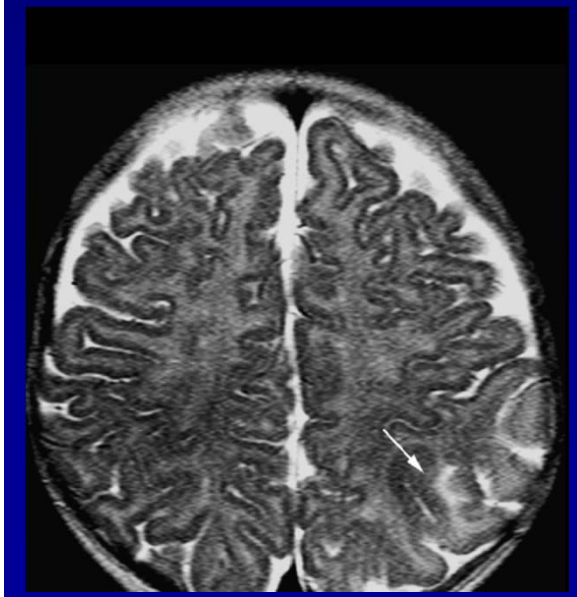
Tugba Hirfanoglu, MD and Ajay Gupta, MD

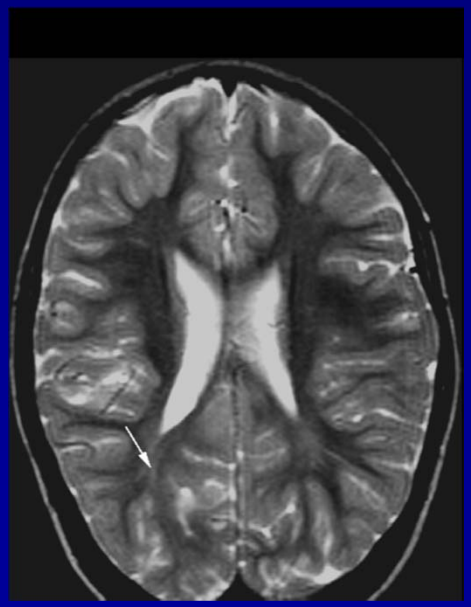
- Study of epilepsy surgery: < 18 yr for FCD
- 5/105 (~ 4%) had epilepsy due to a solitary FCD but without other TSC MRI stigmata
- Were later diagnosed with TSC
  - TSC 2 (3/5) mutations
  - TSC 1 (1/5) mutations
  - 1/5 met diagnostic clinical criteria for TSC (no mutation found on only TSC 1 sequencing)

Hirfanoglu & Gupta, Pediatr Neurol 2010; 42: 343-347

TSC MRI Phenotype of Solitary FCD







Suspect TSC if FCD:

- Infantile spasms/early onset epilepsy
- Ca++ in FCD
- Familial epilepsy

Hirfanoglu & Gupta, Pediatr Neurol 2010; 42: 343-347

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Research Paper

Epilepsy and Neurodevelopmental Comorbidities in Tuberous Sclerosis Complex: A Natural History Study

Ajay Gupta, MD [a, *], Gwendolyn de Bruyn, MD [a, b, c, d], Simon Tousseyn, MD, PhD [a, d], Balu Krishnan, PhD [a], Lieven Lagae, MD, PhD [b], Nitin Agarwal, MD [e], The TSC Natural History Database Consortium[†]

