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Epilepsies (ERN EpiCARE)

European Commission

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Helping patients with rare or low-prevalence complex diseases

EPILEPSY AND TUBEROUS SCLEROSIS COMPLEX

Katarzyna Kotulska

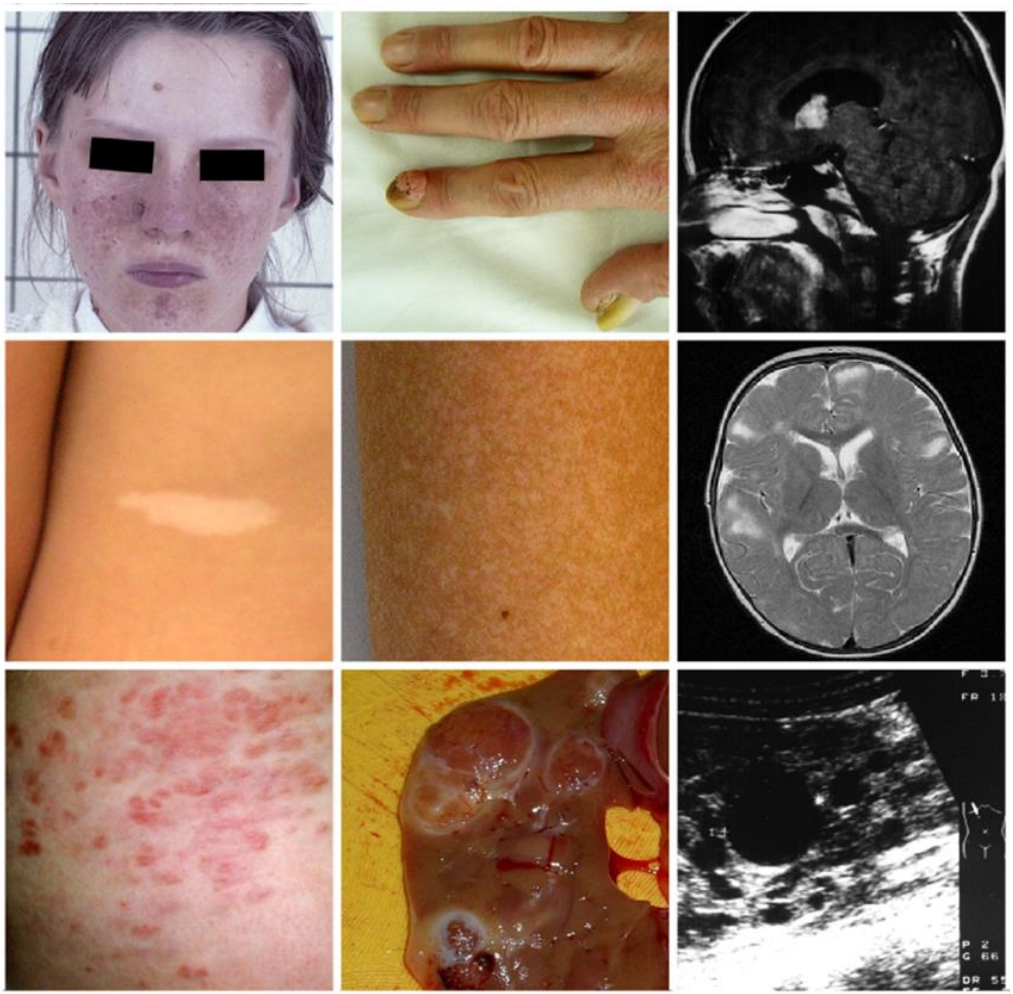
The Children's Memorial Health Institute, Warsaw, Poland

27th February, 2020

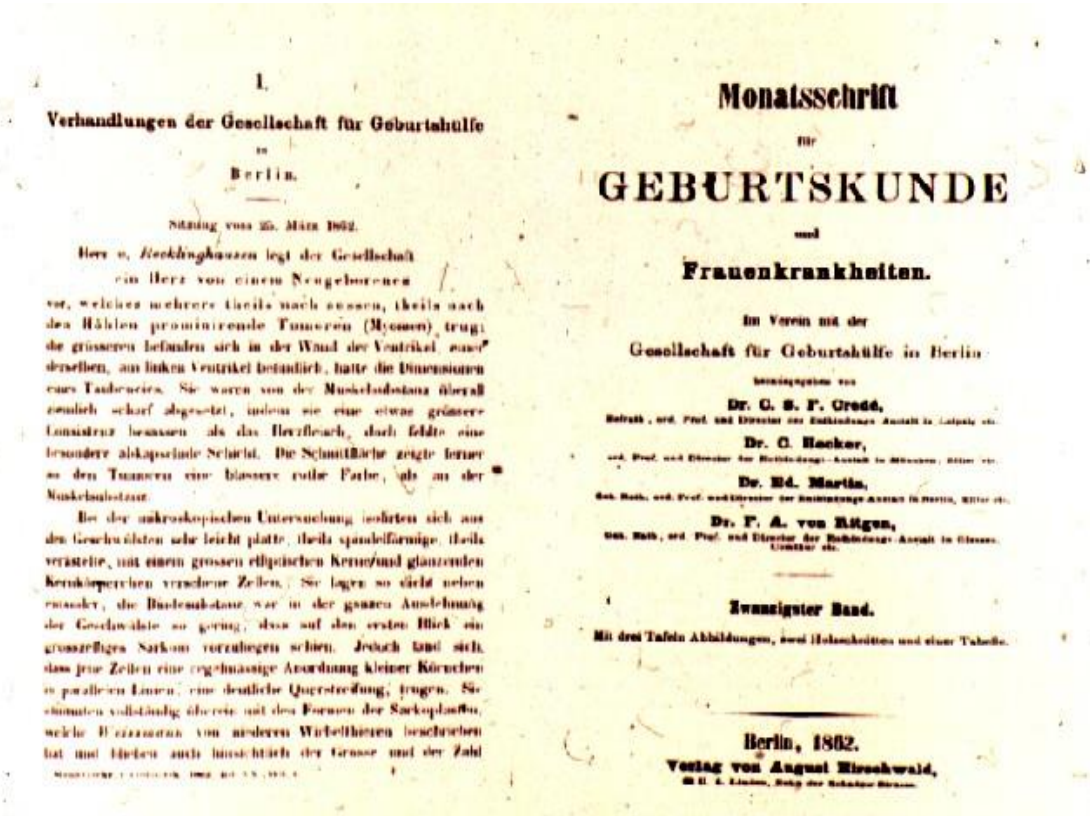
Co-founded by the EU

Tuberous Sclerosis Complex

- Incidence: 1:6,000 livebirths
- One milion individuals affected worldwide
- Autosomal dominant mode of inheritance
- Two genes:
  - TSC1 (chromosome 9)
  - TSC2 (chromosome 16)
- Multiorgan involvement (skin, brain, eye, kidneys, liver, heart)



von Recklinghausen, 1862


1.

Verhandlungen der Gesellschaft für Geburtshülfe

zu

Berlin.

Sitzung vom 25. März 1862.

Herr v. *Recklinghausen* legt der Gesellschaft ein Herz von einem Neugeborenen vor, welches mehrere theils nach aussen, theils nach den Höhlen prominirende Tumoren (Myomen) trug; die grösseren befanden sich in der Wand der Ventrikel, einer derselben, am linken Ventrikel befindlich, hatte die Dimensionen eines Taubeneies. Sie waren von der Muskelsubstanz überall ziemlich scharf abgesetzt, indem sie eine etwas grössere Consistenz besassen als das Herzfleisch, doch fehlte eine besondere abkapselnde Schicht. Die Schnittfläche zeigte ferner an den Tumoren eine blassere rothe Farbe, als an der Muskelsubstanz.

Bei der mikroskopischen Untersuchung isolirten sich aus den Geschwülsten sehr leicht platte, theils spindelförmige, theils verästelte, mit einem grossen elliptischen Kerne und glänzenden Kernkörperchen versehene Zellen. Sie lagen so dicht neben einander, die Bindesubstanz war in der ganzen Ausdehnung der Geschwülste so gering, dass auf den ersten Blick ein grosszelliges Sarkom vorzuliegen schien. Jedoch fand sich, dass jene Zellen eine regelmässige Anordnung kleiner Körnchen in parallelen Linien, eine deutliche Querstreifung, trugen. Sie stimmten vollständig überein mit den Formen der Sarkoplasten, welche Weismann von niederen Wirbelthieren beschrieben hat und blieben auch hinsichtlich der Grösse und der Zahl

Monatsschrift

für

GEBURTSKUNDE

und

Frauenkrankheiten.

Im Verein mit der

Gesellschaft für Geburtshülfe in Berlin

herausgegeben von

Dr. C. S. F. Credé,

Dr. C. Hecker,

Dr. Ed. Martin,

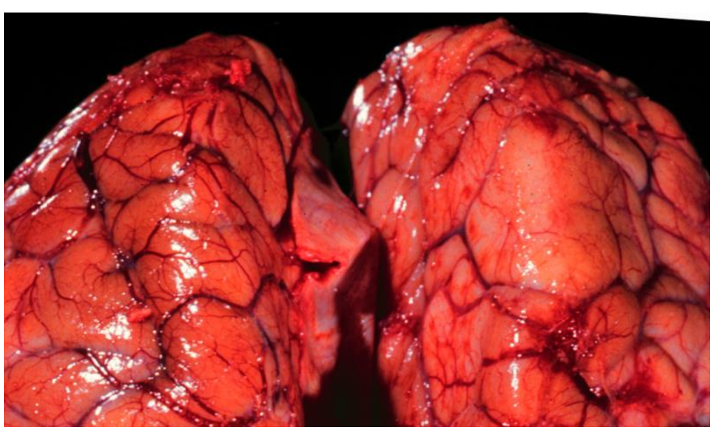
Dr. F. A. von Ritgen,

Zwanzigster Band.

Mit drei Tafeln Abbildungen, zwei Holzschnitten und einer Tabelle.

Berlin, 1862.

Verlag von August Hirschwald.



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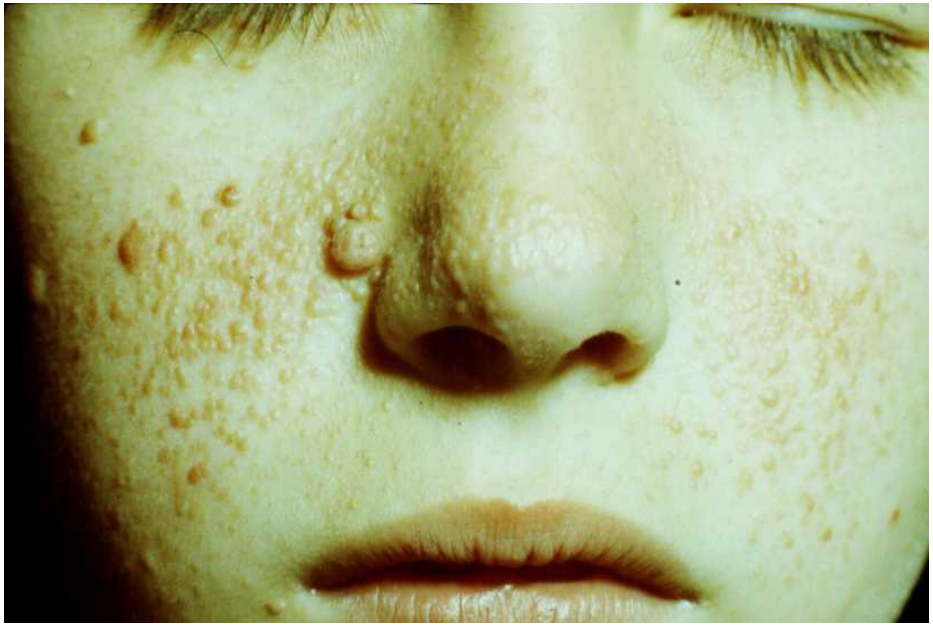
First Diagnostic criteria of tuberous sclerosis

Vogt's triad (1908)

- Adenoma sebaceum (angiofibroma) (90%)
- Epilepsy (80-90%)
- Mental retardation (50-60%)



Only 40% present with all, 5-10% of TSC patients do not present with any of these features

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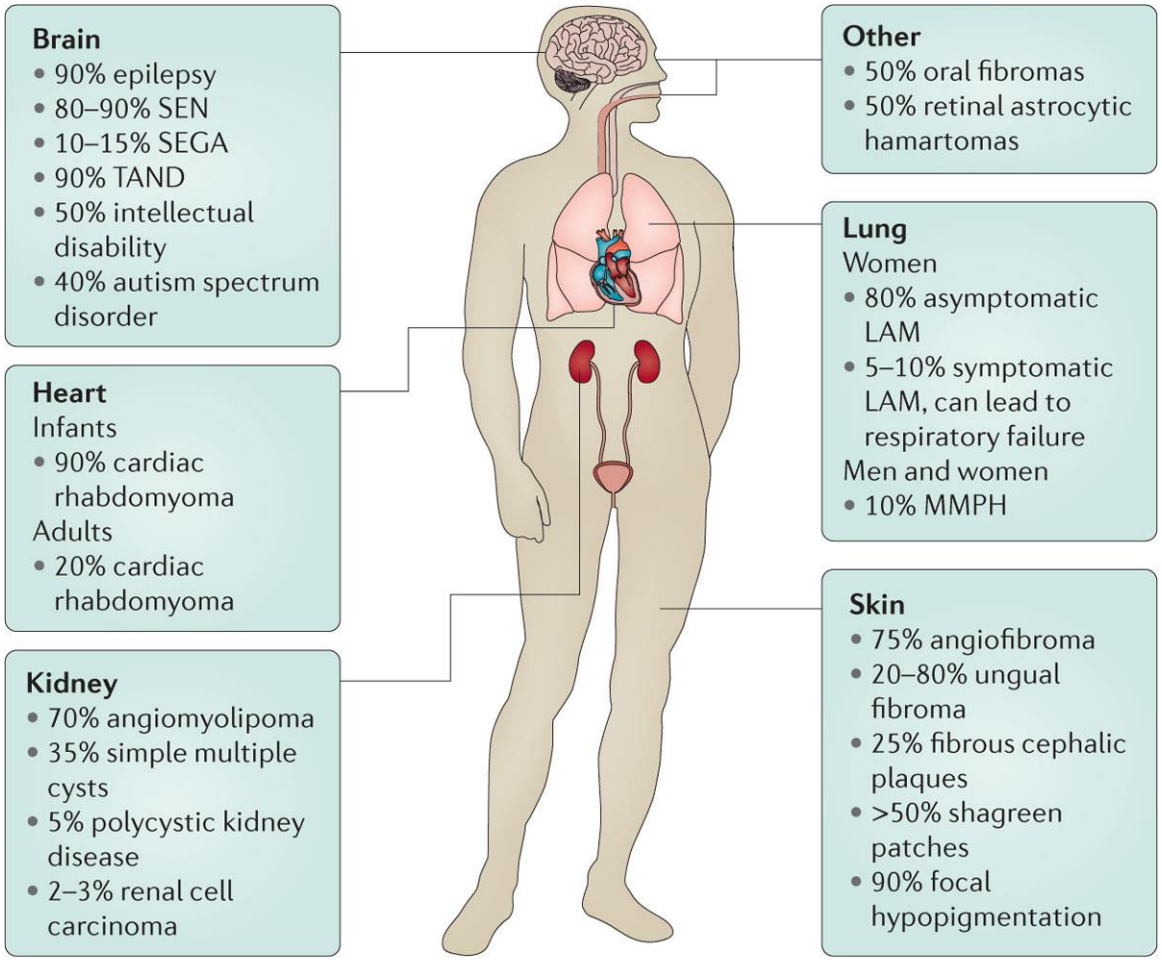
Symptoms of Tuberous Sclerosis Complex



Nature Reviews | Disease Primers

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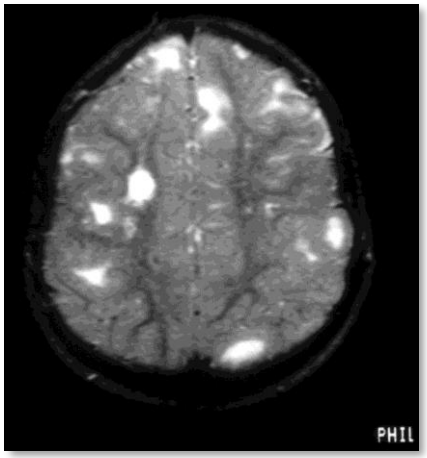
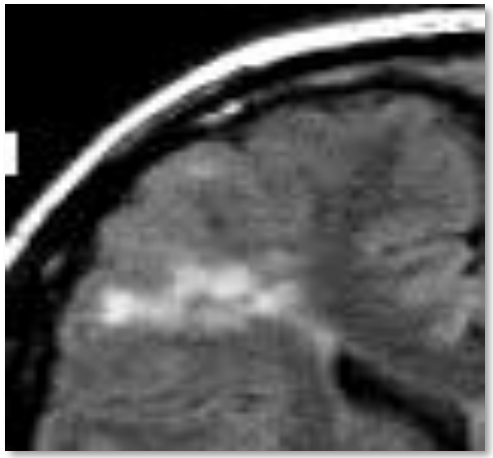
NEUROPATHOLOGIES ASSOCIATED WITH TSC

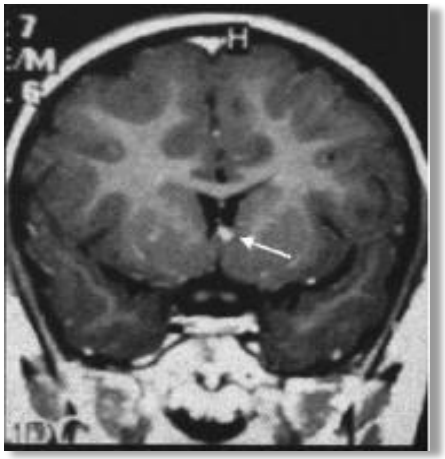
Tubers



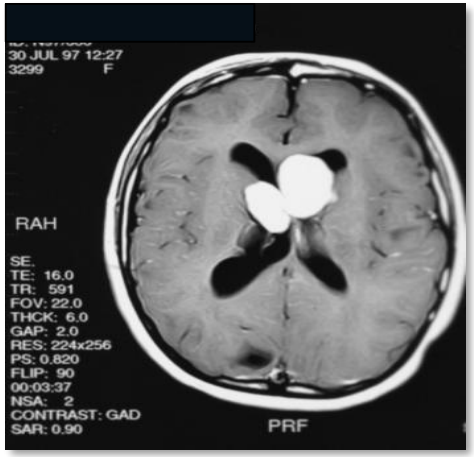
White Matter Tracts



SENs



SEGAs



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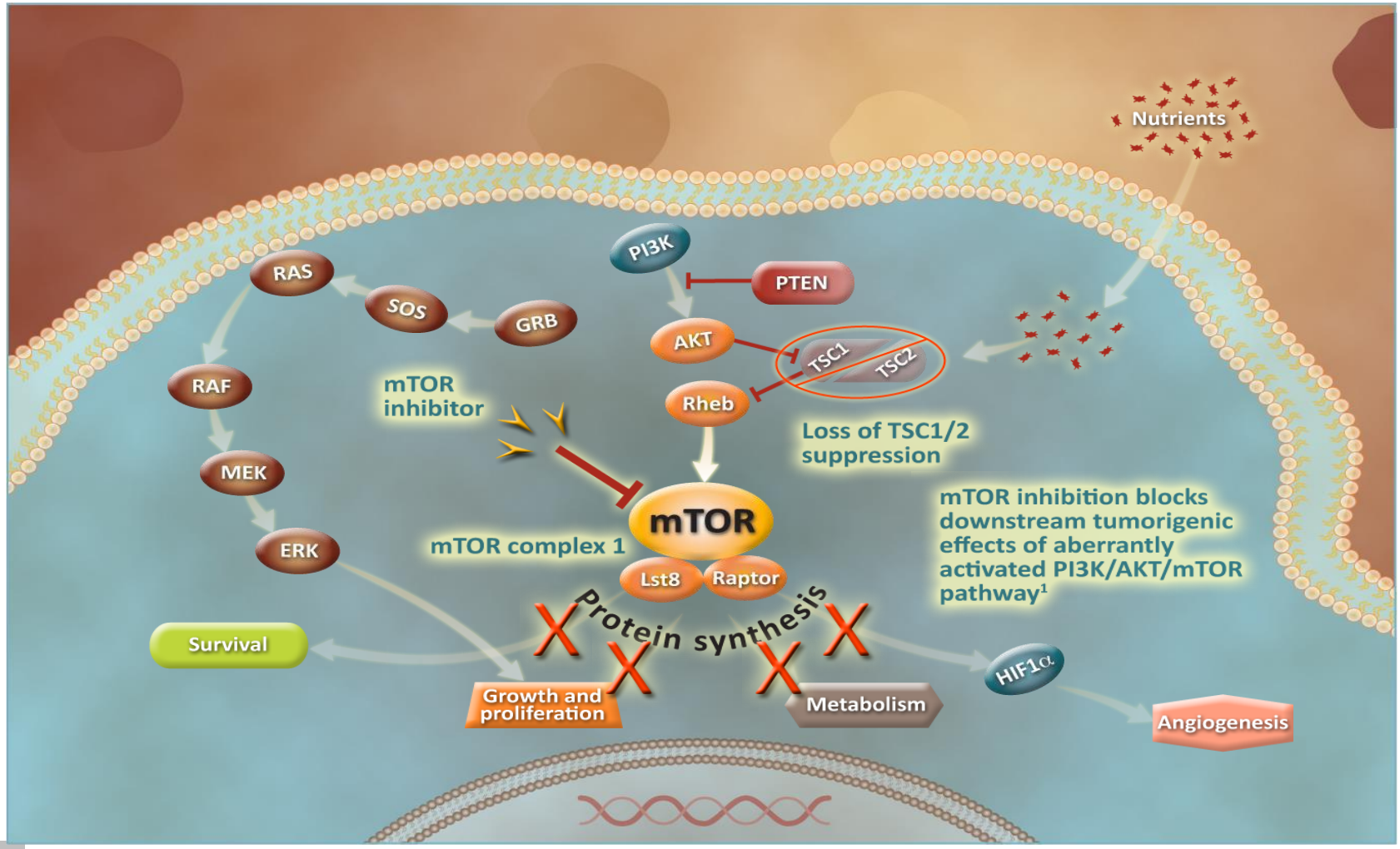
Pathogenesis of TSC



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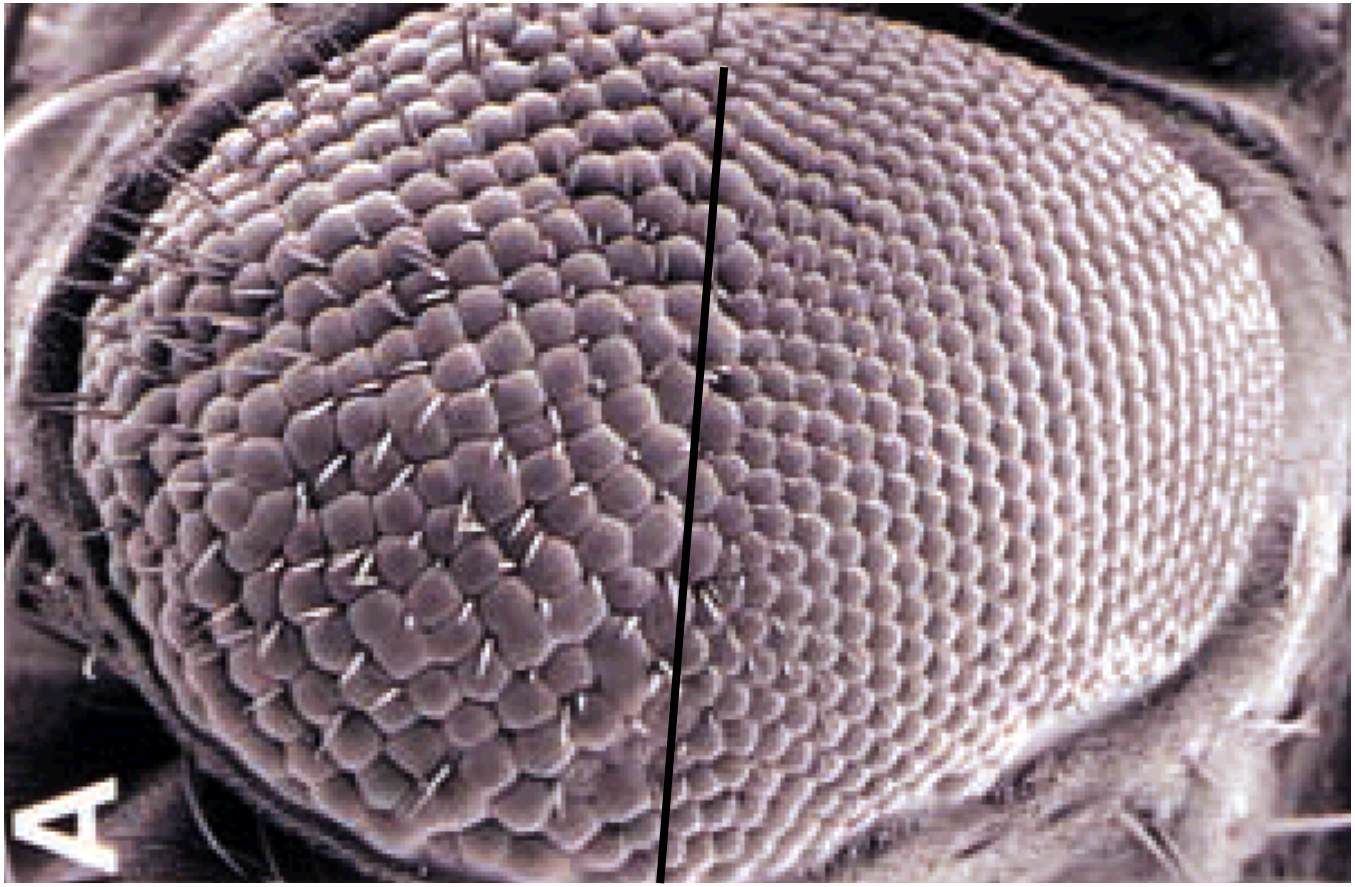
The role of TSC1/2 in the proliferation and cell growth regulation



Tsc1 -/-

WT

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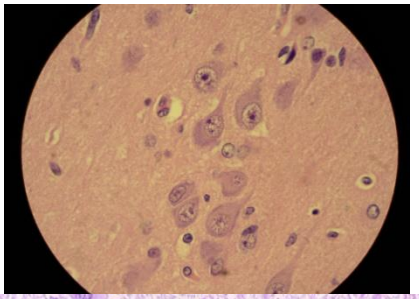
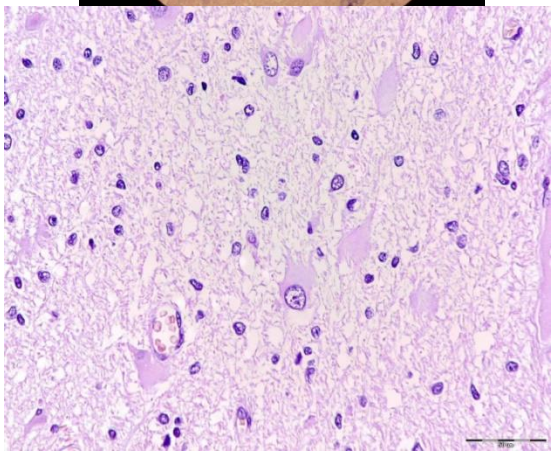
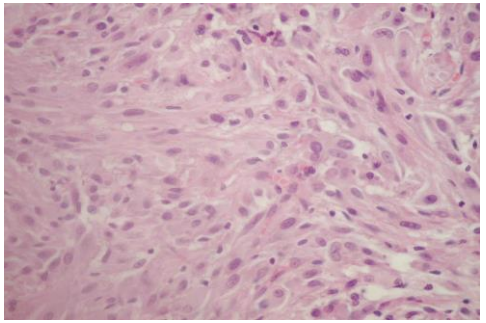
Microscopic Characteristics of Brain Lesion in TSC

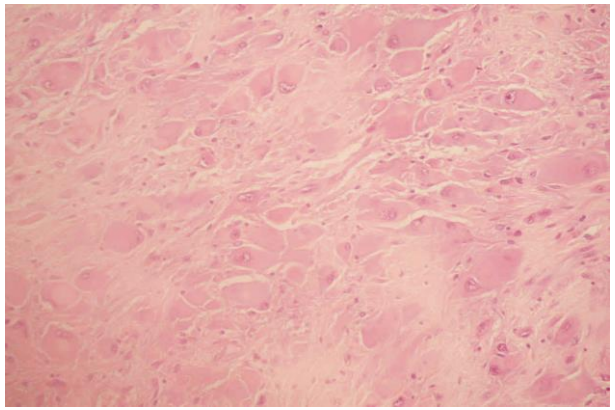
Cortical tuber





- SEGA





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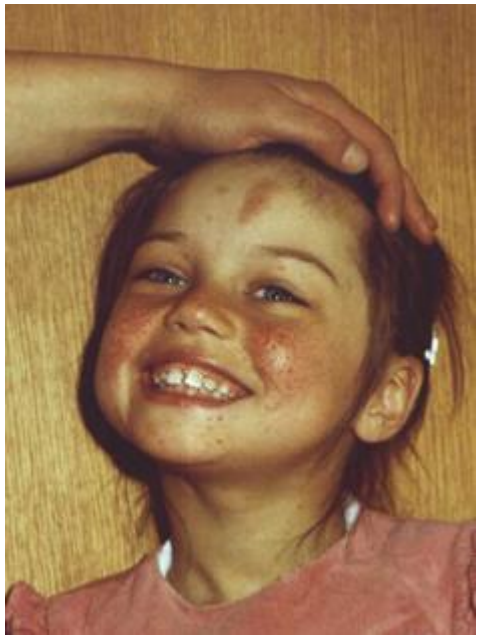
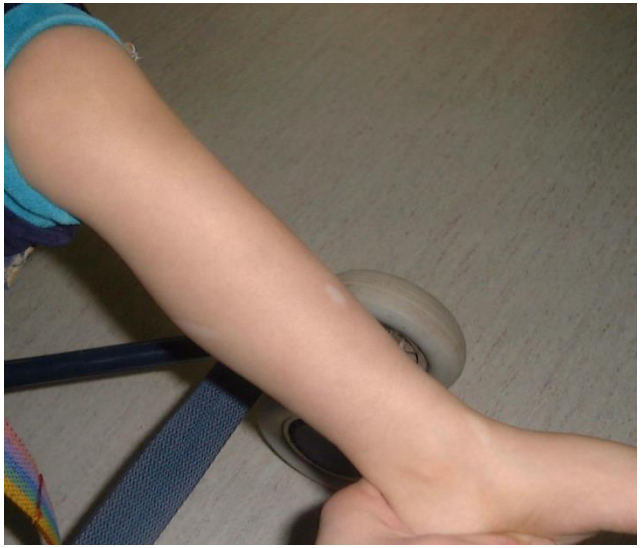
Revised diagnostic criteria
major features
TSC Consensus Conference 2012



- Facial angiofibromas or forehead plaque
- Non-traumatic periunqual fibroma (at least 2)
- Depigmented spots (at least 3)



- Shagreen patch
- Multiple retinal hamartoma
- Cortical dysplasias (tubers or migration lines)
- Subependymal nodules
- SEGA
- Cardiac rhabdomyomas
- LAM
- Renal angiomyolipomas (at least 2)

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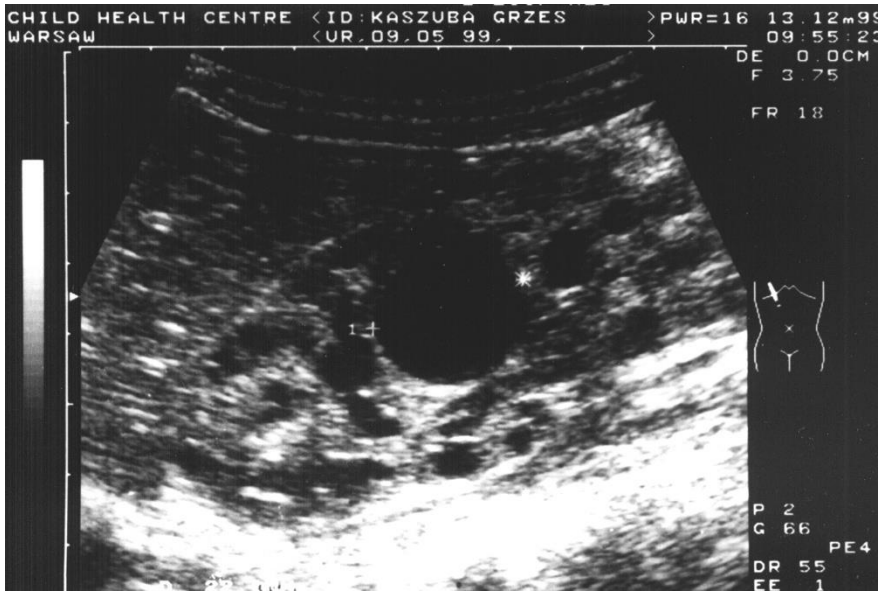
Revised diagnostic criteria
minor features
TSC Consensus Conference 2012

- Multiple enamel pits
- Intraoral fibromas
- Non-renal hamartoma
- Retinal achromic patch
- "Confetti" lesions
- Multiple renal cysts



Northrup H et al. *Pediatr Neurol*. 2013;49:243-54.

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Revised diagnostic criteria
TSC Consensus Conference 2012

- Genetic diagnosis is independent criterion sufficient for diagnosis

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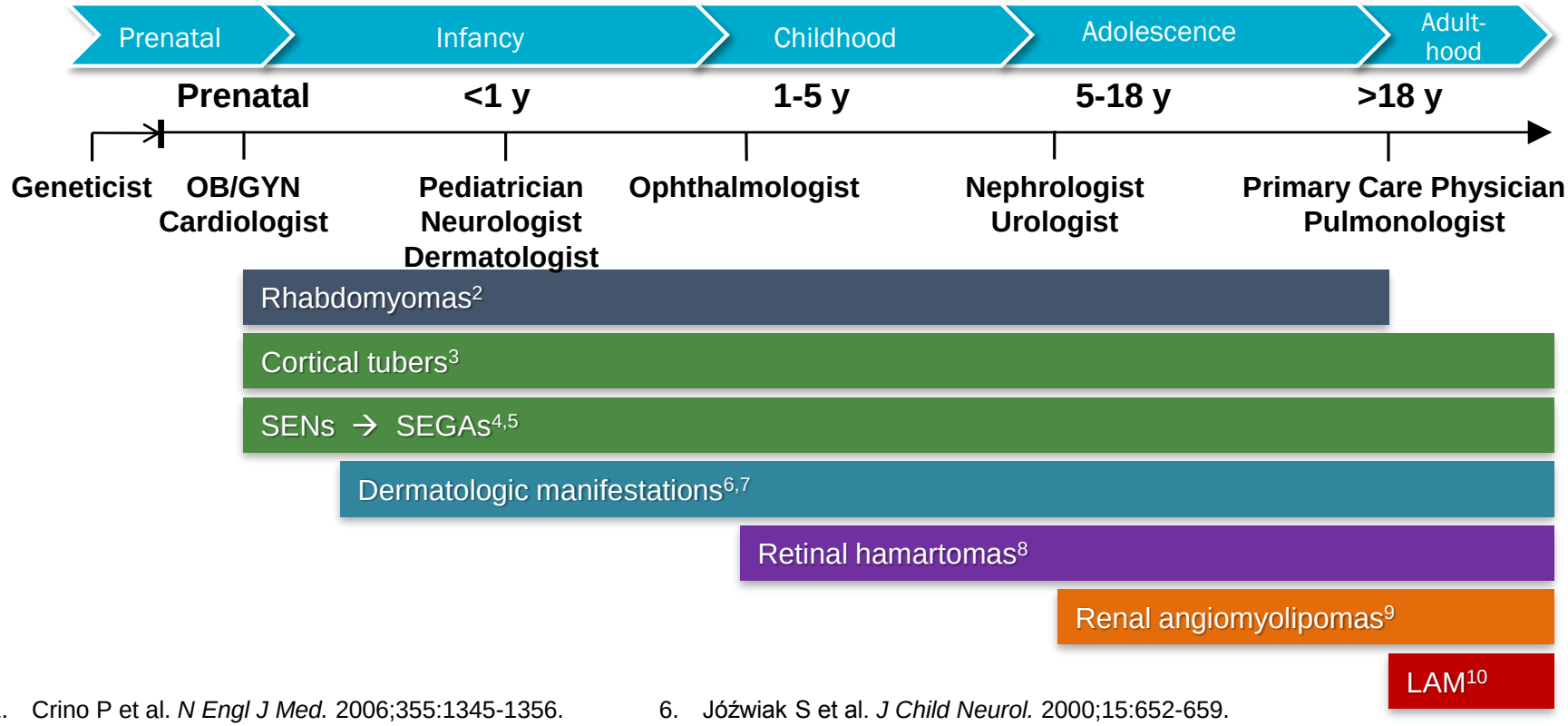
Clinical Manifestations of TSC Over Time

- Clinical manifestations of TSC vary widely[1]
- Some occur prenatally and others develop over time[1]



1. Crino P et al. *N Engl J Med.* 2006;355:1345-1356.
2. Jóźwiak S et al. *Pediatrics*. 2006;118;e1146-1151.
3. Richardson EP Jr. *Ann NY Acad Sci*. 1991;615:128-139.
4. Park SH et al. *Acta Neuropathol*. 1997;94:180-186.
5. Wiestler OD et al. *Brain Pathol*. 1996;6:376-377.
6. Jóźwiak S et al. *J Child Neurol.* 2000;15:652-659.
7. Sweeney SM. *Adv Dermatol.* 2004;20:117-135.
8. Franz DN. *J Child Neurol*. 2004;19:690-698.
9. Roach ES et al. *J Child Neurol*. 2004;19:643-649.
10. Sparagana SP et al. *Curr Opin Neurol*. 2000;13:115-119.

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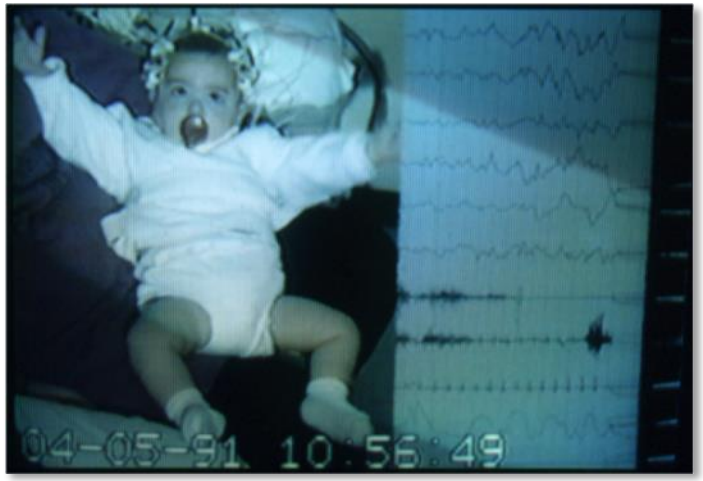
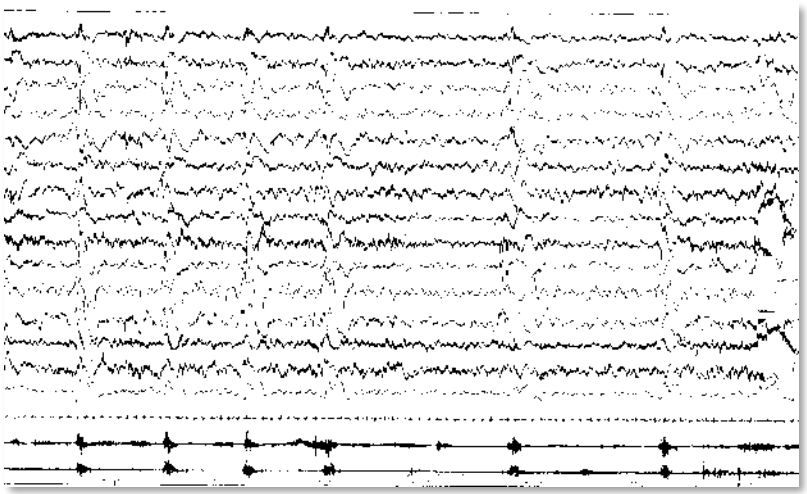
EPILEPSY IN TSC - A NATURAL HISTORY

- 80-90% of TSC patients also have epilepsy
  - The likelihood of developing epilepsy after the first seizure is 100%
- 63%-71% of patients experience seizure onset in the first year of life (in 58% the first seizures appear in the first six months of life)
- 6% had first seizures at the age of 5 or more
- 35-40% of TSC patients have infantile spasms
  - Focal seizure may precede, coexist with or evolve into infantile spasms
- Spike localization is age-dependent, initiating as occipital foci followed by frontal foci
- High risk of drug-resistance (up to 70%)





Curatolo P, et al. Lancet 2008;372:657-68.
Chu-Shore CJ, et al. Epilepsia 2009;51:1236-41.

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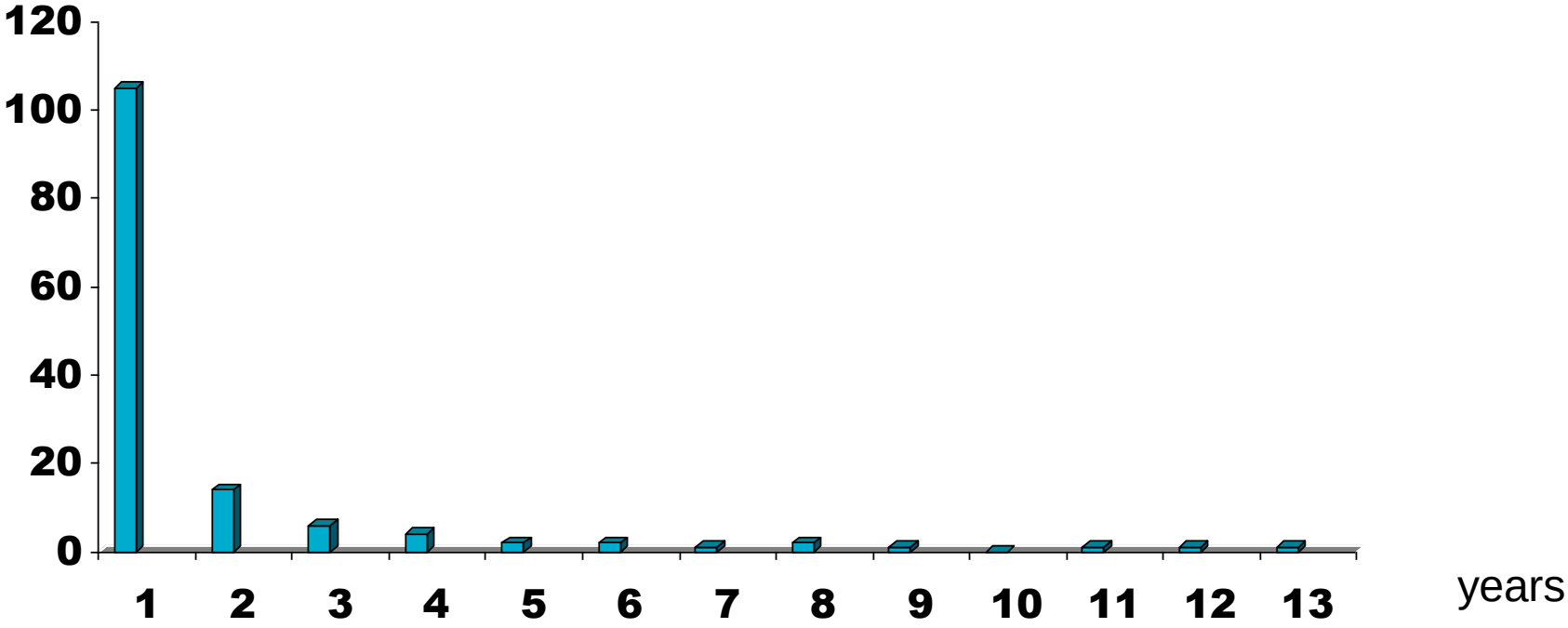
Epilepsy onset in TSC: age distribution



Jóźwiak S, et al. Biology of seizure susceptibility in developing brain. Montrouge, France: John Libbey, EuroText Ltd.;2008:221-31