- **N= 1657(1 month -81 years, median age 16 years)**

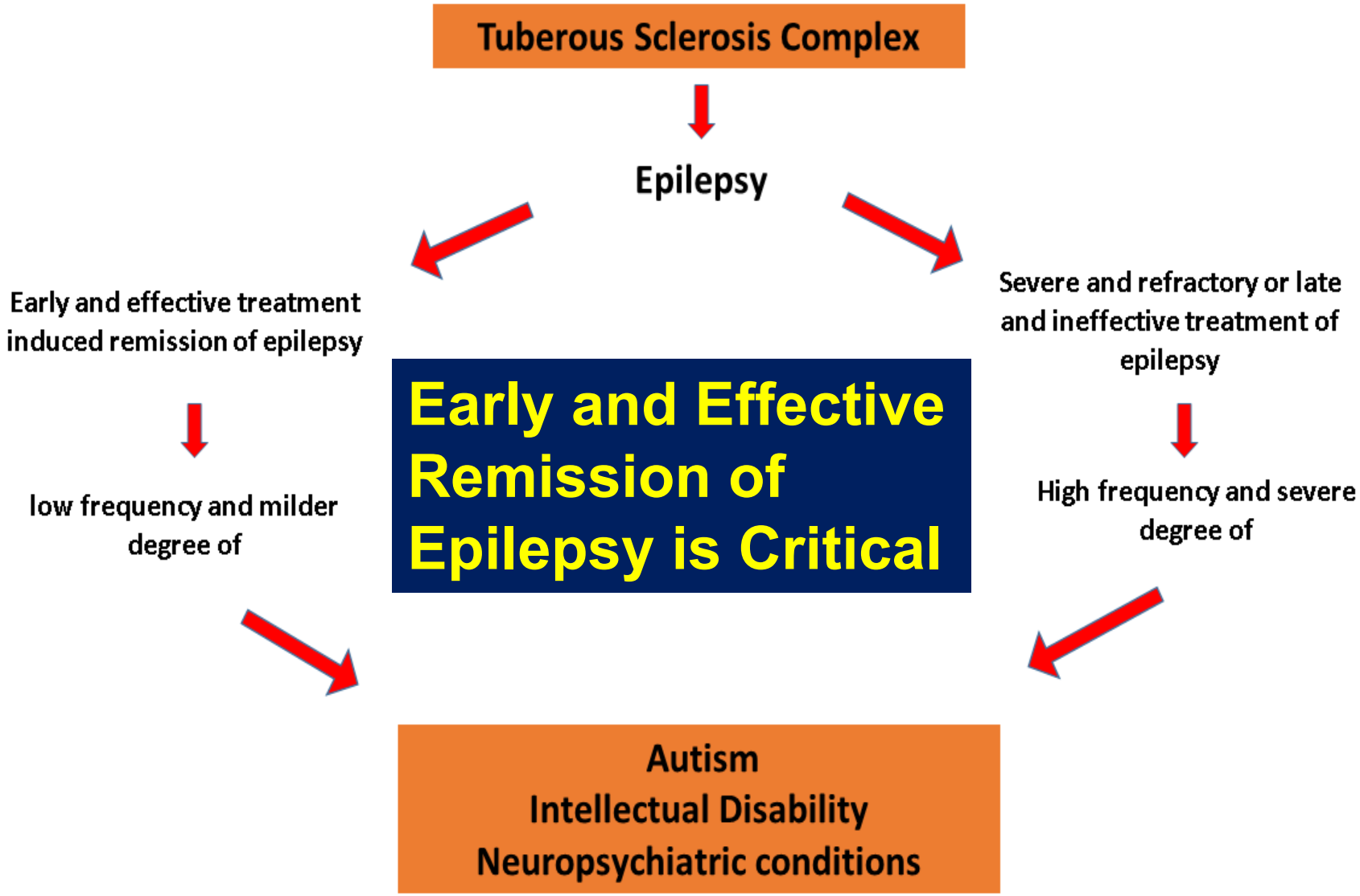
Gupta A et al., Pediatric Neurology 2020

The study provided evidence that in TSC, Epilepsy (not the Genotype alone) is the major driver of:

- Intellectual disability (ID)
- Autism spectrum disorder (ASD)
- ADHD

- TSC2 mutations are more frequent in epilepsy
- ?Combined effect of TSC2 + Epilepsy

Gupta et al., Pediatric Neurology 2020



Gupta et al., Pediatric Neurology 2020

TSC treatment of Epilepsy with Anti-seizure Drugs (ASD)

- Infantile Spasms (not TSC specific)
  - Vigabatrin ?better than ACTH
  - Remission rates 60-80% in IS trials but partial remission and relapses common in TSC
- TSC specific FDA approval
  - Epidiolex: Median sz. reduction 48%; Responder rates 44% in pivotal trials
- Partial epilepsy ASD are good choices
  - Monitor multi-organ system effect of ASD
- Lennox Gastaut Syndrome
  - Clobazam, Rufinamide are FDA approved
  - Overall median reduction ~40% in trials for all seizures, but higher for drop seizures
  - VPA, LTG, TPM, ZNS are commonly used as well