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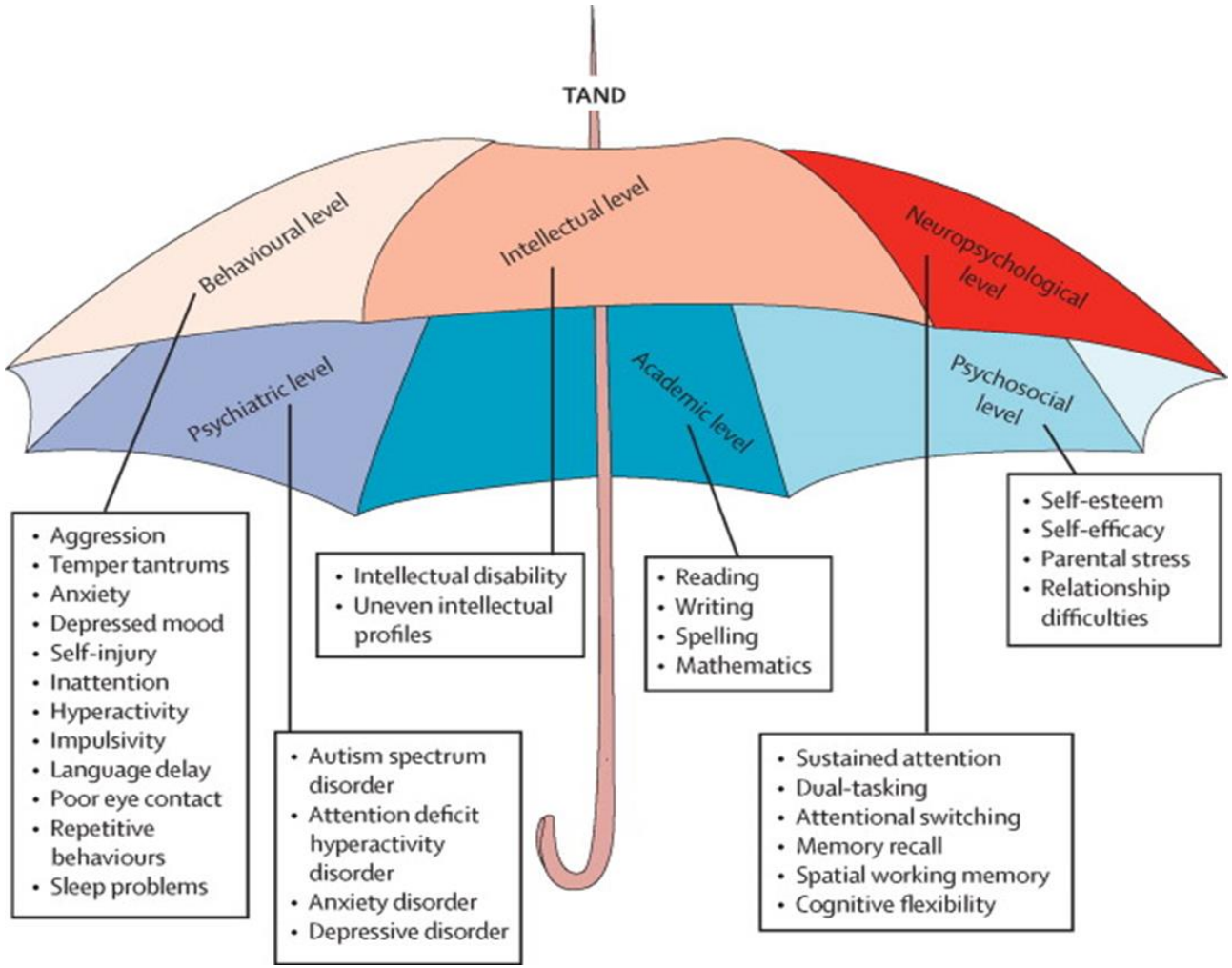
EPILEPSY COMORBIDITIES IN TSC

- Systemic

- Tumors in the brain, skin, kidney, liver, heart, lungs and other organs

- Neuropsychiatric



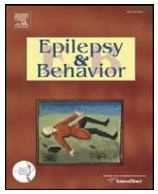
TAND=Tuberous Sclerosis-Associated Neuropsychiatric Disorders

Epilepsy & Behavior 22 (2011) 735–739

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

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



Long-term neurological outcome in children with early-onset epilepsy associated with tuberous sclerosis

Raffaella Cusmai [a], Romina Moavero [b], Roberta Bombardieri [b], Federico Vigevano [a], Paolo Curatolo [b,*]

[a] *Division of Neurology, Bambino Gesù Children's Hospital, Rome, Italy*
[b] *Pediatric Neurology Unit, Neuroscience Department, University Hospital of Tor Vergata, Rome, Italy*

A B S T R A C T

In tuberous sclerosis complex, early seizure onset is associated with high risk of intractable epilepsy and cognitive/behavioral impairment. We retrospectively evaluated the long-term outcome of 44 infants presenting with seizures in the first 12 months who received vigabatrin, and were followed up for at least 3.5 years. At the final evaluation 55% of patients were still having seizures, 80% had intellectual disability, and 30% had autism. Sixty-five percent of children who had been treated earlier with vigabatrin after seizure onset achieved seizure freedom, compared with 24% of subjects who received vigabatrin treatment later ($P<0.01$). Intellectual disability was present in 61% of the children treated early (group A) and in 100% of the children treated later (group B). Nine percent of group A and 52% of group B had autism ($P\approx0.001$).

Deferred treatment is associated with 100% intellectual disability

Early recognition of seizures and early treatment improve epilepsy outcome

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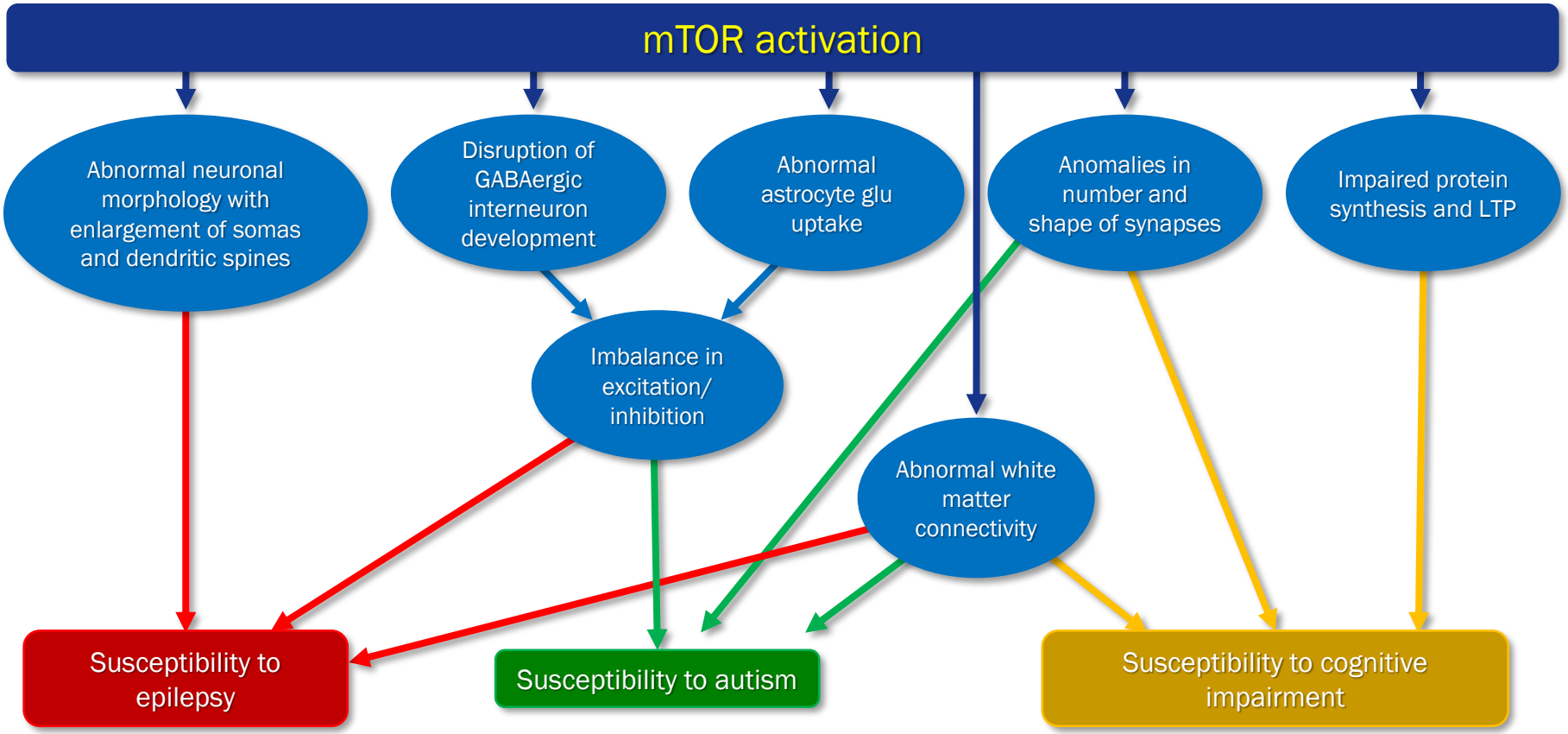
mTOR Overactivity and Other Neurologic Phenotypes



Napolioni V, et al. Brain & Dev 2009;31:104–113.

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Mental status in relationship to seizures (experience from Mayo Clinic)

Intellectual disability was present ONLY in patients with history of epilepsy

	Normal	Intellectual Disability
Seizures (n=129)	40 (31%)	89 (69%)
Without seizures (n=19)	19 (100%)	–

Gomez MR., Tuberous sclerosis, 2nd ed. 1988

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Intellectual Disability (ID) in TSC

Age at Onset of Epilepsy	Profound ID	Severe ID	Moderate ID	Mild ID	Less Than Normal	Average	Total
< 6 mo	13	21	19	13	12	3	81 (57.9%)
6–12 mo	2	7	6	5	3	1	24 (17.1%)
1–2 yrs	1	1	2	2	4	4	14 (10.0%)
2–5 yrs	-	1	1	3	3	4	12 (8.6%)
>5 yrs	-	-	-	2	2	5	9 (6.4%)
Total	16 (11.4%)	30 (21.4%)	28 (20.0%)	25 (17.9%)	24 (17.1%)	17 (12.2%)	140

82%

ID, intellectual disability.

Józwiak S, et al. Biology of seizure susceptibility in developing brain. Montrouge, France: John Libbey, EuroText Ltd.;2008:221-31.

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Epilepsy and intellectual disability in TSC1 and TSC2 patients

TSC1

- Epilepsy in 64%
- Infantile spasms - 1/11
- Average onset of epilepsy - 4,6 years
- Intellectual disability 36%

TSC2

- Epilepsy in 91%*
- Infantile spasms - 36/56***
- Average onset of epilepsy - 1,0 year*
- Intellectual disability 61%

*****p<0,001, *p<0,05**

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Evolution of seizures in infants with TSC

Normal

↓

Focal seizures

↓

Infantile spasms

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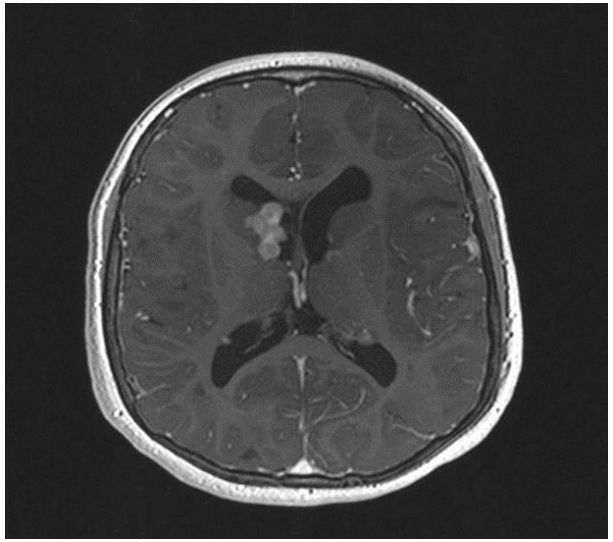
Domanska et al. EJPN, 2014, 18: 458-468

PATIENT LN, AGE 3

- Born with multiple cardiac tumors and multiple hypomelanotic macules. Neonatal brain MRI revealed multiple cortical tubers.
- TSC2 mutation

- Focal seizures started at 5/12
- Treated with VGB – transient improvement
- After 3 months seizures again
- VGB+VPA- no effect
- +TPM – still having daily seizures
- Infantile spasms developed
- ACTH with response

- Age 3: drug-resistant epilepsy, intellectual disability



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EUROPEAN RECOMMENDATIONS IN INFANTILE SPASMS IN TSC

Original article

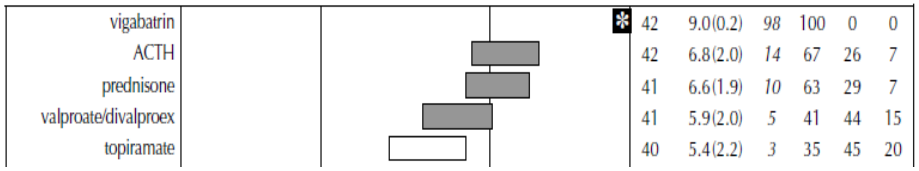
Epileptic Disord 2007; 9 (4) 353-412

Treatment of pediatric epilepsy: European expert opinion, 2007

James W. Wheless[1], Dave F. Clarke[1], Alexis Arzimanoglou[2], Daniel Carpenter[3]

4B. Treatment selection for infantile spasms: survey results

Question 21. A healthy 6-month-old is diagnosed with *infantile spasms secondary to tuberous sclerosis complex* and is starting therapy for the first time. Assume that you begin with monotherapy. Assume that the parents are amenable to all possible therapies and will be compliant with the therapy. Rate the appropriateness of each of the following treatments.



	N	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
vigabatrin	42	9.0(0.2)	98	100	0	0
ACTH	42	6.8(2.0)	14	67	26	7
prednisone	41	6.6(1.9)	10	63	29	7
valproate/divalproex	41	5.9(2.0)	5	41	44	15
topiramate	40	5.4(2.2)	3	35	45	20

AMERICAN RECOMMENDATIONS IN INFANTILE SPASMS IN TSC

Journal of Child Neurology
http://jcn.sagepub.com

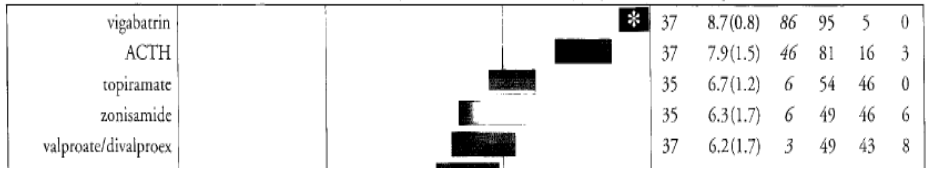
Treatment of Pediatric Epilepsy: Expert Opinion, 2005

James W. Wheless, Dave F. Clarke and Daniel Carpenter

J Child Neurol 2005; 20; S1
DOI: 10.1177/08830738050200101

4B. Treatment Selection for Infantile Spasms: Survey Results

Question 21. A *healthy 6-month-old* is diagnosed with *infantile spasms secondary to tuberous sclerosis complex* and is starting therapy for the first time. Assume that you begin with monotherapy. Assume that the parents are amenable to all possible therapies and will be compliant with the therapy. Rate the appropriateness for each of the following treatments.



	N	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
vigabatrin	37	8.7(0.8)	86	95	5	0
ACTH	37	7.9(1.5)	46	81	16	3
topiramate	35	6.7(1.2)	6	54	46	0
zonisamide	35	6.3(1.7)	6	49	46	6
valproate/divalproex	37	6.2(1.7)	3	49	43	8

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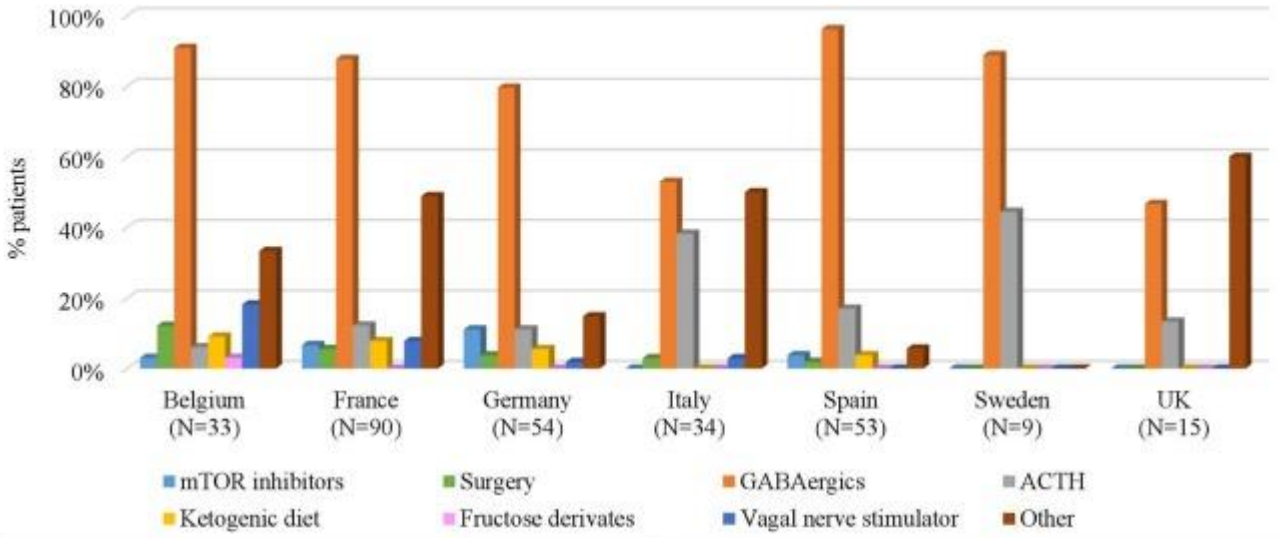
TREATMENT OF INFANTILE SPASMS IN TOSCA STUDY



	Belgium (N=33)	France (N=90)	Germany (N=54)	Italy (N=34)	Spain (N=53)	Sweden (N=9)	UK (N=15)
mTOR inhibitors	1 (3.0%)	6 (6.7%)	6 (11.1%)	0 (0.0%)	2 (3.8%)	0 (0.0%)	0 (0.0%)
Surgery	4 (12.1%)	5 (5.6%)	2 (3.7%)	1 (2.9%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
GABAergics	30 (90.9%)	79 (87.8%)	43 (79.6%)	18 (52.9%)	51 (96.2%)	8 (88.9%)	7 (46.7%)
ACTH	2 (6.1%)	11 (12.2%)	6 (11.1%)	13 (38.2%)	9 (17.0%)	4 (44.4%)	2 (13.3%)
Ketogenic diet	3 (9.1%)	7 (7.8%)	3 (5.6%)	0 (0.0%)	2 (3.8%)	0 (0.0%)	0 (0.0%)
Fructose derivates	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vagal nerve stimulator	6 (18.2%)	7 (7.8%)	1 (1.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	11 (33.3%)	44 (48.9%)	8 (14.8%)	17 (50.0%)	3 (5.7%)	0 (0.0%)	9 (60.0%)

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POLL #1

- What would you recommend as a first – choice antiepileptic drug in an TSC infant with focal seizures?

- 1. Carbamazepine
- 2. Vigabatrin
- 3. Levetiracetam
- 4. Other

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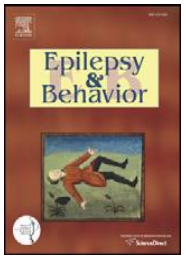
Epilepsy & Behavior 27 (2013) 118–120

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

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



Vigabatrin for partial-onset seizure treatment in patients with tuberous sclerosis complex

Daniel Friedman *, Miles Bogner, Kimberly Parker-Menzer, Orrin Devinsky

Comprehensive Epilepsy Center, NYU Langone Medical Center, New York, NY 10016, USA

IN 49 PATIENTS WITH TSC AND DRUG-RESISTANT PARTIAL SEIZURES VGB WAS USED AS ADD-ON THERAPY. THIRTEEN PATIENTS (24,5%) BECAME SEIZURE FREE OR EXPERIENCED AT LEAST 90% REDUCTION OF SEIZURES

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EUROPEAN RECOMMENDATIONS IN EPILEPSY IN TSC (ROME 2012)

-vigabatrin is the first-line therapy for infantile spasms with TSC

-vigabatrin for focal seizures before the age of 1 year

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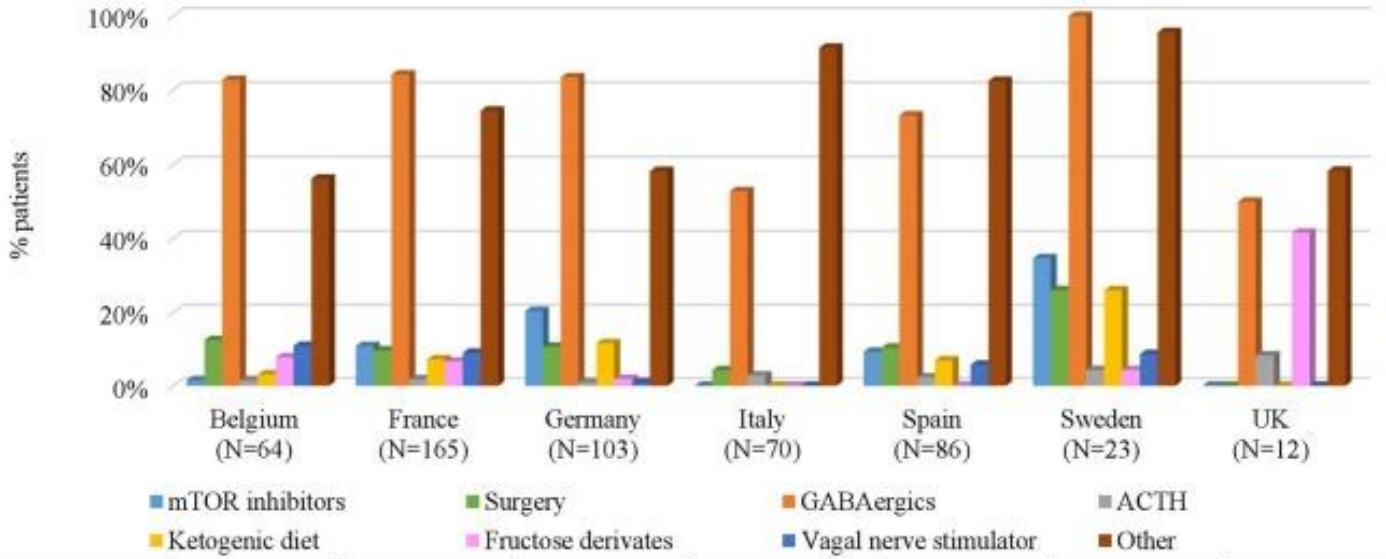
Curatolo et al. Eur. J.Paediatr. Neurol. 2012, 16(6): 582-589.