EXIST 3 TRIAL: Everolimus approval for epilepsy treatment in TSC

- Seizure efficacy: 12 weeks treatment
  - Responder rates: 28% (LT, 3-7ng/mL), 40% (HT, 9-15ng/mL) vs Placebo (15%)
  - Median % reduction: LT:HT:Placebo- 29%:39%:15%
  - Dose of Everolimus – 3-6mg/m^2, trough of 5-15 ng/mL
- Side effects: Stomatitis, diarrhea, URIs, fever, cough, pneumonitis, rash
- Everolimus NO MORE effective than ASD
  – overall 40% median Sz. Reduction

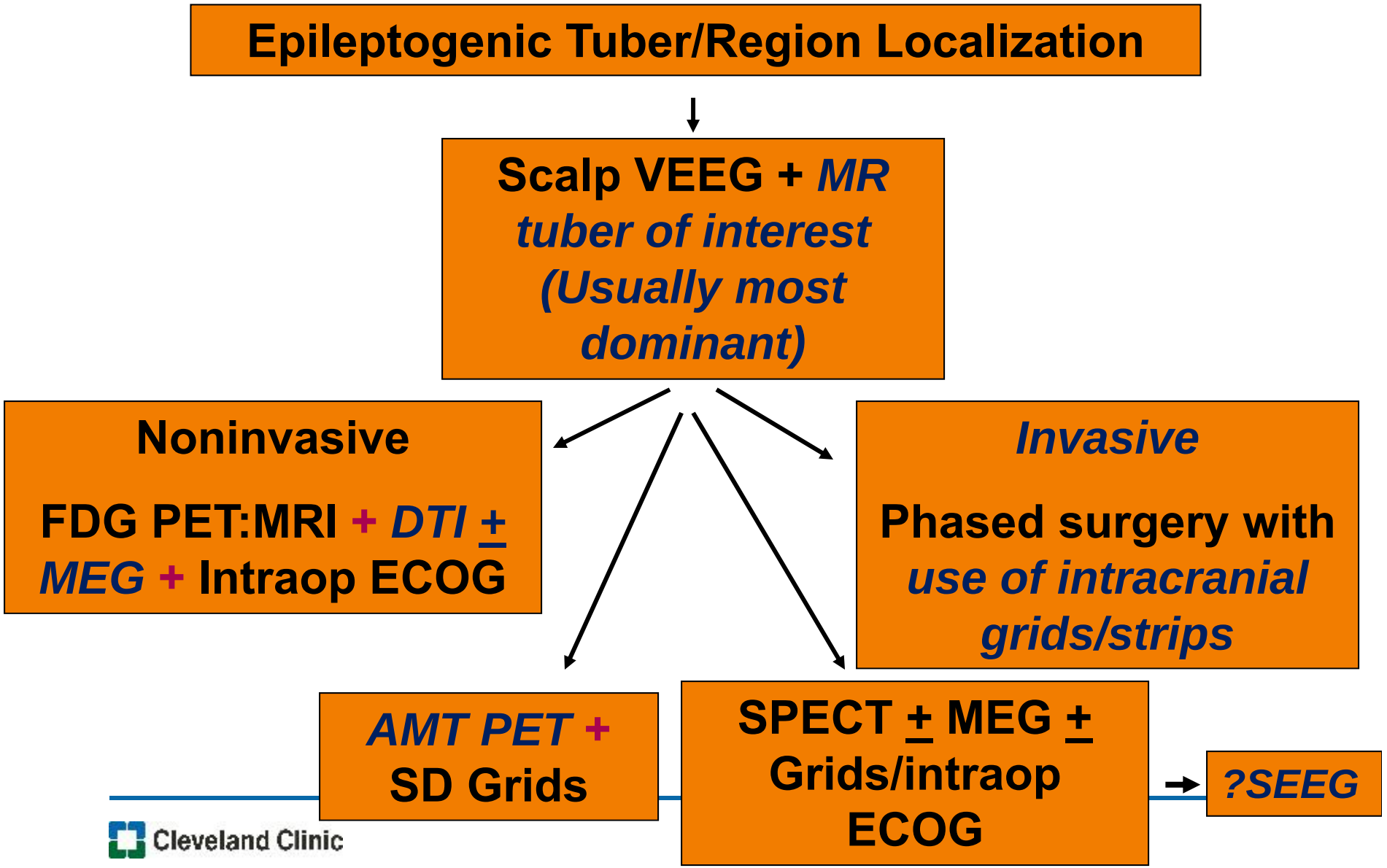
Exist 3 study group, Lancet 2016; 388: 2153-63