TREATMENT FOR FOCAL SEIZURES ASSOCIATED WITH TSC – TOSCA STUDY



	Belgium (N=64)	France (N=165)	Germany (N=103)	Italy (N=70)	Spain (N=86)	Sweden (N=23)	UK (N=12)
mTOR inhibitors	1 (1.6%)	18 (10.9%)	21 (20.4%)	0 (0.0%)	8 (9.3%)	8 (34.8%)	0 (0.0%)
Surgery	8 (12.5%)	16 (9.7%)	11 (10.7%)	3 (4.3%)	9 (10.5%)	6 (26.1%)	0 (0.0%)
GABAergics	53 (82.8%)	139 (84.2%)	86 (83.5%)	37 (52.9%)	63 (73.3%)	23 (100.0%)	6 (50.0%)
ACTH	1 (1.6%)	3 (1.8%)	1 (1.0%)	2 (2.9%)	2 (2.3%)	1 (4.3%)	1 (8.3%)
Ketogenic diet	2 (3.1%)	12 (7.3%)	12 (11.7%)	0 (0.0%)	6 (7.0%)	6 (26.1%)	0 (0.0%)
Fructose derivates	5 (7.8%)	11 (6.7%)	2 (1.9%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	5 (41.7%)
Vagal nerve stimulator	7 (10.9%)	15 (9.1%)	1 (1.0%)	0 (0.0%)	5 (5.8%)	2 (8.7%)	0 (0.0%)
Other	36 (56.3%)	123 (74.5%)	60 (58.3%)	64 (91.4%)	71 (82.6%)	22 (95.7%)	7 (58.3%)

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DOSE OF VIGABATRIN: USE HIGHER

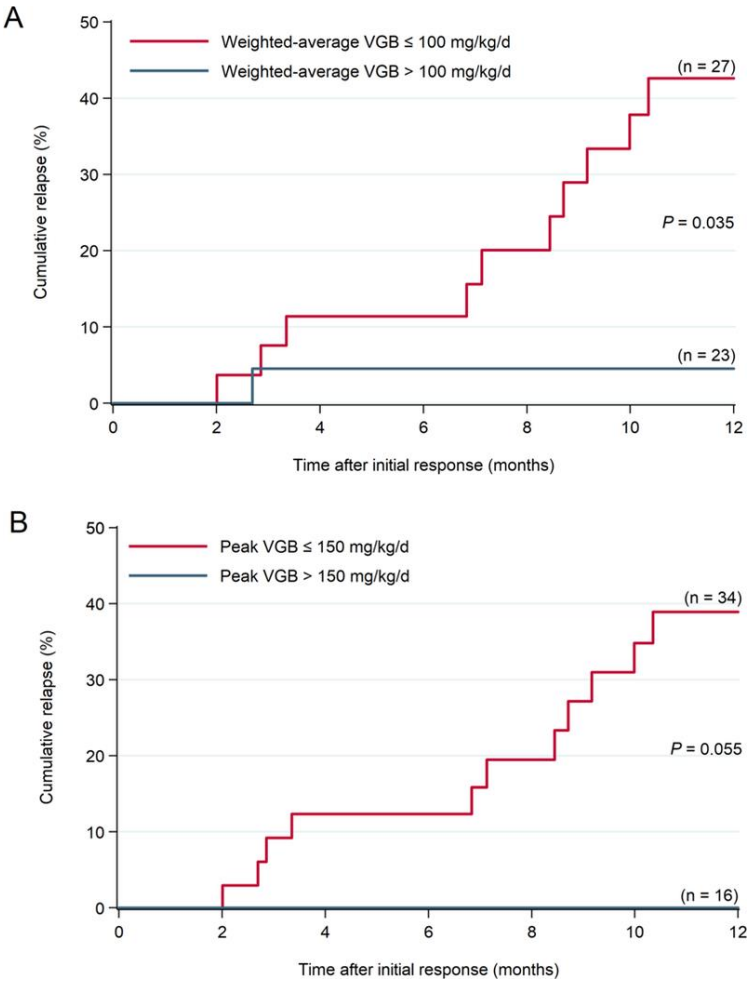
Epilepsy Res. 2018 Dec; 148: 1–7.

High vigabatrin dosage is associated with lower risk of infantile spasms relapse among children with tuberous sclerosis complex

- Shaun A. Hussain,[1] Ernst Schmid,[1] Jurriaan M. Peters,[2] Monisha Goyal,[3] E. Martina Bebin,[3] Hope Northrup,[4] Mustafa Sahin,[2] Darcy A. Krueger,[5] and Joyce Y. Wu[1], the Tuberous Sclerosis Complex Autism Center of Excellence Network.

Abstract

- After initially successful treatment of infantile spasms, the long-term cumulative risk of relapse approaches 50%, and there is no established protocol to mitigate this risk. Although vigabatrin may be an effective means to prevent relapse, there is little guidance as to ideal duration and dosage. Using a cohort of children with infantile spasms and tuberous sclerosis complex (TSC), we evaluated the potential association of post-response VGB treatment and the rate of infantile spasms relapse. Patients with infantile spasms and clinical response to vigabatrin were identified among a multicenter prospective observational cohort of children with TSC. For each patient we recorded dates of infantile spasms onset, response to vigabatrin, relapse (if any), and quantified duration and dosage of vigabatrin after response. Time to relapse as a function of vigabatrin exposure was evaluated using survival analyses. We identified 50 children who responded to VGB. During a median follow-up of 16.6 months (IQR 10.3 – 22.9), 12 (24%) patients subsequently relapsed after a median of 7.8 months (IQR 3.1 — 9.6). Relapse occurred after VGB discontinuation in four patients, and during continued VGB treatment in the remaining eight cases. In survival analyses, risk of relapse was unaffected by the presence or absence of VGB treatment (HR 0.31, 95%CI 0.01 – 28.4, *P*= 0.61), but weighted-average dosage was associated with marked reduction in relapse risk: Each 50 mg/kg/d increment in dosage was associated with 61% reduction in risk (HR 0.39, 95%CI 0.17 – 0.90, *P* = 0.026). This study suggests that the risk of infantile spasms relapse in TSC may be reduced by high -dose vigabatrin treatment.



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EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 14 (2010) 146–149

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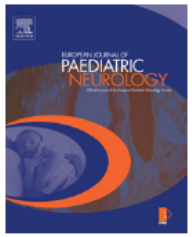

Original article

Early control of seizures improves long-term outcome in children with tuberous sclerosis complex

*Roberta Bombardieri, Mariangela Pinci, Romina Moavero, Caterina Cerminara, Paolo Curatolo**

Department of Neuro

Long term outcome:

Median IQ 54

Table 1 – Clinical findings and characteristics of our 8 patients.

Cases	Genetic mutation	Seizures onset	Seizures type	VGB efficacy after 1 month	VGB treatment duration	AEDs	Seizures type and outcome	Age at final evaluation	Cognitive status
Case 1, F	No mutation identified	8 m	PMS	Poor seizure control	6 m	VPA, TPM, CLB	PCS + SBS	4 y, 9 m	TIQ 45 (WPPSI)
Case 2, F	No DNA available	5 m	IS	Seizure free	7 m	VPA	Seizure free	9 y, 4 m	TIQ 59 (WISC-III) inattention
Case 3, F	TSC2, Exon 15 substitution c.1714C > T, p.Gln572X) *de novo mutation*	5 m	IS	Seizure free	9 m	CBZ, ZNS	PCS + SBS	4 y	TIQ 50 (WPPSI) hyperactivity
Case 4, F	TSC2, Exon 33 Del (4428_4429delGA) *de novo mutation*	8 m	PMS	Poor seizure control	10 m	TPM	Atypical absences	12 y, 3 m	TIQ 46 (WISC-III) hyperactivity
Case 5, F	TSC2, Exon 26 Ins G on 3064 position *de novo mutation*	11 m	PMS	Seizure free	6 m	CBZ	Seizure free	7 y, 1 m	TIQ 104 (WISC-III) hyperactivity
Case 6, M	TSC2, Del exons 16–21 *de novo mutation*	2 m	IS	Seizure free	49 m	CBZ	Seizure free	6 y, 7 m	TIQ 55 (WPPSI) hyperactivity
Case 7, F	TSC2, Intron 9 substitution (976-15G > A) *de novo mutation*	7 m	IS	Seizure free	23 m	TPM	Seizure free	9 y, 1 m	TIQ 83 (WISC-III) inattention
Case 8, F	TSC2, Del Exon 40 (5238_5255del18) *de novo mutation*	6 m	IS	Seizure free	30 m	TPM	Seizure free	3 y	DQ 0.90 (BL)
Case 9, F	TSC2, Exon 40 substitution (c.5227C > T, p.Arg1743Trp) *de novo mutation*	3 m	PMS	Seizure free	48 m	VPA, TPM, CBZ	PCS	12 y, 6 m	TIQ 53 (WISC-III) hyperactivity
Case 10, M	TSC2, Ex 13 *de novo mutation*	2 m	PMS + IS	Poor seizure control	11 m	TPM, VPA	PCS	6 y, 9 m	TIQ 44 (WISC-III) Inattention

BL: Brunet–Lèzine; DQ: developmental quotient; IQ: intelligence quotient; PMS: partial motor seizures; IS: infantile spasms; SBS: secondary bilateral synchrony; PCS: partial complex seizures.

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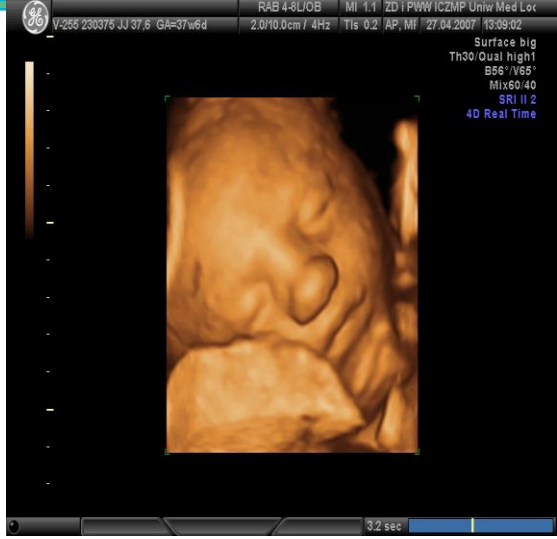
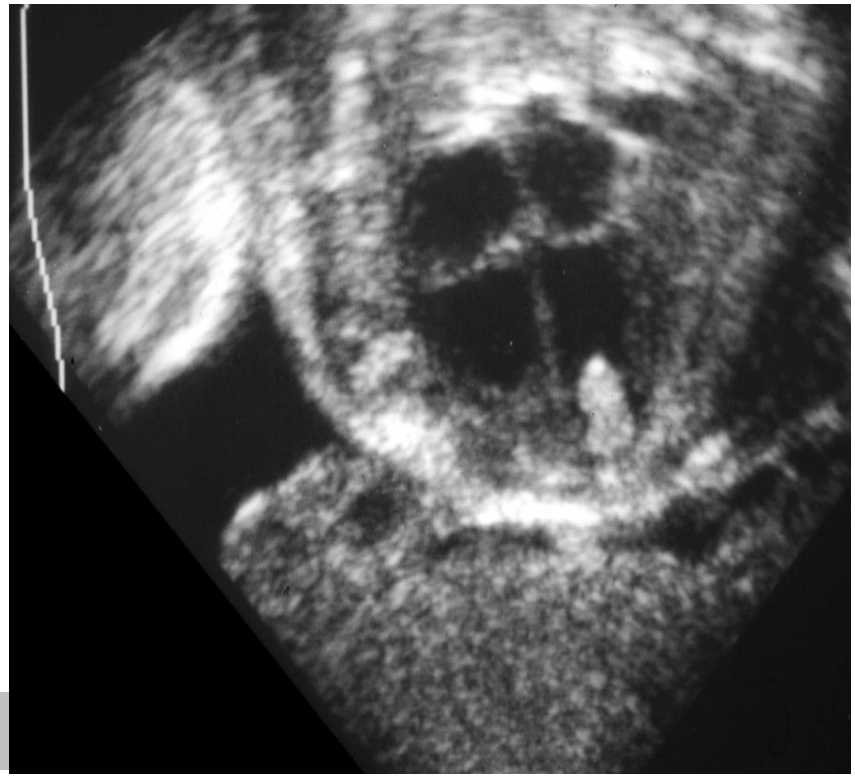
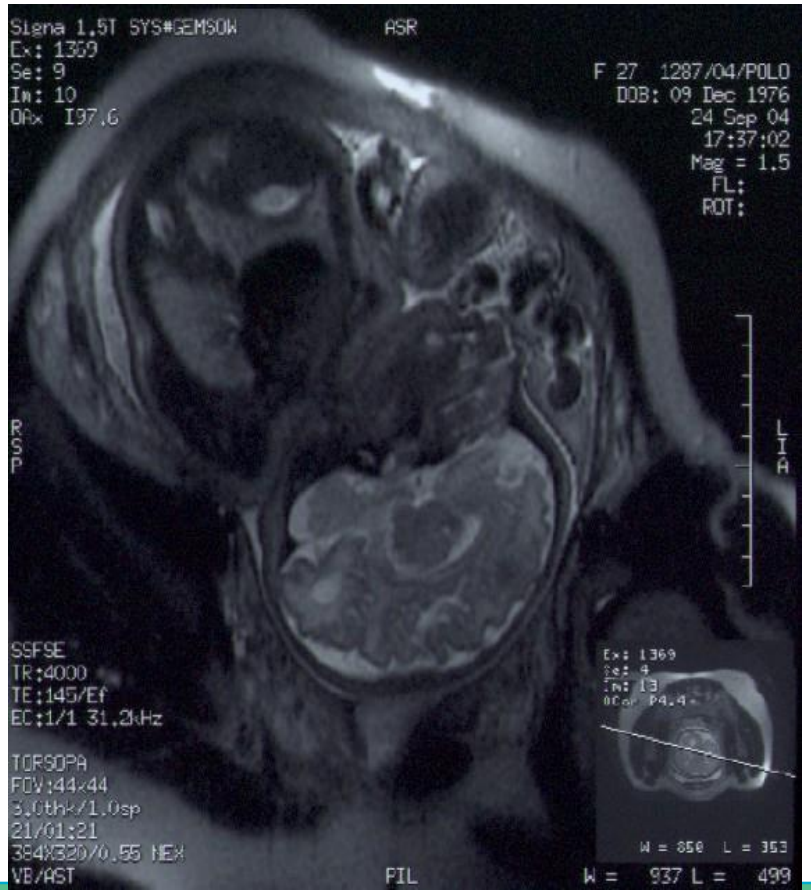
TSC is increasingly diagnosed prenatally

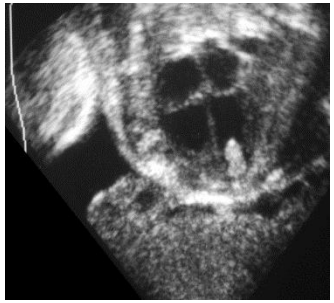


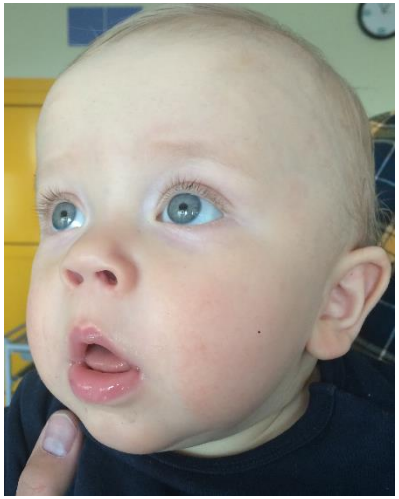


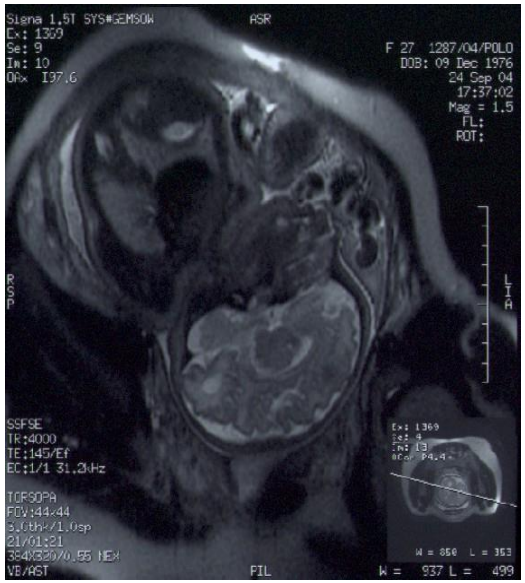


NEWBORN/YOUNG INFANT WITH TSC

- looks healthy
- Brain lesions visible on MRI, but asymptomatic
- cardiac tumors, usually asymptomatic
- no seizures, normal EEG
- normal development initially







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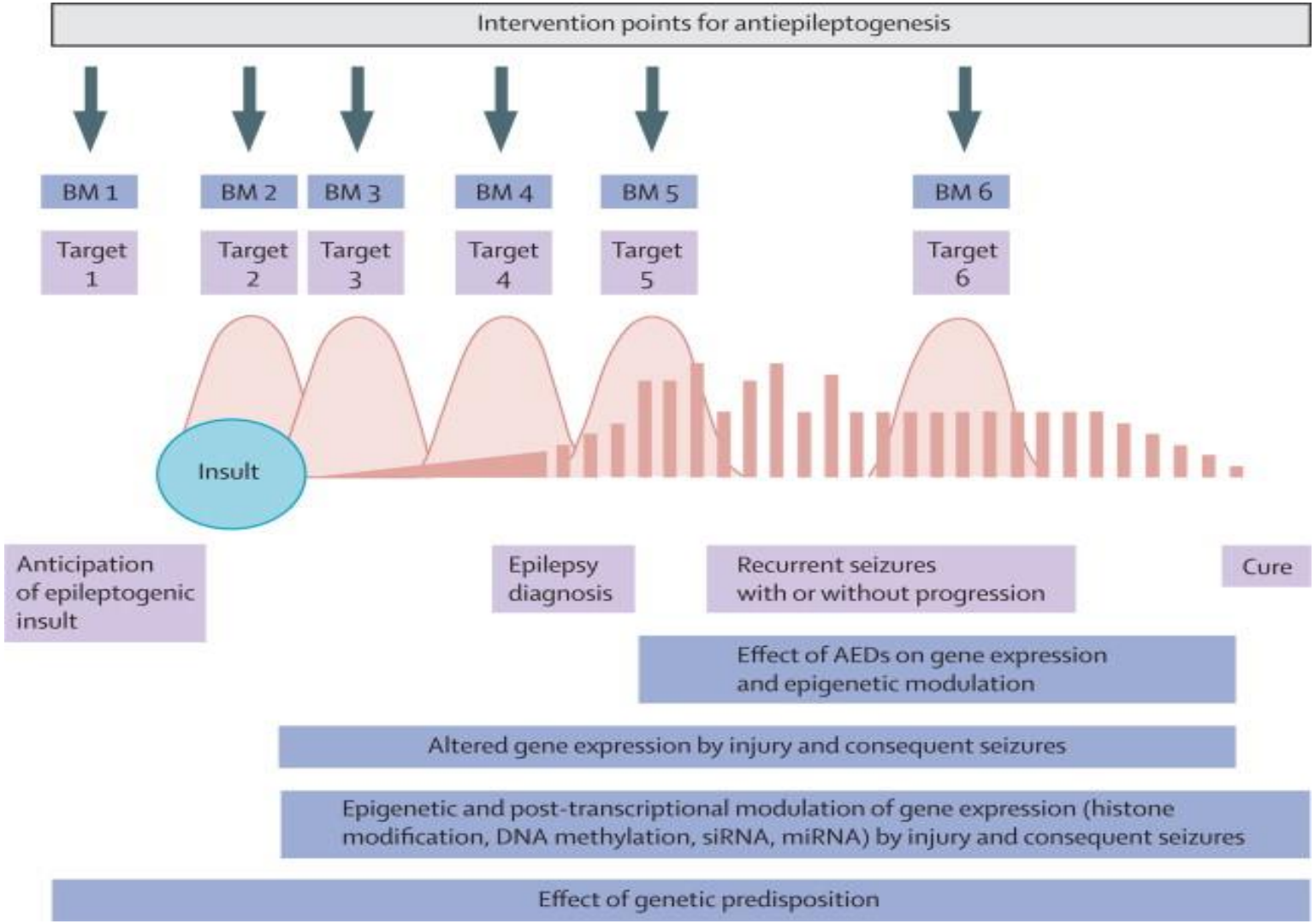
EPILEPTOGENESIS



Evolution of epileptogenesis in infants with TSC

Normal EEG

↓

Spikes

↓

Multifocal spike and wave complexes (subtle focal seizures)

↓

generalized activity/ hypsarhythmia (infantile spasms)

Domanska et al. EJPN, 2014, 18: 458-468

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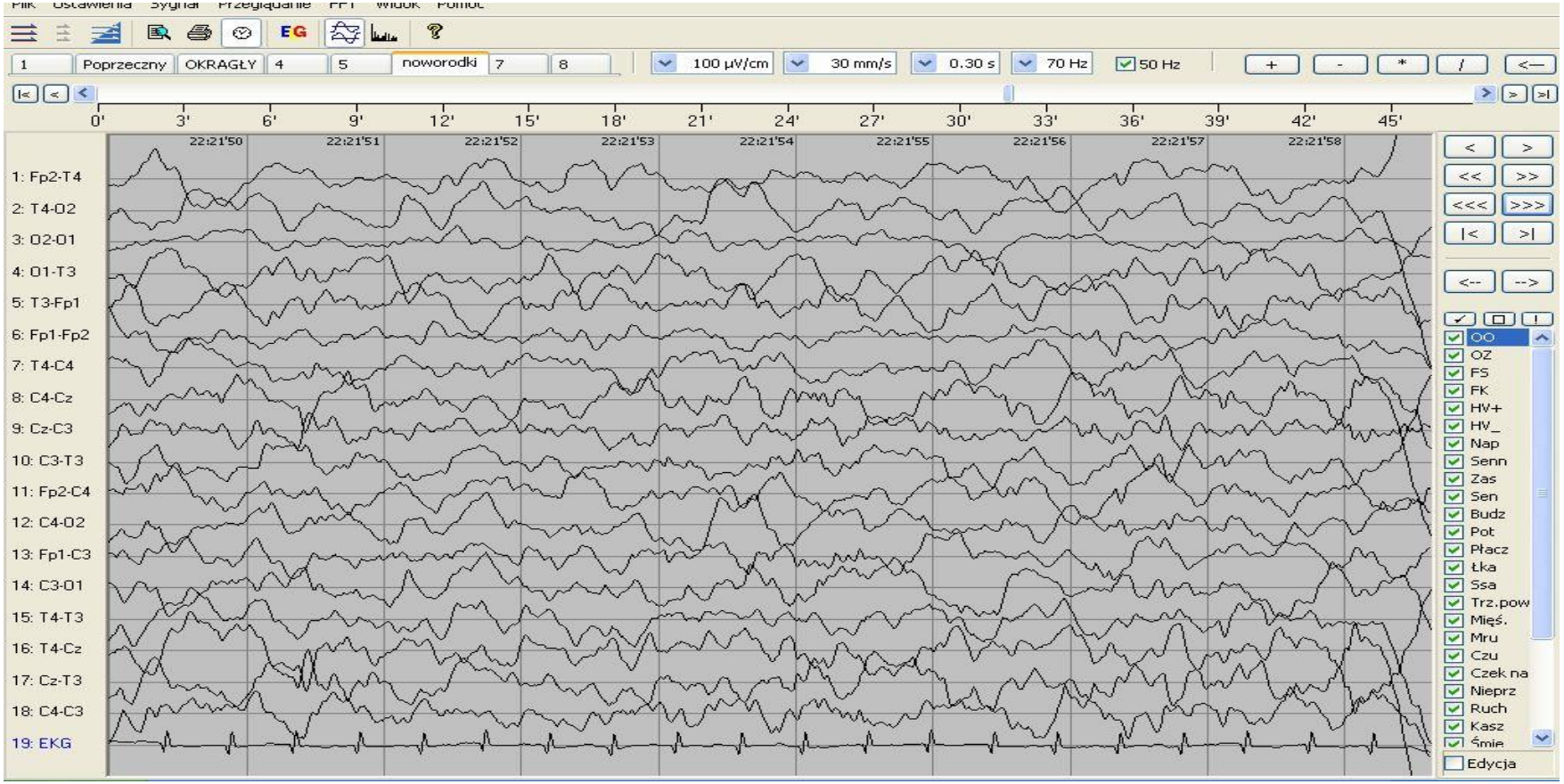
W.S. SLEEP EEG 2/12 NORMAL