Preventing epilepsy and Preserving Cognition using VGB in infants with TSC

- Phase IIb prospective, randomized, placebo-controlled, double-blind clinical trial.
- Enrolled 80 infants with TSC who are < 6 months of age prior to the onset of their first seizure
- The primary outcome measure is cognitive assessment scores on the Bayley Scales of Infant and Toddler Development at 24 months.

NINDS funded

Epilepsy Surgery: *Touted Tests* For Measuring Epileptogenic Region



DOI: 10.1111/epi.16410

FULL-LENGTH ORIGINAL RESEARCH

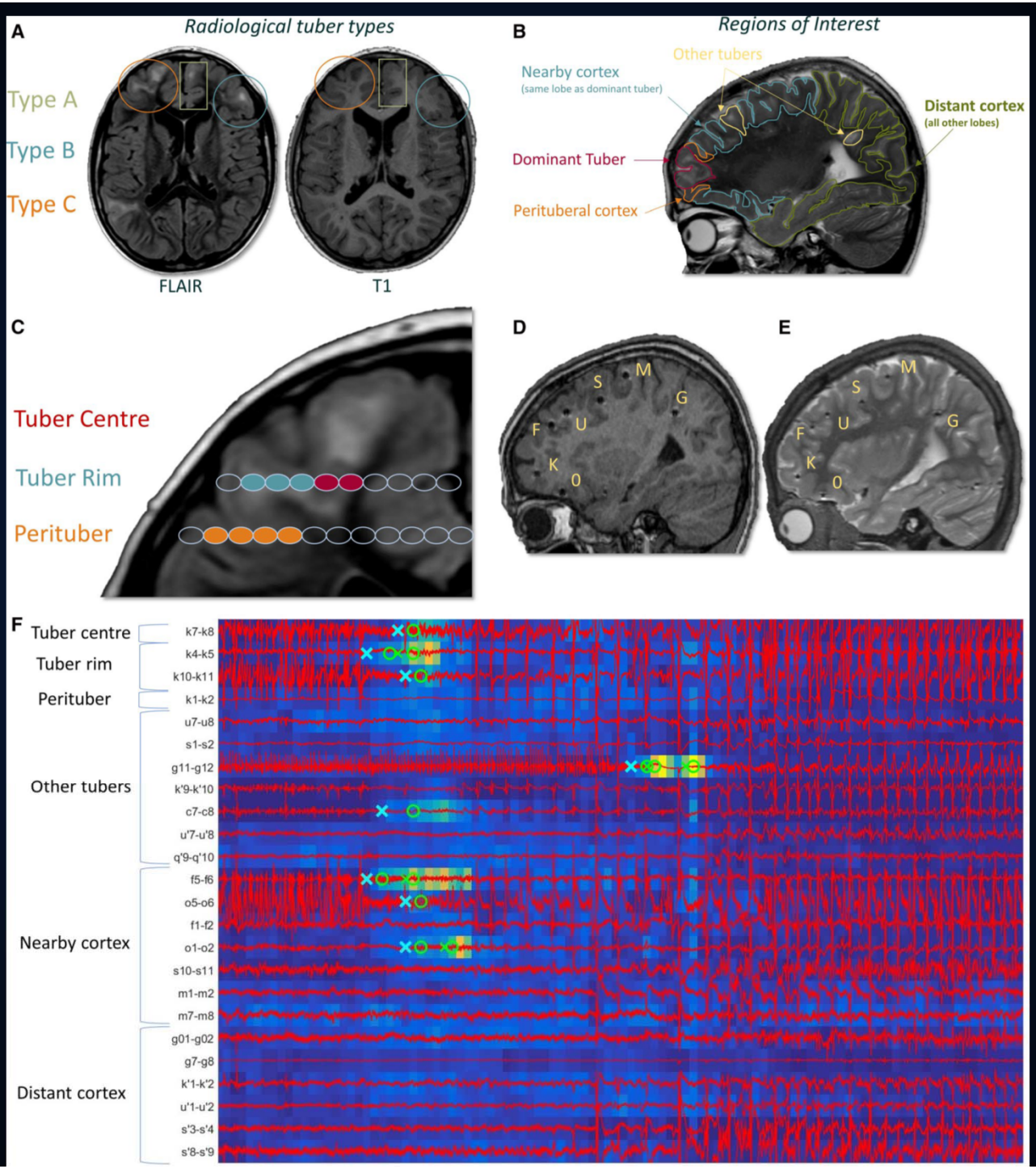
Epilepsia

N=18; 13 with adequate tuber sampling

Epileptogenicity in tuberous sclerosis complex: A stereoelectroencephalographic study

Results: The most epileptogenic ROI was the dominant tuber, with higher EI than perituber cortex, secondary tuber, nearby cortex, and distant cortex ($P < .001$). A focal tuber EZ organization was identified in seven patients. This group had 80% Engel IA postsurgical outcome and distinct dominant tuber characteristics: continuous interictal discharges (IEDs; 100%), fluid-attenuated inversion recovery (FLAIR) hypointense center (86%), center-to-rim EI gradient, and stimulation-induced seizures (71%). In contrast, six patients had a complex EZ organization, characterized by nearby cortex as the most epileptogenic region and 40% Engel IA outcome. At the intratuber level, the combination of FLAIR hypointense center, continuous IEDs, and stimulation-induced seizures offered 98% specificity for a focal tuber EZ organization.

- Focal onset seizures in distantly located tubers
- Merit of SEEG over Intraop in such cases


A
Radiological tuber types
Type A
Type B
Type C
FLAIR
T1
B
Regions of Interest
Other tubers
Nearby cortex
(same lobe as dominant tuber)
Distant cortex
(all other lobes)
Dominant Tuber
Perituberal cortex
C
Tuber Centre
Tuber Rim
Perituber
D
E
M
S
G
F
U
K
O
F
Tuber centre
Tuber rim
Perituber
Other tubers
Nearby cortex
Distant cortex
k7-k8
k4-k5
k10-k11
k1-k2
u7-u8
s1-s2
g11-g12
k'9-k'10
c7-c8
u'7-u'8
q'9-q'10
f5-f6
o5-o6
f1-f2
o1-o2
s10-s11
m1-m2
m7-m8
g01-g02
g7-g8
k'1-k'2
u'1-u'2
s'3-s'4
s'8-s'9

JFE 2018 (French meeting of epilepsy)

Resective surgery in tuberous Sclerosis complex, from Penfield to 2018: A critical review

Table 3 – Seven series since 1993 with at least 10 patients followed for at least 2 years.

First Author	Year	Country	Journal	Number of patients operated	Number of patients with a Follow-up ≥ 2 years	Follow-up at 2 years (% Class 1 of Engel)
Weiner	2006	USA, NYC	Pediatrics	25	14	57%
Teutonico	2008	Italy, Milan	Child Nerv Syst	21	20	50%
Liu	2012	China, Changping	Epilepsy Res	17	15	60%
Kresk	2013	USA, Miami	Epilepsia	33	33	55%
Arya	2015	USA, Cincinatti	J Neurosurg Pediat	37	37	57%
Liang	2017	China, Beijing	J. Neurol	65	51	59%
Fohlen	2018	France, Paris	Seizure	15	14	60%

FU: follow-up.

Ostrowsky-Coste et al., 2018; 175: 163-182

JFE 2018 (French meeting of epilepsy)

Resective surgery in tuberous Sclerosis complex, from Penfield to 2018: A critical review

Table 4 – Three meta-analyses, prognosis factors.