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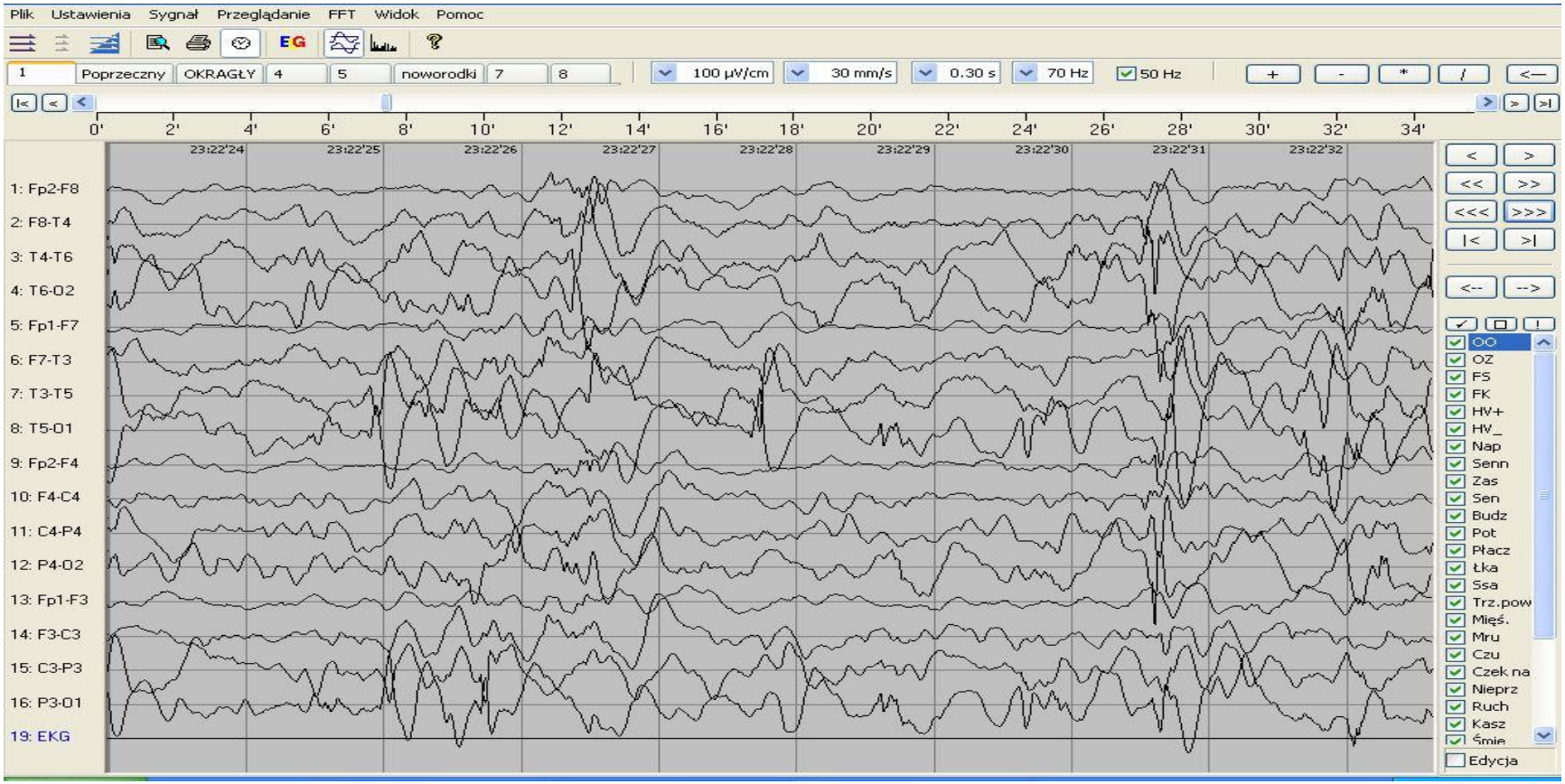
SLEEP EEG 5/12

SPIKE AND WAVE COMPL.(SWC) AT PARIETOOCIPITAL AND POSTERO-TEMPORAL REGIONS BILATERAL, SPREADING TO FRONTAL REGIONS



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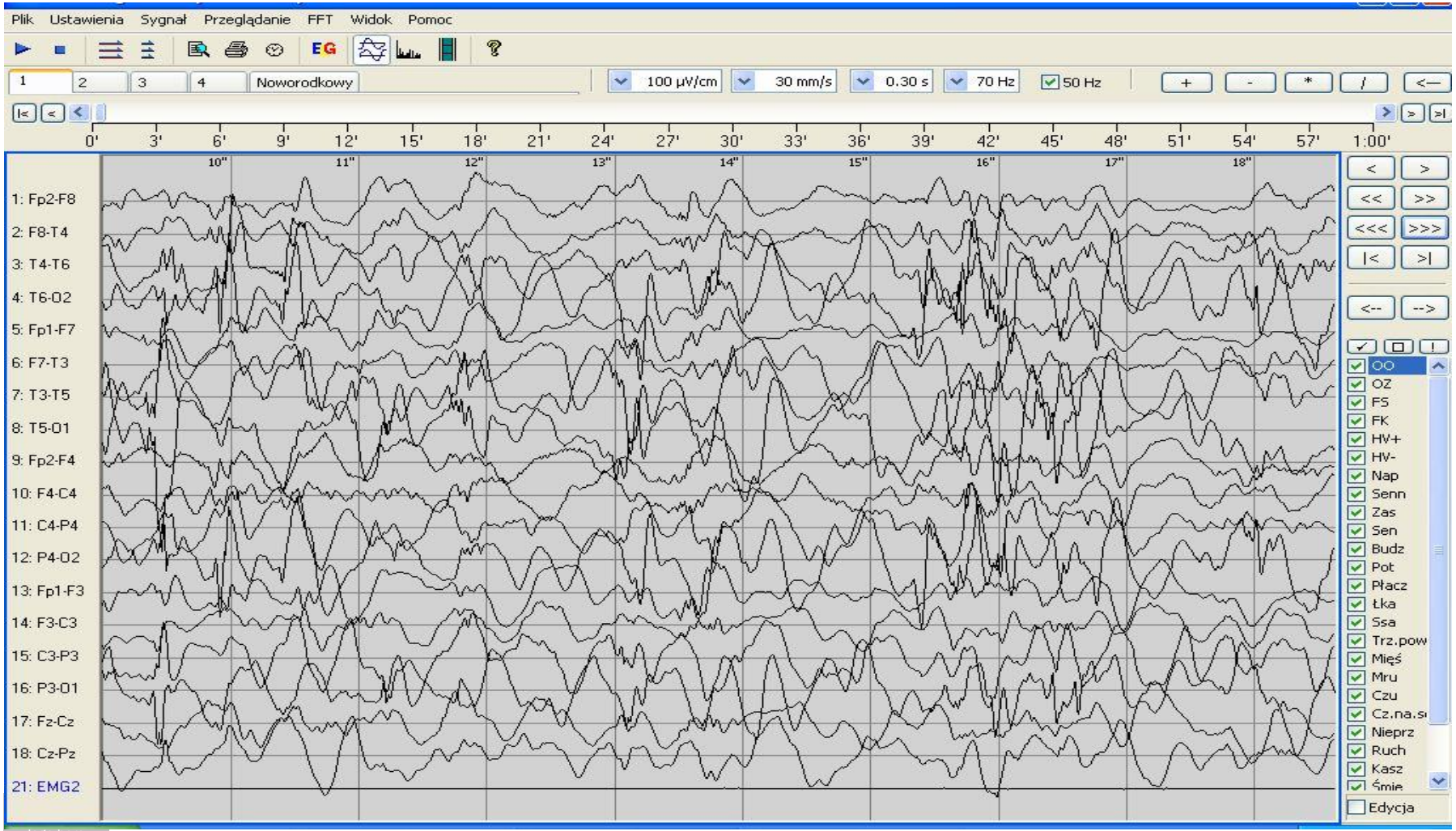
SLEEP EEG 5/12 1 WEEK

ABSENCE OF SLEEP SPINDLES, GROUPS OF SWC AT PARIETOOCIPTAL AND TEMPORAL REGIONS SPREADING TO FRONTAL REGIONS



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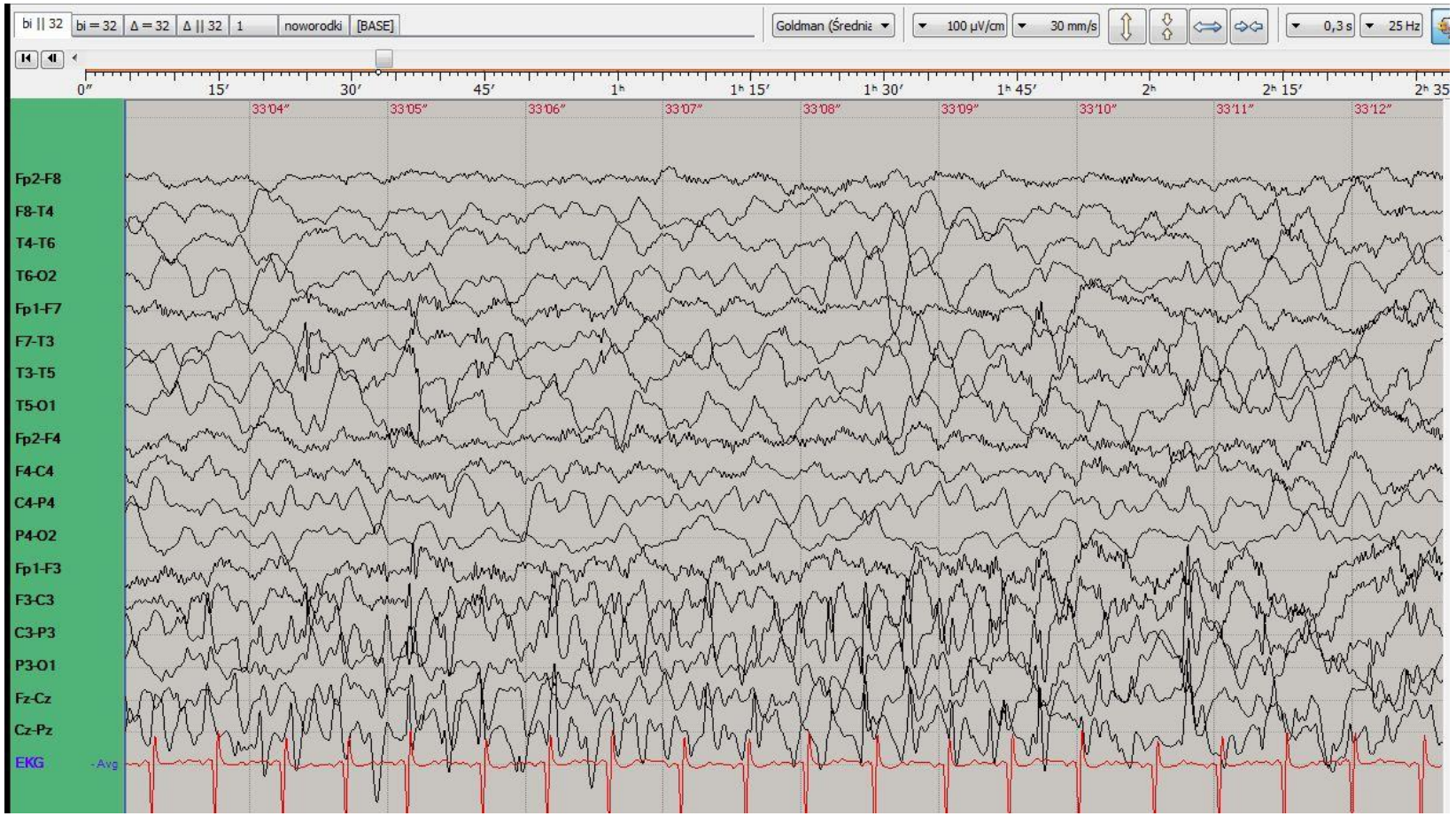
SEIZURE



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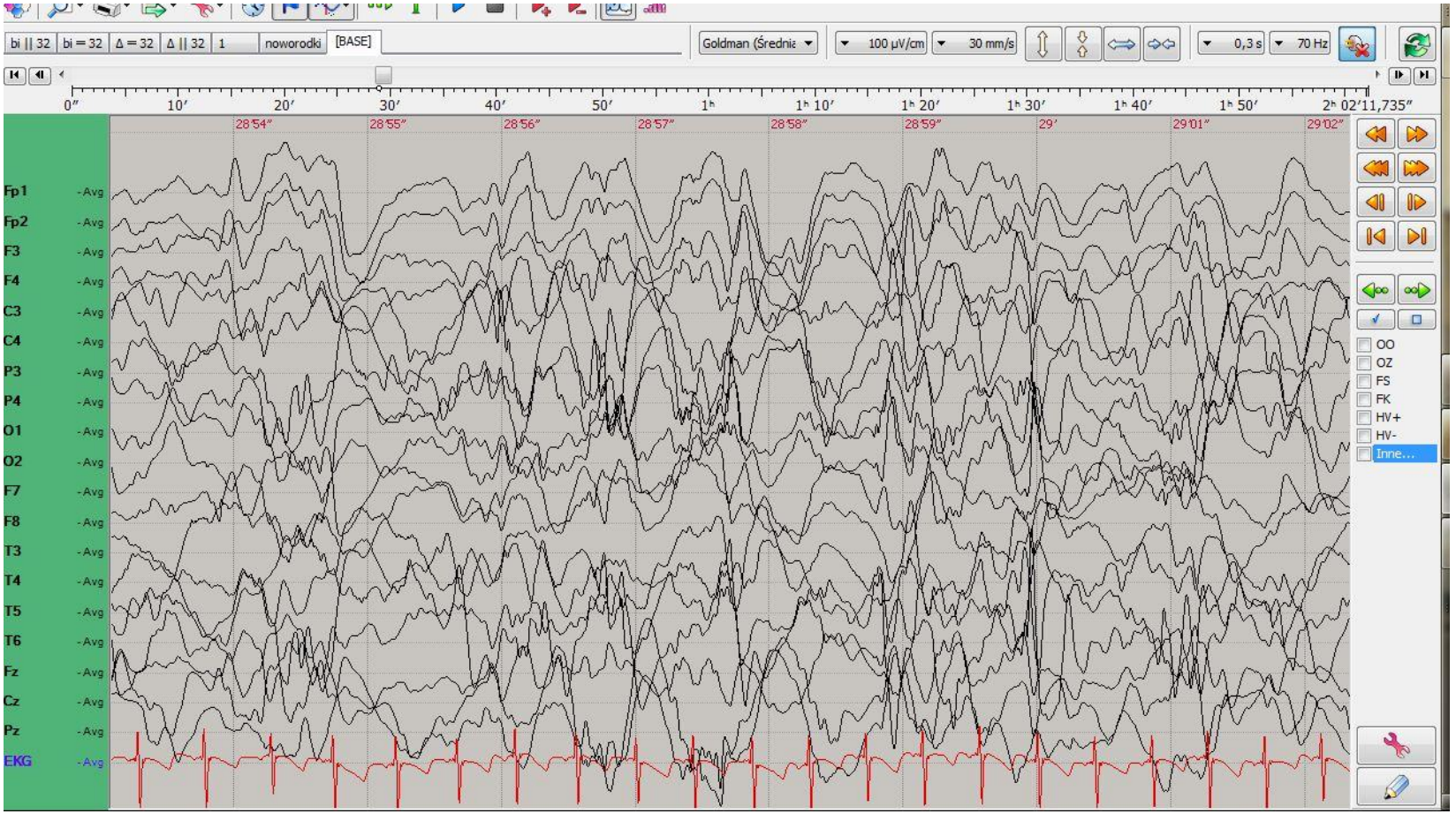
AGE 8/12 - HIPSARRHYTHMIA



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Pediatric Neurology 54 (2016) 29–34

Contents lists available at ScienceDirect

Pediatric Neurology

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Original Article

Clinical Electroencephalographic Biomarker for Impending Epilepsy in Asymptomatic Tuberous Sclerosis Complex Infants

Joyce Y. Wu MD [a], Jurriaan M. Peters MD, PhD [b], Monisha Goyal MD [c], Darcy Krueger MD, PhD [d], Mustafa Sahin MD, PhD [b], Hope Northrup MD [e], Kit Sing Au MD [e], Gary Cutter PhD [c], E. Martina Bebin MD, MPA [c,*]

[a] *Division of Pediatric Neurology, Mattel Children's Hospital at UCLA, Los Angeles, California*
[b] *Department of Neurology, Boston Children's Hospital, Boston, Massachusetts*
[c] *Department of Neurology, University of Alabama Birmingham, Birmingham, Alabama*
[d] *Cincinnati Children's Hospital, Cincinnati, Ohio*
[e] *University of Texas Houston, Houston, Texas*

In conclusion, this study is the first multicenter prospective study to evaluate serial EEGs as a biomarker for subsequent epilepsy in the infant population with TSC. Our study demonstrates the feasibility and importance of close EEG surveillance in infants with TSC, with high PPV of epileptiform discharges for predicting those who subsequently develop epilepsy. This interim analysis highlights the value of early diagnosis of infants with TSC and the value of serial EEG beginning at the time of diagnosis. Importantly, our study suggests there is a critical window of time between emergence of epileptiform discharges and clinical seizure onset, which provides a unique opportunity to investigate potentially disease-modifying antiepileptogenic treatment strategies in this population.

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9. Datta AN, Hahn CD, Sahin M. Clinical presentation and diagnosis of tuberous sclerosis complex in infancy. *J Child Neurol.* 2008;23:268-273.
10. Jozwiak S, Kotulska K, Domanska-Pakiela D, et al. Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex. *Eur J Paediatr Neurol.* 2011;15:424-431.
11. Bombardieri R, Pinci M, Moavero R, Cerminara C, Curatolo P. Early control of seizures improves long-term outcome in children with tuberous sclerosis complex. *Eur J Paediatr Neurol.* 2010;14:146-149.
12. Jozwiak S, Goodman M, Lamm SH. Poor mental development in patients with tuberous sclerosis complex: clinical risk factors. *Arch*

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Scalp EEG spikes predict impending epilepsy in TSC infants: A longitudinal observational study

Epilepsia. 2019 Dec; 60(12): 2428–2436.

- Joyce Y. Wu, 1 Monisha Goyal, 2 Jurriaan M. Peters, 3 Darcy Krueger, 4 Mustafa Sahin, 3 Hope Northrup, 5 Kit S. Au, 5 Sarah O'Kelley, 2 Marian Williams, 6 Deborah A. Pearson, 5 Ellen Hanson, 3 Anna W. Byars, 4 Jessica Krefting, 2 Mark Beasley, 2 Gary Cutter, 2 Nita Limdi, 2 and E. Martina Bebin 2

Objective

- To determine if routine electroencephalography (EEG) in seizure-naive infants with tuberous sclerosis complex (TSC) can predict epilepsy and subsequent neurocognitive outcomes.

Methods

- Forty infants 7 months of age or younger and meeting the genetic or clinical diagnostic criteria for tuberous sclerosis were enrolled. Exclusion criteria included prior history of seizures or treatment with antiseizure medications. At each visit, seizure history and 1-hour awake and asleep video-EEG, standardized across all sites, were obtained until 2 years of age. Developmental assessments (Mullen and Vineland-II) were completed at 6, 12, and 24 months of age.

Results

- Of 40 infants enrolled (mean age of 82.4 days), 32 completed the study. Two were lost to follow-up and six were treated with antiepileptic drugs (AEDs) due to electrographic seizures and/or interictal epileptiform discharges (IEDs) on their EEG studies prior to the onset of clinical seizures. Seventeen of the 32 remaining children developed epilepsy at a mean age of 7.5 months (standard deviation [SD] = 4.4). Generalized/focal slowing, hypsarrhythmia, and generalized/focal attenuation were not predictive for the development of clinical seizures. Presence of IEDs had a 77.3% positive predictive value and absence a 70% negative predictive value for developing seizures by 2 years of age. IEDs preceded clinical seizure onset by 3.6 months (mean). Developmental testing showed significant decline, only in infants with ongoing seizures, but not infants who never developed seizures or whose seizures came under control.

Significance

- IEDs identify impending epilepsy in the majority (77%) of seizure-naive infants with TSC. The use of a 1-hour awake and asleep EEG can be used as a biomarker for ongoing epileptogenesis in most, but not all, infants with TSC. Persistent seizures, but not history of interictal epileptiform activity or history of well-controlled seizures, correlated with low scores on the Vineland and Mullen tests at 2 years of age.

EUROPEAN RECOMMENDATIONS IN EPILEPSY IN TSC (ROME 2012)

-VideoEEG monitoring: every 4 weeks up to the age of 6 mo, every 6 weeks between 7-12 months of age and every 2 months between 13-24 months of age

-treatment should be initiated, in infants and children within 24 months of life if ictal discharges occur, with or without clinical manifestations.

-vigabatrin is the first-line therapy for infantile spasms with TSC

-vigabatrin for focal seizures before the age of 1 year

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Curatolo et al. Eur. J.Paediatr. Neurol. 2012, 16(6): 582-589.