First Author	Year	Journal	Number of patients	% of Patients Engel I	Bad prognosis	Good prognosis
Jansen	2003	Epilepsia	177	57%	Presence of tonic seizures IQ < 70	
Zhang	2013	Epilepsy Res	229	59%		Onset of seizure > 1 year Lateralized ictal and interictal EEG Lobectomy
Fallah	2013	PloS ONE	181	56%		No generalized semiology No or mild developmental delay Unifocal ictal EEG EEG and MRI concordant

Ostrowsky-Coste et al., 2018; 175: 163-182

LASER ABLATION: INCONCLUSIVE DATA

TABLE 3. Neocortical Epilepsy

Study	N	iEEG (n)	LITT technique	F/u, months, median (range)	Engel I outcome, n (%)		Adverse events
					Last F/u	*≥1-Yr F/u*	
Curry 2012[26]	1 FCD	0/1	V + CRW	3 (3)	1/1 (100)	-	None
Lewis 2015[49]	16 peds: 11 FCD, 4 TS, 1 RE	NR	V + Leksell	15.8 (4-36)	7/16 (44)	4/11 (36)	1 inaccurate fiber placement leading to IVH, aseptic meningitis, and ventriculostomy; required reoperation to complete ablation; 1 mechanical cooling malfunction with broken and retained fiber; 1 post-ablation edema with steroid induced gastritis
Devine 2016[62]	1 FCD	1/1	NR	12 (12)	1/1 (100)	1/1 (100)	None
Ellis 2016[63]	1 FCD[a]	1/1	V + CRW	12 (12)	1/1 (100)	1/1 (100)	None
Perry 2017[64]	20 peds insula[b]: 3 FCD, 14 NL, 2 TS, 1 BFIP	14/20	V + Leksell/ROSA	18.5 (7-39)	10/20 (50)	6/13 (46)	6 (30%) mild/transient hemiparesis; 1 (5%) transient expressive aphasia[c]
Brown 2018[36]	4 FCD; 2 NL	NR	NR	NR (NR); 3 (3)	2/4 (50); 1/2 (50)	NR -	NR
Ross 2018[65]	3 NL	3	V + ROSA	26 (20-44)	3/3 (100)	3/3	None
Marashly 2018[66]	1 NL	1/1	V + Leksell	17	1/1 (100)	1/1 (100)	None
Tovar-Spinoza 2018[67]	7 TS	0/7	V/NB + Leksell	Mean 19.3 (4-49)	[d]3/7 (43)	NR	None
Hooten 2018[68]	1 TS	0	NB + AXiiiS (without head fixation or anchor bolt)	6	0/1 (0)	-	None
Kuo 2019[69]	5 peds: 2 GG, 1 FCD, 1 gliosis, 1 RN	1/5	V + CRW	NR (0-20)	NR	1/1 (100)	1 (20%) EDH requiring evacuation
Cobourn 2019[70]	4 peds: 2 FCD, 2 TS	4/4	V + ClearPoint/ROSA	8 (5-16)	3/4 (75)	1/1 (100)	None
Alexander 2019[71]	4 NL insula	4/4	V + ROSA	Mean 3.4 (NR)	3/4 (75)	-	None
Hale 2019[72]	14 total insula[b]: 7 FCD 6 NL 1 TS	14/14	NR	19 (12-38)	6/14 (43)	6/14 (43)	5 (36%) unilateral weakness; 1 (7%) dysphagia; 1 (7%) facial droop (all resolved within 3 months)[c]
Upadhyayula 2019[73]	1 NL	1/1	V + ROSA	23	0/1	0/1	None

Youngerman et al., Neurosurg 2020

Invited Editorial Comment

Epileptic Disord 2009; 11 (1): 80-1

"Epilepsy surgery recipes galore": in quest for the epileptogenic tuber in tuberous sclerosis complex

Ajay Gupta

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<guptaa1@ccf.org>

- **No one 'recipe' could claim better outcome**
- **Noninvasive approaches are appealing for this population**
- **Customized approach for each TSC case remain critical**

THANK YOU

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