PATIENT 1. KS (35 MONTHS)

Prenatal diagnosis: multiple cardiac tumors;
surgical intervention in the 4th day of life

At birth – several hypomelanotic macules

First EEG (2 mo)- normal

First seizure (6 mo)- multiple focal seizures (>50/day)

EEG (6 mo)- few sharp waves in the left temporal area;

Vigabatrin – poor effect; developed infantile spasms; VGB+VPA – no spasms, focal seizures present, VPA+LTG+TPM – sporadic seizures

Control EEG at 13 mo, 16 mo – epileptic activity

Brain MRI (18 mo) –multiple cortical tubers

Age 2: rare seizures, intellectual disability, autistic

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Topical Review Article

Treatment of Infantile Spasms: Emerging Insights From Clinical and Basic Science Perspectives

Journal of Child Neurology
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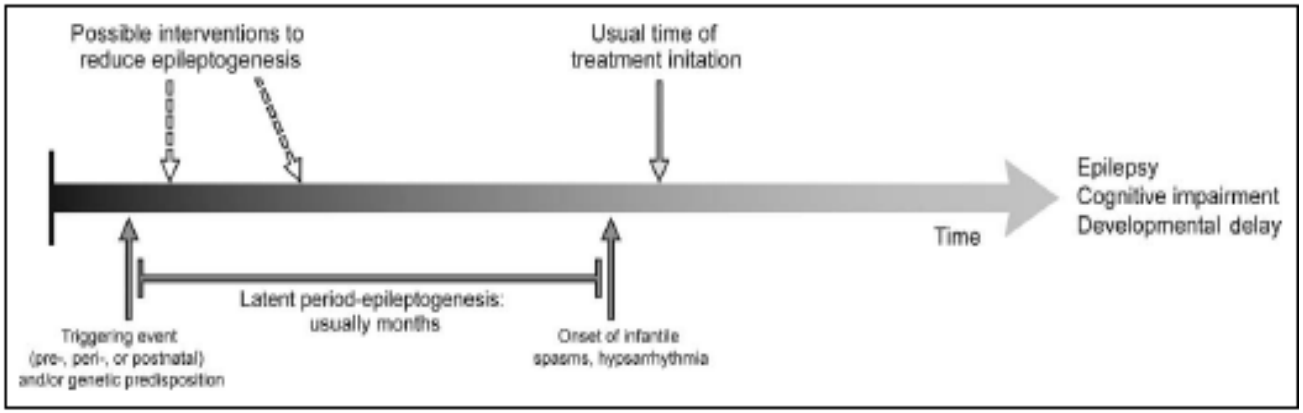
DOI: 10.1177/0883073811413129
http://jcn.sagepub.com
SAGE

Carl E. Stafstrom, MD, PhD[1], Barry G. W. Arnason, MD[2], Tallie Z. Baram, MD, PhD[3], Anna Catania, MD[4], Miguel A. Cortez, MD[5], Tracy A. Glauser, MD[6], Michael R. Pranzatelli, MD[7], Raili Riikonen, MD, PhD[8], Michael A. Rogawski, MD, PhD[9], Shlomo Shinnar, MD, PhD[10], and John W. Swann, PhD[11]



Antiepileptogenic/disease modifying treatment

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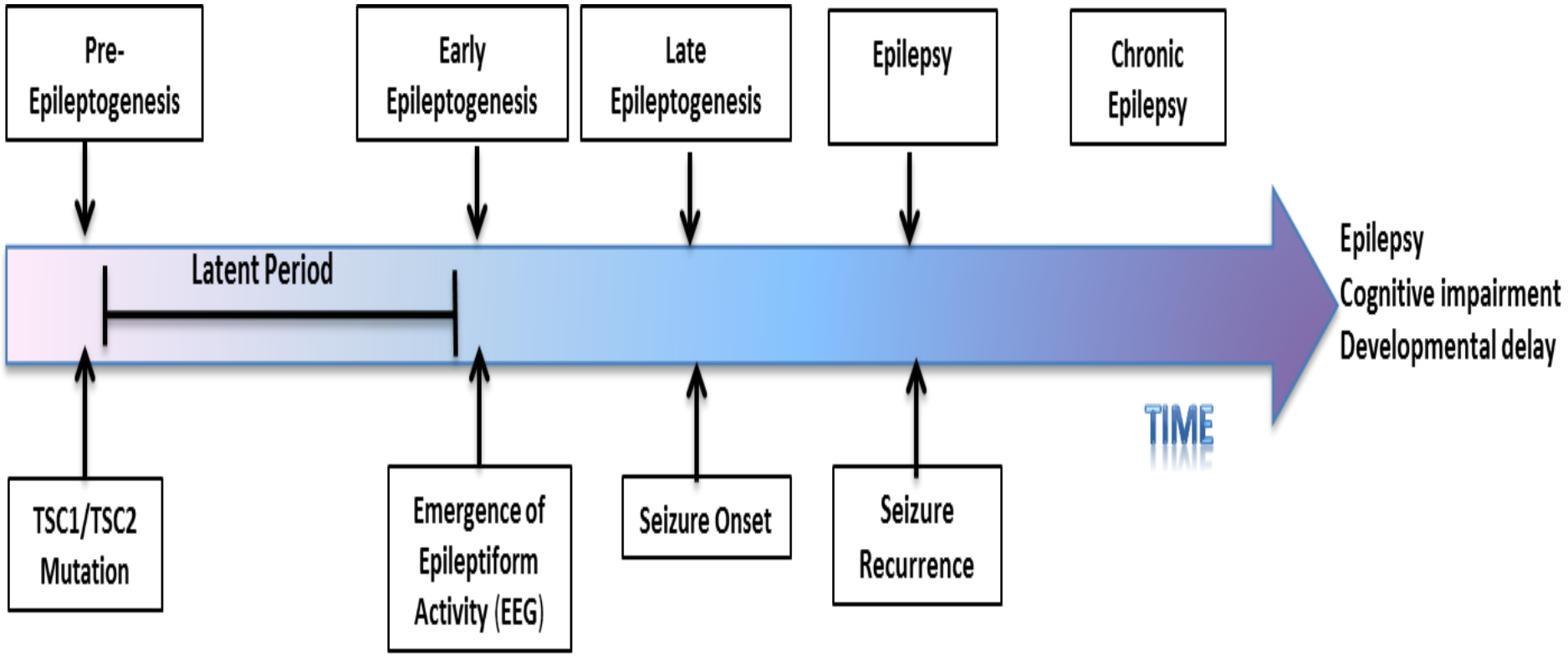
How Do Seizures Develop in TSC?



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POLL # 2

Have you heard about preventive antiepileptic treatment in TSC?

1. Yes
2. No

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POLL # 3

Do you think it is rational to introduce antiepielptic treatment in TSC infants before seizures development?

1. Yes, if EEG shows multifocal discharges
2. Yes, in every case, because the risk of epilepsy is very high
3. No
4. I do not know

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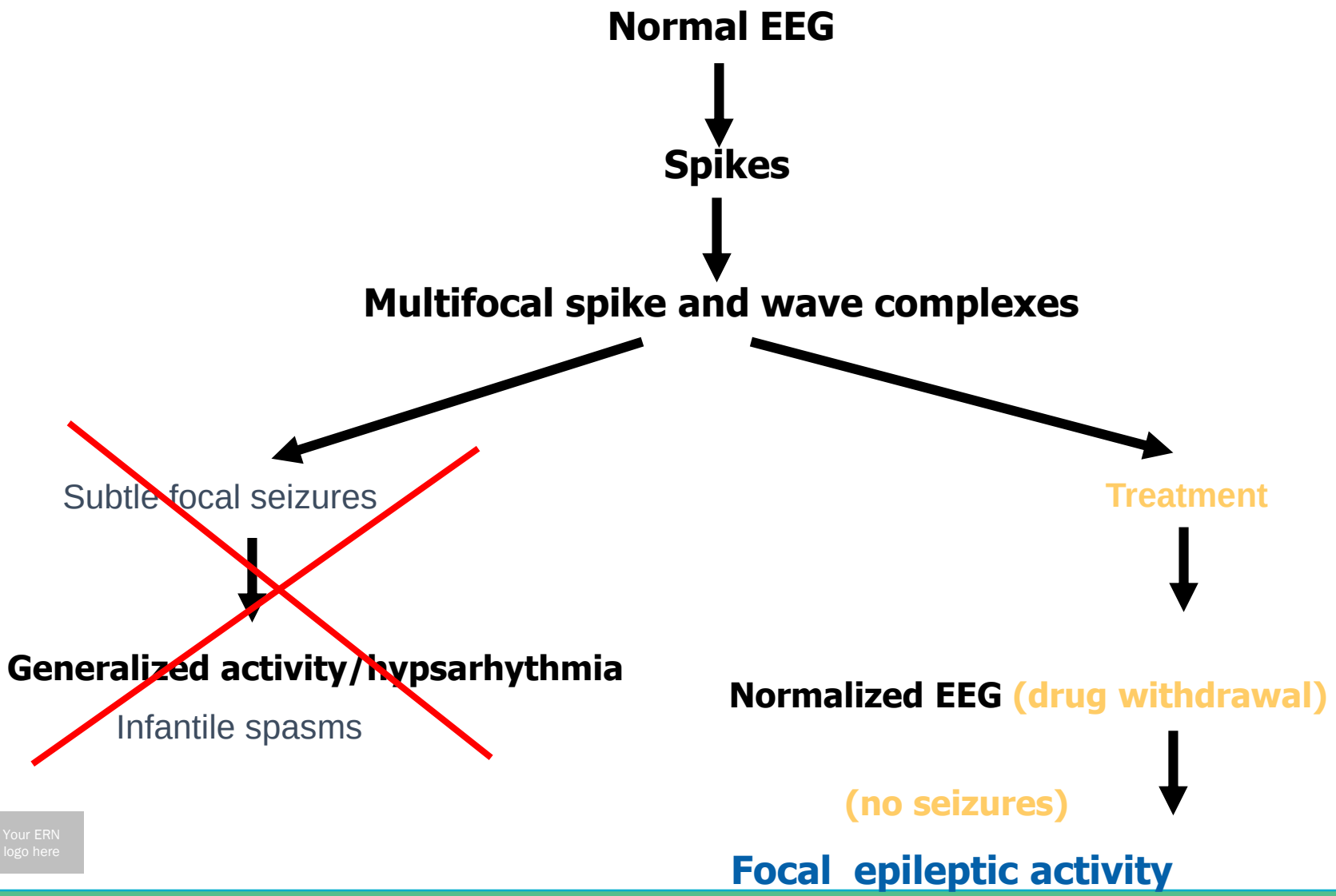
OPEN –LABEL STUDY OF PREVENTIVE ANTIEPILEPTIC TREATMENT (WARSAW, 2011)



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METHODS

Prospective EEG studies (every4-6 weeks) in all patients with early (prenatal or neonatal) diagnosis of TSC until the end of 24 months of life

- no epileptic activity > only follow up

- multifocal epileptic activity or hypsarrhythmia>

treatment with vigabatrin until end of second year of life

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EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 15 (2011) 424–431

ELSEVIER

Official Journal of the European Paediatric Neurology Society

Original article

Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex

Sergiusz Jóźwiak [a,*], Katarzyna Kotulska [a], Dorota Domańska-Pakieła [a], Barbara Łojszczyk [a], Małgorzata Syczewska [b], Dariusz Chmielewski [a], Dorota Dunin-Wąsowicz [a], Tomasz Kmieć [a], Joanna Szymkiewicz-Dangel [c], Maria Kornacka [c], Wanda Kawalec [d], Dariusz Kuczyński [a], Julita Borkowska [a], Katarzyna Tomaszek [a], Elżbieta Jurkiewicz [e], Maria Respondek-Liberska [f]

Table 4 – Comparison of seizure severity and mental outcome in standard and preventative treatment groups.

	Standard care group ($n = 31$)	Preventative group ($n = 14$)	p-Value
Number of patients with epilepsy	22 (71.0%)	6 (42.9%)	0.072
Median age at epilepsy onset (months)	5.0	5.5	0.138
Patients with infantile spasms	11 (35.5%)	2 (14.3%)	0.151
Patients requiring epilepsy polytherapy	17 (54.8%)	3 (21.4%)	0.039*
Patients with drug-resistant epilepsy	13 (41.9%)	1 (7.1%)	0.021*
Seizure-free patients at the age of 24 months	11 (35.4%) 2/22 with epilepsy	13 (92.9%) 5/6 with epilepsy	0.004* 0.0003*
Mean IQ score at the age of 24 months	68.7 Median 74.0 (Range 24–111)	92.3 Median 95.5 (Range 58–132)	$p < 0.05$*
Patients with intellectual disability at the age of 24 months	15 (48.4%)	2 (14.3%)	0.031*
Patients with mild intellectual disability at the age of 24 months	5 (16.1%)	2 (14.3%)	0.876
Patients with moderate, severe, and profound intellectual disability at the age of 24 months	10 (32.4%)	0 (0%)	0.036*

IQ, intellectual quotient.
*Statistically significant values.

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www.EPISTOP.eu

Long-term, prospective study evaluating clinical and molecular biomarkers of epileptogenesis in a genetic model of epilepsy – tuberous sclerosis complex

AIMS:

1. **To prove that early treatment of subclinical seizures significantly reduces drug-resistancy and neurodevelopmental delay in children**
2. **Prospective analysis of clinical and molecular biomarkers (genes and proteins expression) in the course of epileptogenesis**

Completed, results submitted

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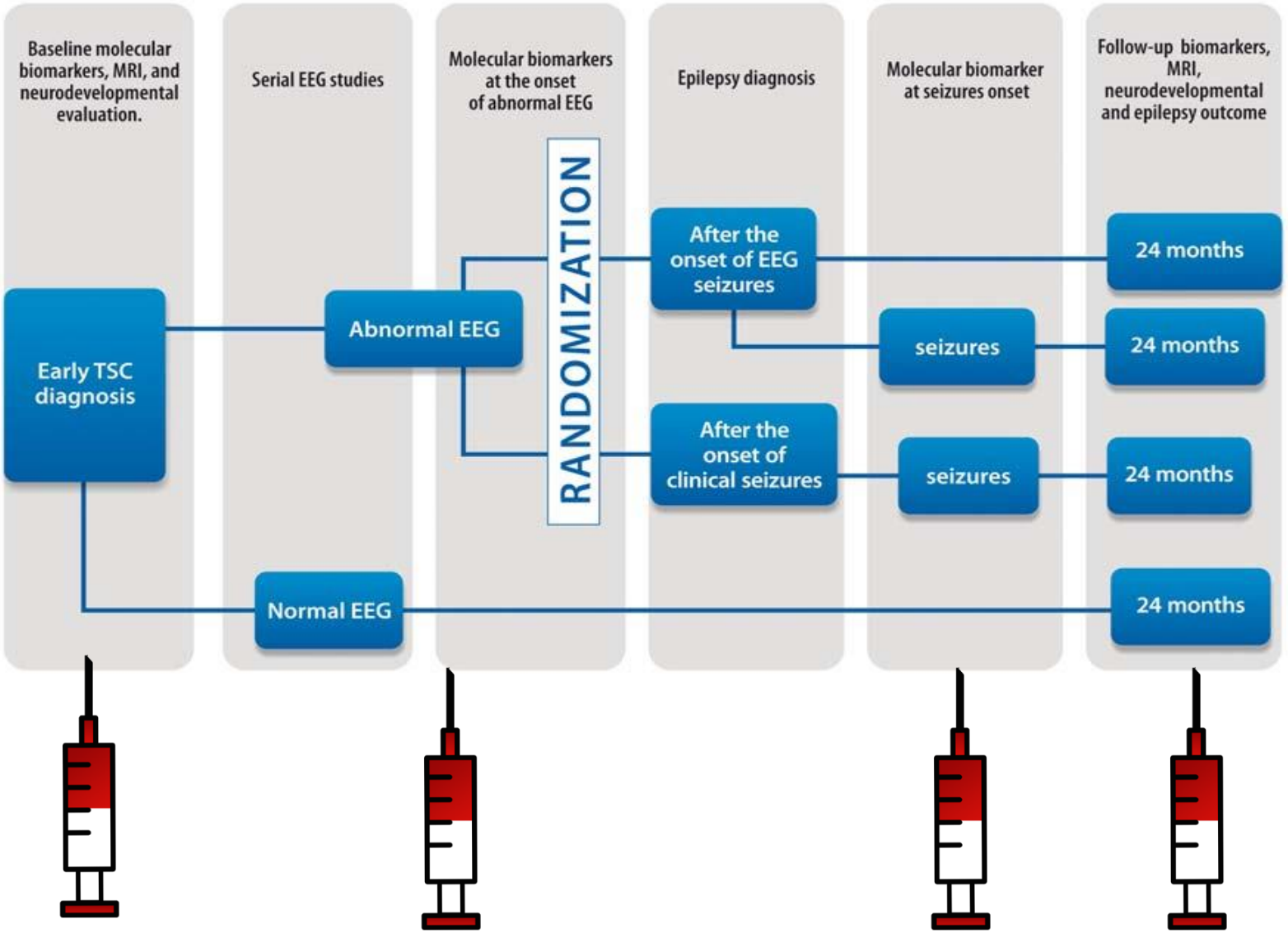
CAPACITIES

European Commission



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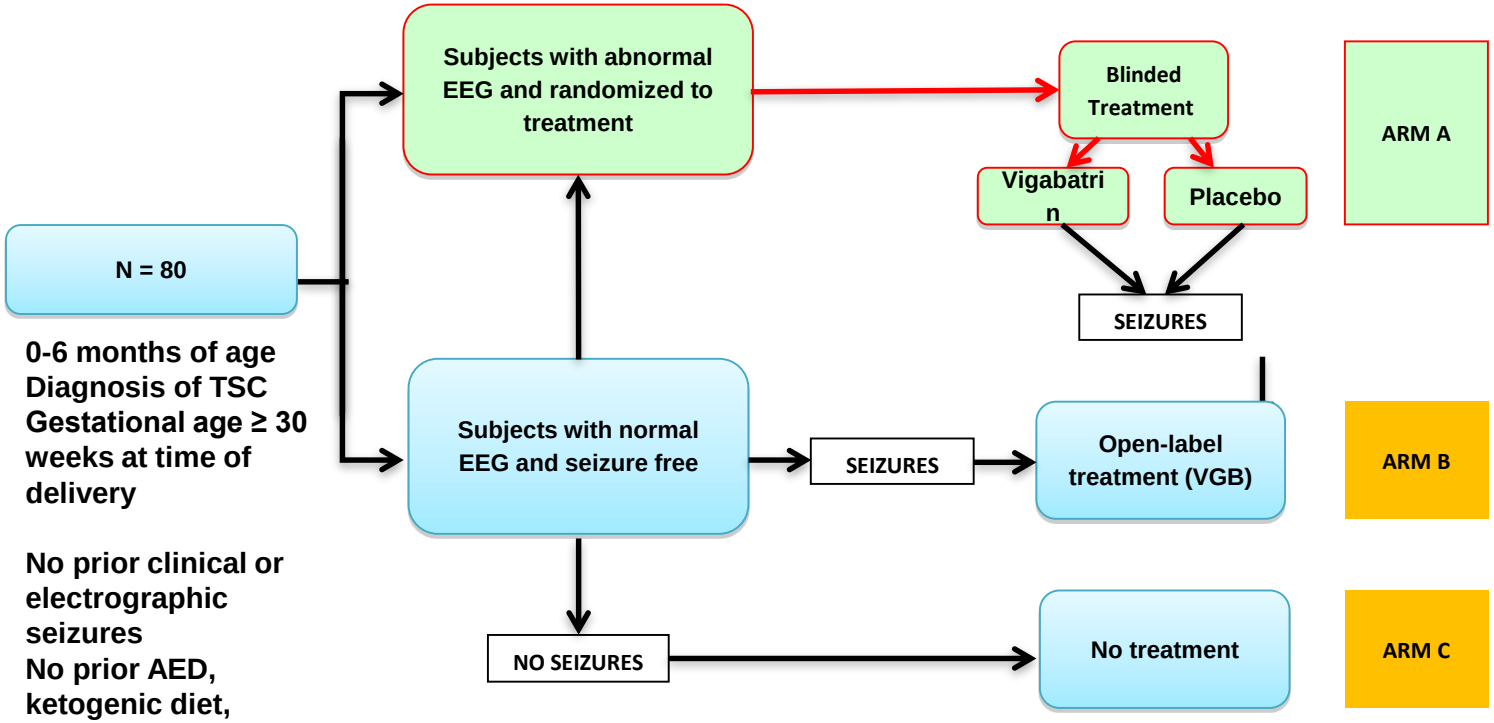
PREVeNT:

PReventing Epilepsy using Vigabatrin in iNfants with TSC

Recruiting



- 0-6 months of age
- Diagnosis of TSC
- Gestational age ≥ 30 weeks at time of delivery

- No prior clinical or electrographic seizures
- No prior AED, ketogenic diet, mTOR inhibitor, or other antiseizure therapeutic agent/treatment
- No prenatal/perinatal medical complications

- EEG every 6 weeks (0-12 months), then every 3 months (13-24 months), then once at 36 months
- Treatment with vigabatrin or placebo until 24 months of age
- Final clinical outcome assessment at 36 months of age

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TSC-CRC Tuberous Sclerosis Complex Clinical Research Consortium

National Institute of Neurological Disorders and Stroke

Tuberous Sclerosis Alliance

Lundbeck

Bcureful

PERF

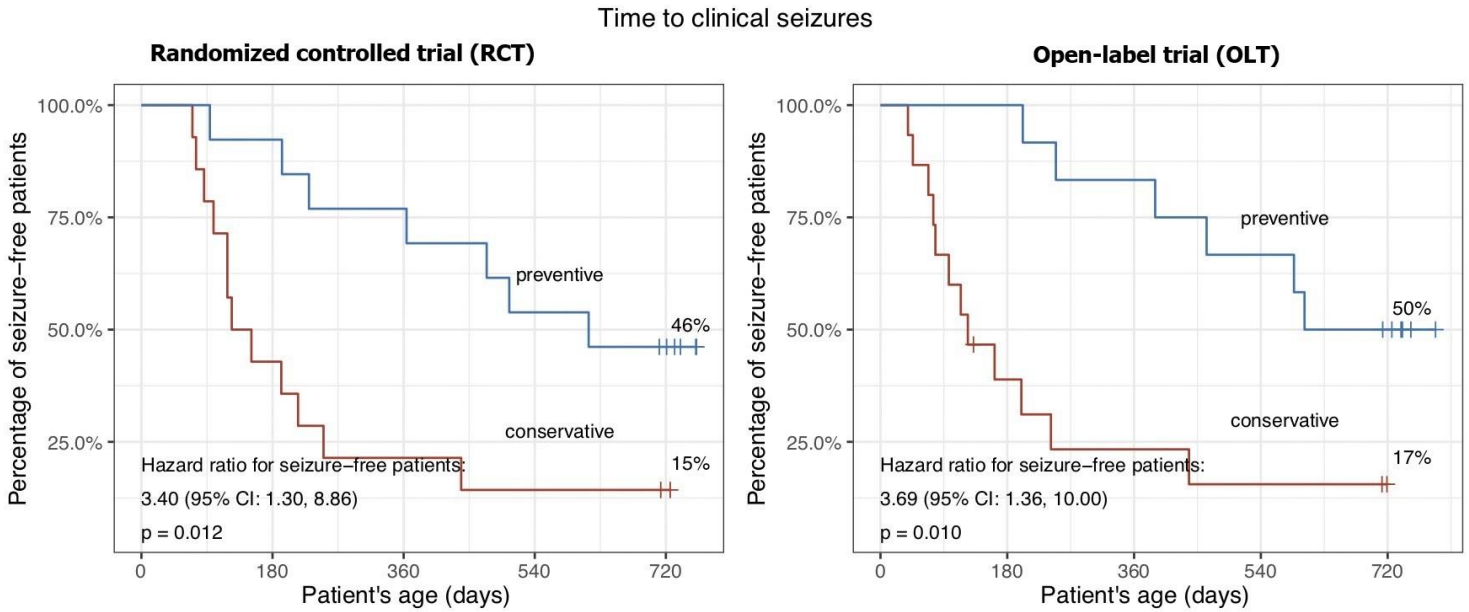
Preventing Epilepsy Using Vigabatrin In Infants With Tuberous Sclerosis Complex

PREVeNT Trial Network

- Phase IIb clinical trial Start Date: December 1, 2016
- Multicenter: 7 sites across the U.S.

1. University of Alabama at Birmingham (UAB)
2. Boston Children's Hospital (BCH)
3. Cincinnati Children's Hospital Medical Center (CCHMC)
4. Mattell Children's Hospital UCLA (UCLA)
5. University of Texas at Houston (UTH)
6. Stanford University
7. Minnesota Epilepsy Group

LESSONS FROM EPISTOP TRIAL



Kotulska et al., submitted

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WARSAW 2011 COHORT – LONG-TERM FOLLOW-UP

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Pediatric Neurology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Pediatric Neurology

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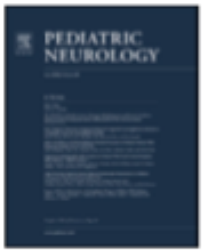

Research Paper

Preventive Antiepileptic Treatment in Tuberous Sclerosis Complex: Long-Term, Prospective Trial

Sergiusz Jozwiak, MD, PhD [a, b, *], Monika Słowińska, MD [a], Julita Borkowska, MD [b], Krzysztof Sadowski, MD, PhD [b], Barbara Łojszczyk, MA [b], Dorota Domańska-Pakieła, MD, PhD [b], Dariusz Chmielewski, MD [b], Magdalena Kaczorowska-Frontczak, MD [b], Jagoda Głowacka, Msc-Eng [b, c], Kamil Sijko, MA [b, c], Katarzyna Kotulska, MD, PhD [b]

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Figure 1. History of epilepsy, antiepileptic treatment, and EEG results in a preventative group.
There are presentedEEG results at 12th and 24th month, 5th and 7th year and last available EEG. N – normal EEG, F- focal discharges, G – generalized discharges

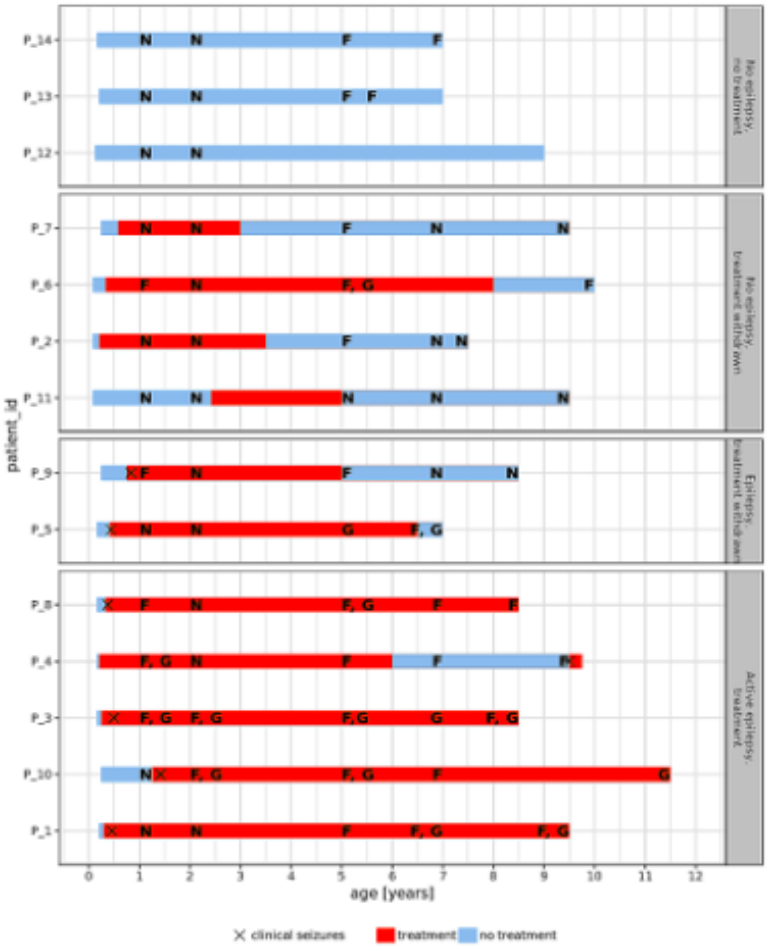

Table 3. Comparison of intellectual outcome and seizure severity at last follow-up visit between preventive and standard group.

	Standard group (n=25)	Preventive group (n=14)	p-value
Mean IQ at last observation (median)	52.8 (46)	81.6 (94)	<0.03*
Mean IQ at last observation in patients treated with AEDs (median)	53.2 (46.5)	80.4 (93)	<0.04*
Patients with intellectual disability	18 (72%)	3 (21%)	0.003*
Patient with moderate, severe, and profound intellectual disability	15 (60%)	3 (21%)	0.02*
Patients with epilepsy	24 (96%)	7 (50%)	0.001*
Patients requiring epilepsy polytherapy	13 (52%)	4 (29%)	0.16
Patients with drug-resistant epilepsy	10 (40%)	4 (29%)	0.5
Mean number of AEDs in use	1.6	0.9	<0.04*
Patients in whom AEDs were withdrawn	4/24 (17%)	6/11 (55%)	<0.03*
Mean (median) age of AEDs withdrawal (years)	7.1 (6.25)	5.2 (5)	-

IQ - intelligence quotient; *statistically significant values

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2020

ARTICLE IN PRESS

EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY XXX (2018) 1–10

ELSEVIER

Official Journal of the European Paediatric Neurology Society

Original article

Early predictors of clinical and mental outcome in tuberous sclerosis complex: A prospective study

Barbora Benova [a,b], Borivoj Petrak [a], Martin Kyncl [b,c], Petr Jezdik [a,e], Alice Maulisova [d,f], Alena Jahodova [a,b], Vladimir Komarek [a,b], Pavel Krsek [a,b,]*

CZECH Republic: vEEG surveillance and tx subclinical seizures

Pediatric Neurology 72 (2017) 76–80

Contents lists available at ScienceDirect

Pediatric Neurology

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

Clinical Observations

The Utility of Surveillance Electroencephalography to Guide Early Antiepileptic Drug Therapy in Infants With Tuberous Sclerosis Complex

Robyn Whitney MD [a,1], Saber Jan MBBS, MPH [a,b,1], Maria Zak MN, NP [a], Bláthnaid McCoy MB BCh BAO [a,c,*]

[a] Division of Pediatric Neurology, Department of Pediatrics, The Hospital for Sick Children, Toronto, Ontario, Canada
[b] Department of Pediatrics, Taibah University, Medina, Saudi Arabia
[c] Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada

ABSTRACT

BACKGROUND: Seizures are a common early presentation in infants with tuberous sclerosis complex (TSC) and can be preceded by electrographic changes on electroencephalography (EEG) before clinical seizure onset. A limited number of studies have addressed the initial EEG findings in TSC and the outcome of early treatment with antiepileptic medication prior to clinical seizure onset. **METHODS:** We describe two infants with tuberous sclerosis complex whose surveillance EEG showed focal seizures that were not previously recognized by caregivers. We review previously reported patients with TSC with early EEG findings. Our patients were started on vigabatrin after the onset of focal seizures with the aim of preventing seizure recurrence, halting the possible progression to infantile spasms or focal seizures, and preventing neurodevelopmental decline. **RESULTS:** Both patients remain seizure free and have reached appropriate developmental milestones. **CONCLUSIONS:** We recommend early serial EEG monitoring once a diagnosis of TSC is suspected or confirmed in infants. Additional prospective studies are needed to assess the long-term outcome of early antiepileptic drug initiation as soon as electrographic seizure activity is detected.

Keywords: electroencephalography (EEG), tuberous sclerosis complex (TSC), infantile spasms, epilepsy, surveillance, vigabatrin
Pediatr Neurol 2017; 72: 76-80

Canada: vEEG surveillance

Pediatric Neurology 76 (2017) 20–26

Contents lists available at ScienceDirect

Pediatric Neurology

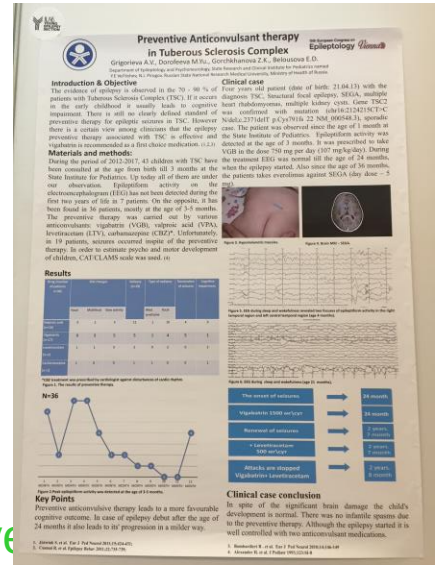
journal homepage: www.elsevier.com/locate/pnu

Original Article

Early Detection of Tuberous Sclerosis Complex: An Opportunity for Improved Neurodevelopmental Outcome

Clara W.T. Chung MBBS [a], John A. Lawson BMed, PhD [b,c], Vanessa Sarkozy MBChB [c,d], Kate Riney MB BCh BAO, PhD [c], Orli Wargon MBBS [f], Antonia W. Shand MBChB [c,g,h], Stephen Cooper MB ChB [i], Harrison King MBBS [a], Sean E. Kennedy MBBS, PhD [c,j], David Mowat MBBS [a,c,*]

Australia: vEEG surveillance and tx subclinical seizures



Preventive Anticonvulsant therapy in Tuberous Sclerosis Complex

Grigorieva A.V., Dorofeeva M.Yu., Grechkanieva Z.K., Belouseva E.D.

Introduction & Objective

Clinical case

Materials and methods:

Results

Key Points

Clinical case conclusion

Russia: Preventative treatment , when paroxysmal EEG (Poster at 13th European Epilepsy Conference 2018)

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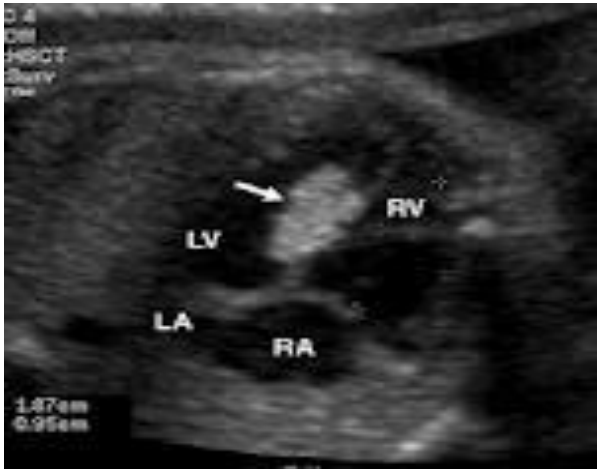
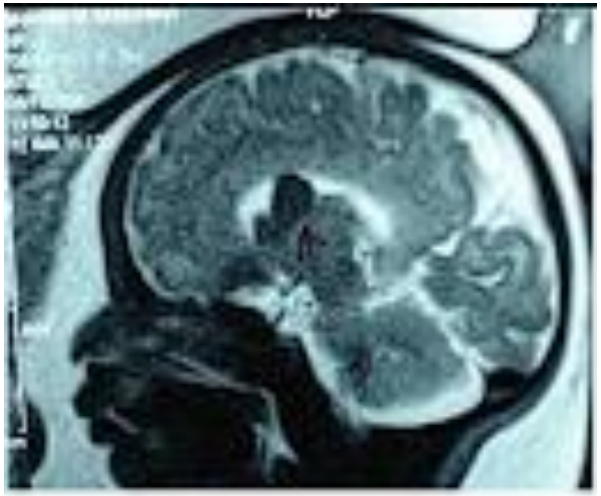
Feasibility for Prevention Trials

- Ability to Dx TSC prenatally
  - Heart-Cardiac Rhabdomyoma-47% of infants also have cardiac dysrhythmias
    - 80% fetuses and infants with TSC have cardiac rhabdomyomas
    - Brain-cortical tubers, subependymal nodules
- Early Diagnosis and referral to neurologist
- Education of parents and care givers on seizure recognition
- EEG at the time of TSC diagnosis





- Exclusion: neonatal epilepsy

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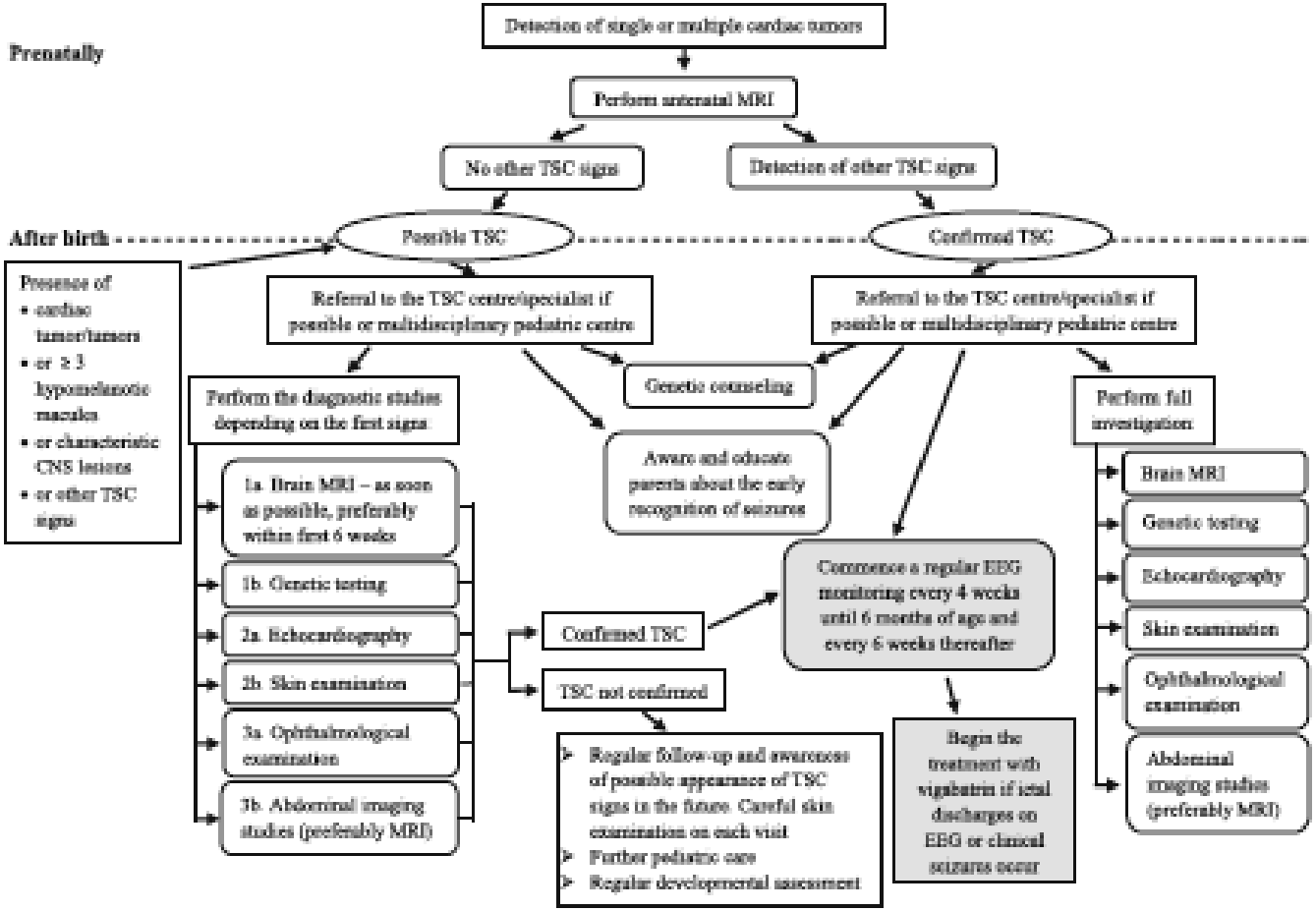
Słowińska et al. Orphanet Journal of Rare Diseases (2018) 13:25
DOI 10.1186/s13023-018-0764-z

Orphanet Journal of Rare Diseases

RESEARCH Open Access

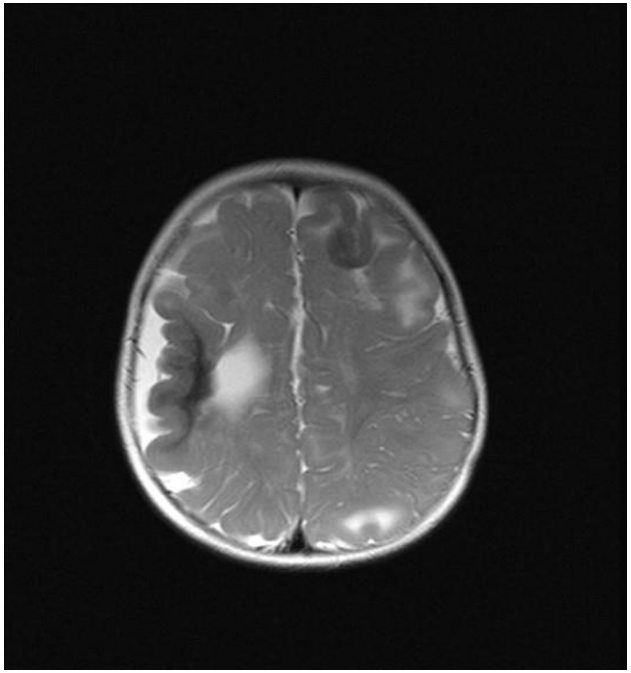
Early diagnosis of tuberous sclerosis complex: a race against time. How to make the diagnosis before seizures?

Monika Słowińska[1,2*†], Sergiusz Jóźwiak[1,2†], Angela Peron[3,4,5], Julita Borkowska[1], Dariusz Chmielewski[1], Krzysztof Sadowski[1], Elżbieta Jurkiewicz[6], Aglaia Vignoli[3,4], Francesca La Briola[3], Maria Paola Canevini[3,4] and Katarzyna Kotulska-Jóźwiak[1]



Neonatal presentation of epilepsy in TSC

- 21/421 (5%) of TSC patients developed seizures in the first month of life.
- 11 (52%) displayed large FCD on brain MRI
- Early epilepsy is associated with high risk of drug-resistance of seizures and poor neurodevelopmental outcome
- Early surgery might be beneficial.



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Eur J Paediatr Neurol. 2014 Nov;18(6):714-21

Poll # 4

- Whould you recommend epilepsy surgery in TSC patients?
- 1. Yes, but only if focal seizures originate from one focus
- 2. Yes, if no infantile spasms
- 3. Yes, for both focal seizures and infantile spasms
- 4. No.

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SURGERY IN TSC-ASSOCIATED EPILEPSY

- Song et al., 2018: among 1110 (83.6%) TSC patients with with epilepsy, 25.3% underwent surgery. 35.1% of them had subsequent surgery.

- Chinese experience in resective surgery (Liu et al., 2019): 364 patients, age range: 0.5–47. The percentage of postoperative seizure freedom was 71% (258/364) at 1-year, 60% (118/ 196) at 4-year, and 51% (36/71) at 10-year follow-up. **:**
- Arya et al., 2015: 37 patients with TSC underwent resective surgery; mean follow-up of 5.68 ± 3.67 years. 56.8% achieved complete seizure freedom (ILAE Class 1) and 86.5% had ILAE Class 4 outcomes or better.

- Early surgery (Fohlen, 2018): 15 TSC patients aged<<6 yrs, who underwent epilepsy surgery. 13 patients (86%) had a dramatic improvement of epilepsy after surgery (Engel 1 and 2) including 9 patients (60%) seizure free (Engel 1 A). In the group of 9 patients younger than 20 months at the time of surgery who presented with catastrophic epilepsies, 77% are Engel 1 A and the other 23% Engel 2. In this subpopulation, no one developed autism and four (44%) regained normal development.

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EPILEPTOGENICITY IN TUBEROUS SCLEROSIS COMPLEX: A STEREOELECTROENCEPHALOGRAPHIC STUDY.

- Epilepsia. 2020 Jan;61(1):81-95. doi: 10.1111/epi.16410. Epub 2019 Dec 20.

- Neal A[1,2,3], Ostrowsky-Coste K[2,4], Jung J[1,2], Lagarde S[5], Maillard L[6], Kahane P[7], Touraine R[8], Catenoix H[1,2], Montavont A[1,2], Isnard J[1,2], Arzimanoglou A[1,4], Bartolomei F[5], Guenot M[1,9], Rheims S[1,2,10].

- **Abstract**
- **OBJECTIVE:**
- In tuberous sclerosis complex (TSC)-associated drug-resistant epilepsy, the optimal invasive electroencephalographic (EEG) and operative approach remains unclear. We examined the role of stereo-EEG in TSC and used stereo-EEG data to investigate tuber and surrounding cortex epileptogenicity.
- **METHODS:**
- We analyzed 18 patients with TSC who underwent stereo-EEG (seven adults). One hundred ten seizures were analyzed with the epileptogenicity index (EI). In 13 patients with adequate tuber sampling, five anatomical regions of interest (ROIs) were defined: dominant tuber (tuber with highest median EI), perituber cortex, secondary tuber (tuber with second highest median EI), nearby cortex (normal-appearing cortex in the same lobe as dominant tuber), and distant cortex (in other lobes). At the seizure level, epileptogenicity of ROIs was examined by comparing the highest EI recorded within each anatomical region. At the patient level, epileptogenic zone (EZ) organization was separated into focal tuber (EZ confined to dominant tuber) and complex (all other patterns).
- **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.
- **SIGNIFICANCE:**
- Tubers with focal EZ organization have a striking similarity to type II focal cortical dysplasia. The presence of distinct EZ organizations has significant implications for EZ hypothesis generation, invasive EEG approach, and resection strategy.

Surgical treatment of epilepsy in TSC – other options

- Corpus callosotomy: 3/7 patients free of spasms after surgery (Okanishi et al. 2019);
- VNS: 9/10 patients achieved at least 50% reduction of seziures, and 5/10 – at least 90% reduction of seizures (Parain, 2001); 3 out of 4 were seizures free and 2 of them stopped AEDs (Grioni, 2019)

Presurgical evaluation is challenging, but crucial.
Infantile spasms do not exclude surgery

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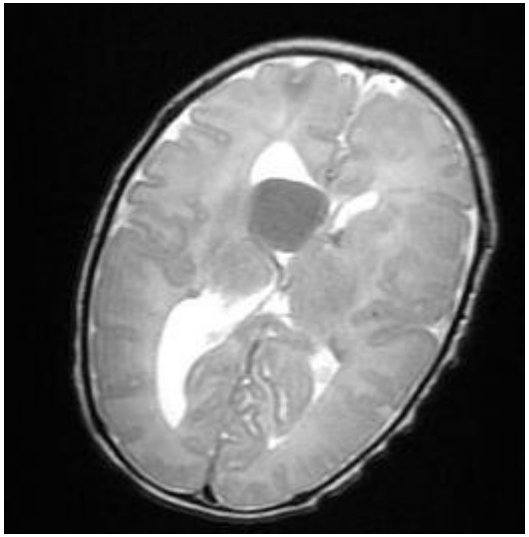
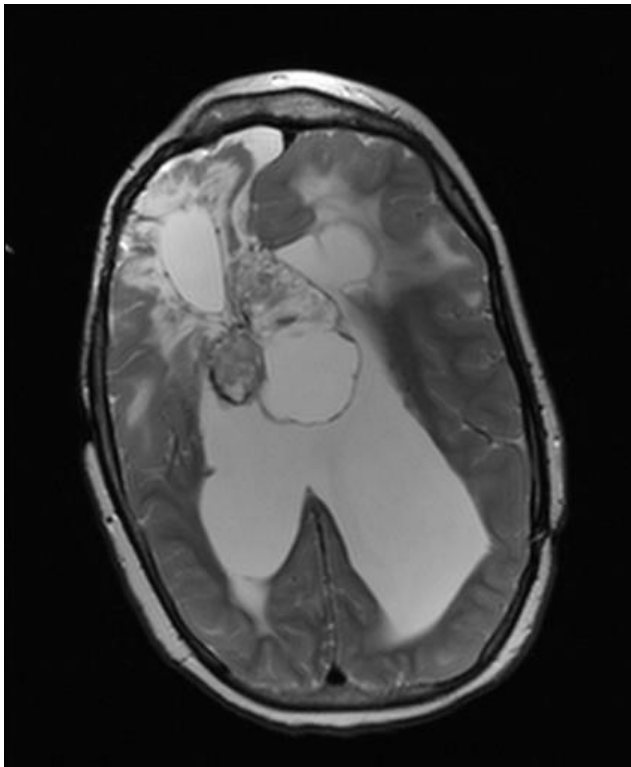
CASE STORY

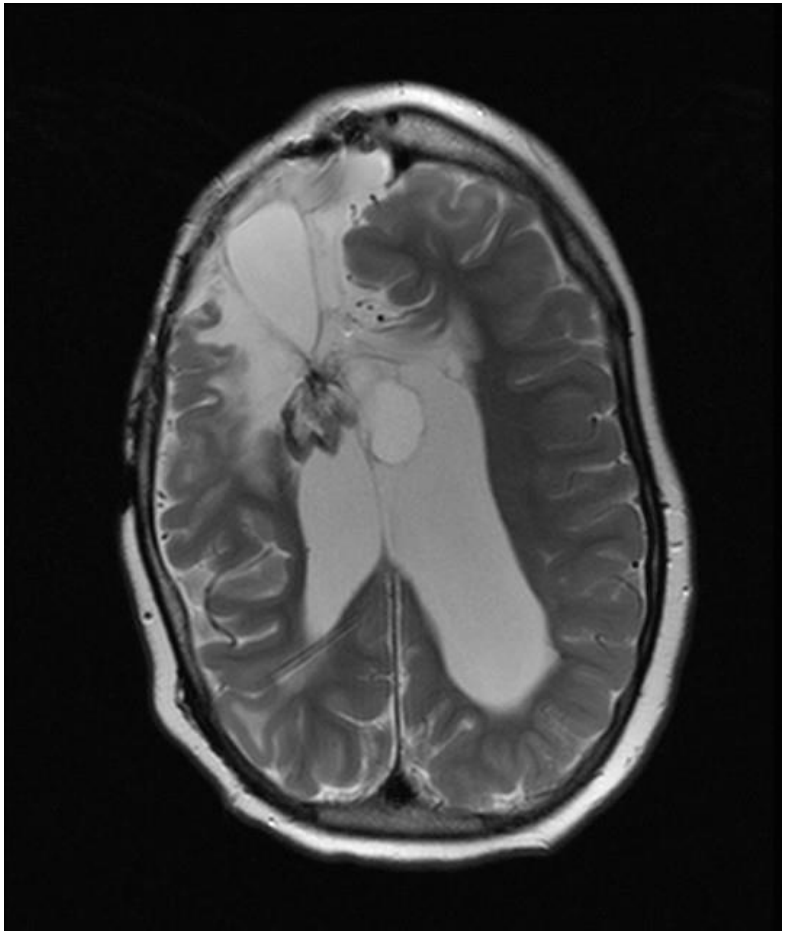
- Boy, born with SEGA and hydrocephalus.
- TSC diagnosis certain: SEGA, cortical tubers, subependymal nodules.
- Subtotal surgery at 1 mo.
- several subsequent surgeries
- cardac arrest at the age of 9 yrs.
- Drug-resistant epilepsy, external drainage, bed-riddden
- tumor size : 5.4 cm





Case story – cont'd

- Rapamycin derivate, everolimus, was introduced
- After 2 months, the tumor markedly decreased in diameter, and CSF protein was low enough (0.18g/dL) to allow implantation of a peritoneal shunt.
- Seizure free, alert, able to respond to simple commands.



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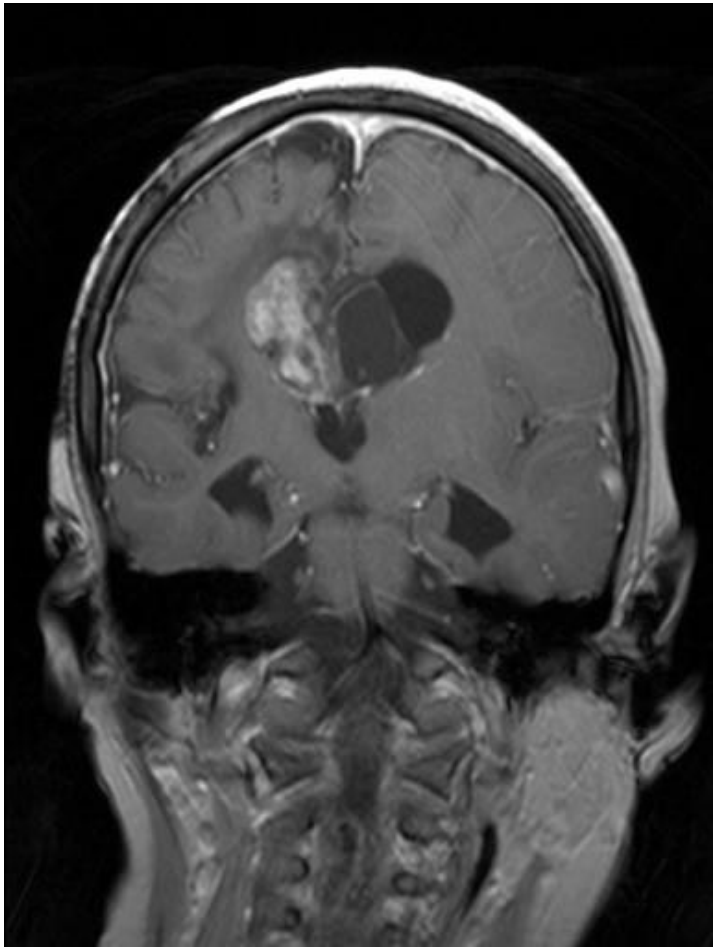
Case story – cont'd

- After 6 months, further decrease in tumor diameter (3.8cm) was seen on MRI.
- Seizure free, started to walk and to speak.
- After 5 yrs: tumor stable, seizure free, back at school



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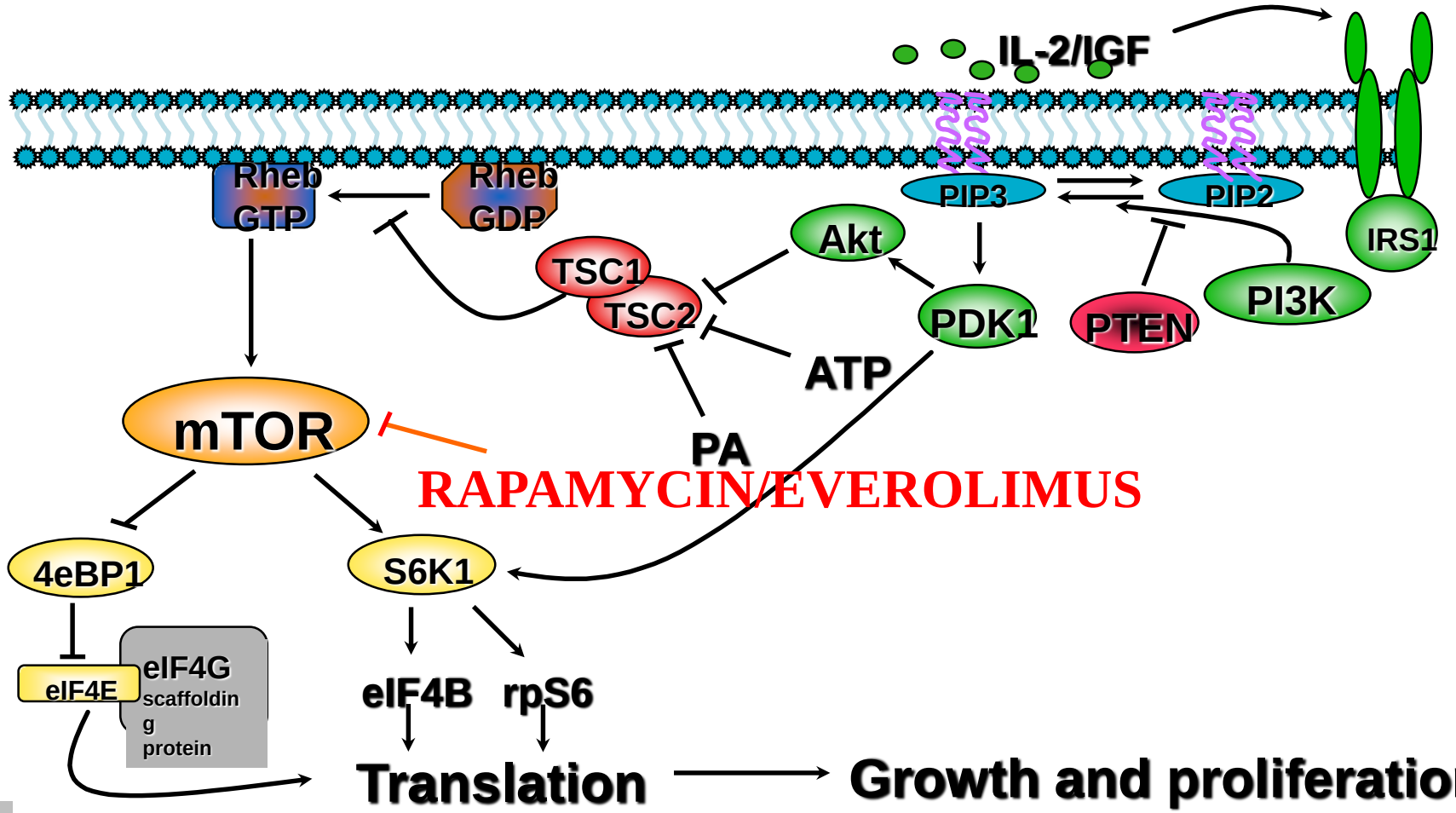
RAPAMYCIN/EVEROLIMUS „REPLACES" TSC1/TSC2



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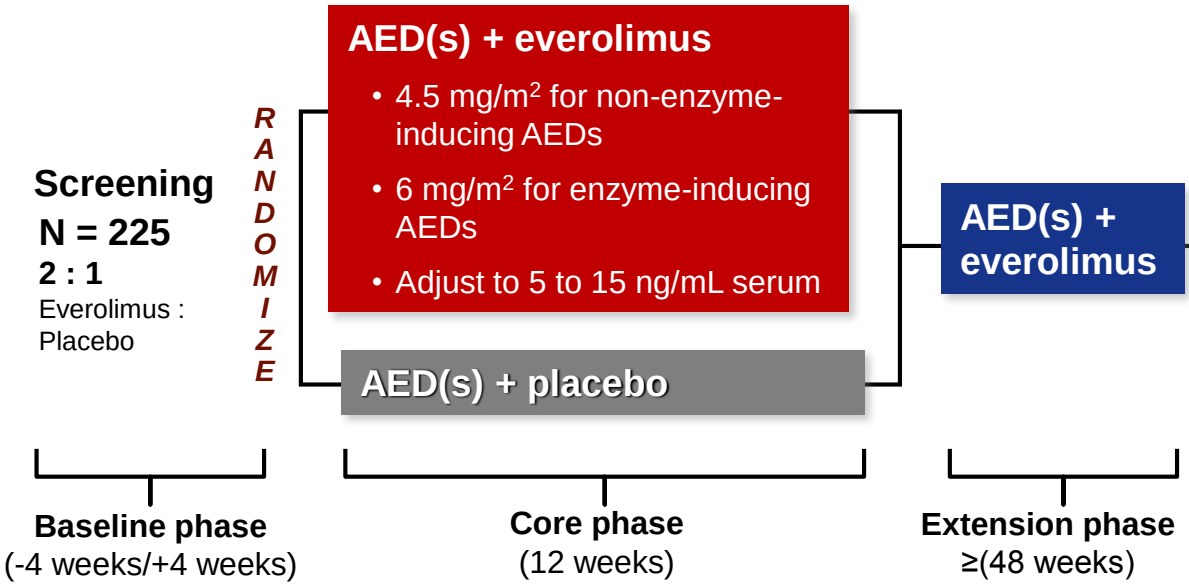
Phase 3 EXIST-3 Trial of Everolimus for Epilepsy with TSC

- Male or female of any age diagnosed with TSC and uncontrolled focal-onset epilepsy after 1-3 AEDs
  - Stable dose of AEDs throughout trial is required



Primary End Point:

•≥ 50% reduction in seizures during core phase

Secondary End Points:

•% reduction in seizures during core phase

•Time to treatment discontinuation during core phase

•Seizure-free rate during core phase

•Changes in tuber volume and white matter (fMRI)

•QoL, cognitive function and behavior change

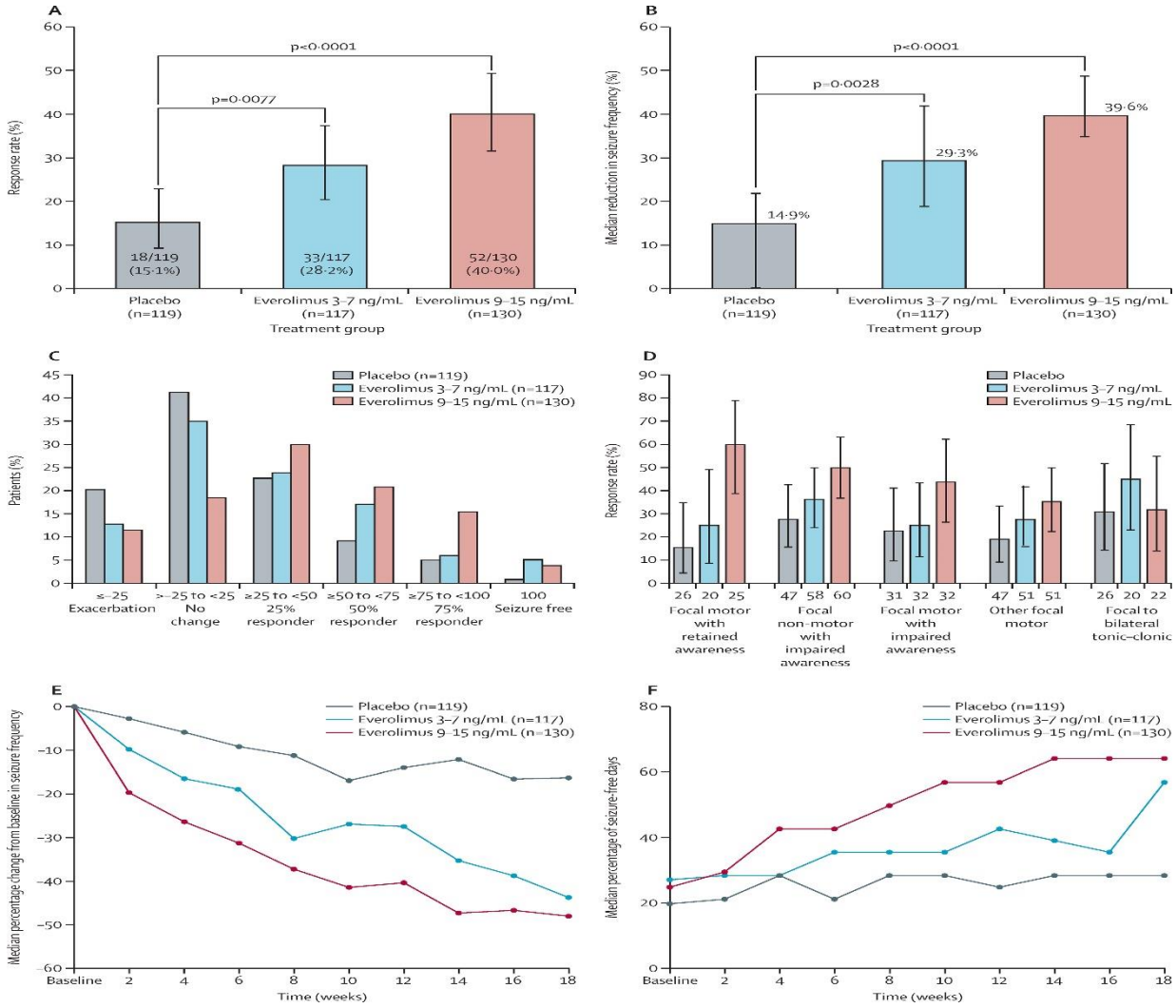
•Skin lesions response

•Safety

•PK of everolimus and AED(s)

AED=antiepileptic drug; fMRI=functional magnetic resonance Imaging; QoL=quality of life.

logo here


A
Response rate (%)
p<0·0001
p=0·0077
18/119 (15·1%)
33/117 (28·2%)
52/130 (40·0%)
Placebo (n=119)
Everolimus 3–7 ng/mL (n=117)
Everolimus 9–15 ng/mL (n=130)
Treatment group
B
Median reduction in seizure frequency (%)
p<0·0001
p=0·0028
14·9%
29·3%
39·6%
Placebo (n=119)
Everolimus 3–7 ng/mL (n=117)
Everolimus 9–15 ng/mL (n=130)
Treatment group
C
Patients (%)
Placebo (n=119)
Everolimus 3–7 ng/mL (n=117)
Everolimus 9–15 ng/mL (n=130)
≤–25 Exacerbation
>–25 to <25 No change
≥25 to <50 25% responder
≥50 to <75 50% responder
≥75 to <100 75% responder
100 Seizure free
D
Response rate (%)
Placebo
Everolimus 3–7 ng/mL
Everolimus 9–15 ng/mL
26 20 25 Focal motor with retained awareness
47 58 60 Focal non-motor with impaired awareness
31 32 32 Focal motor with impaired awareness
47 51 51 Other focal motor
26 20 22 Focal to bilateral tonic–clonic
E
Median percentage change from baseline in seizure frequency
Placebo (n=119)
Everolimus 3–7 ng/mL (n=117)
Everolimus 9–15 ng/mL (n=130)
Baseline
Time (weeks)
F
Median percentage of seizure-free days
Placebo (n=119)
Everolimus 3–7 ng/mL (n=117)
Everolimus 9–15 ng/mL (n=130)
Baseline
Time (weeks)

Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study

Dr Prof Jacqueline A French, MD, John A Lawson, MD, Prof Zuhal Yapici, MD, Hiroko Ikeda, MD, Tilman Polster, MD, Rima Nabbout, MD, Prof Paolo Curatolo, MD, Prof Petrus J de Vries, PhD, Dennis J Dlugos, MD, Noah Berkowitz, MD, Maurizio Voi, MD, Severine Peyrard, MS, Diana Pelov, MS, Prof David N Franz, MD

The Lancet
Volume 388, Issue 10056, Pages 2153-2163 (October 2016)
DOI: 10.1016/S0140-6736(16)31419-2

Everolimus was approved by EMA as an add-on treatment in patients from 2 years of age with seizures (fits) related to tuberous sclerosis that have not responded to other treatments. Votubia is used for partial onset seizures (seizures that start in one part of the brain), which may or may not spread to affect the whole brain (secondary generalisation).

Terms and Conditions

EPILEPSY AND EVEROLIMUS TREATMENT IN YOUNG CHILDREN

- At the Children's Memorial Health Institute, Warsaw, Poland, 8 children under the age of 3 participated in EXIST-1 study.
- The mean follow-up is 24 months (22-27 months) and all children are still on treatment.
- 3/8 children presented with active epilepsy, all drug-resistant
- In 1 child with drug-resistant epilepsy, everolimus treatment resulted in permanent cessation of seizures.
- No new seizures were observed

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KETOGENIC DIET IN TSC-ASSOCIATED EPILEPSY

- Park et al., 2017: 12 children with intractable epilepsy associated with TSC were treated with KD. The mean age at the time of KD initiation was 73.1 ± 38.0 months. Nine patients (75.0%) had a history of infantile spasms. At 3 months after KD initiation, 10 patients (83.3%) had > 50% seizure reduction. Moreover, 7 patients (58.3%) exhibited qualitative improvements in cognition and behavior after KD initiation, as reported by caregivers/parents. The mean duration of dietary therapy was 14.8 ± 12.8 months. Half of the patients in this study eventually underwent epilepsy surgery due to persistent seizures or seizure relapse.
- Kosoff et al., 2005: Twelve children, ages 8 months to 18 years, treated with KD. Eleven (92%) children had a >50% reduction in their seizures at 6 months on the diet, and 8 (67%) had a >90% response. Five children had at least a 5-month seizure-free response. Diet duration ranged from 2 months to 5 years (mean, 2 years).

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CANNABIDIOL IN TSC-ASSOCIATED EPILEPSY

Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex

Evan J. Hess Kirsten A. Moody Alexandra L. Geffrey Sarah F. Pollack Lauren A. Skirvin Patricia L. Bruno Jan L. Paolini Elizabeth A. Thiele

- Epilepsia, 2016

Objective

- Tuberous sclerosis complex (TSC) is an autosomal-dominant genetic disorder with highly variable expression. The most common neurologic manifestation of TSC is epilepsy, which affects approximately 85% of patients, 63% of whom develop treatment-resistant epilepsy. Herein, we evaluate the efficacy, safety, and tolerability of cannabidiol (CBD), a nonpsychoactive compound derived from the marijuana plant, as an adjunct to current antiepileptic drugs in patients with refractory seizures in the setting of TSC.

Methods

- Eighteen of the 56 patients who have enrolled in our current expanded-access study of cannabidiol for patients with treatment-resistant epilepsy carry a diagnosis of TSC. After an initial baseline period of 1 month, patients began treatment with CBD. The initial dose of 5 mg/kg/day was increased by 5 mg/kg/day every week up to a maximum dose of 50 mg/kg/day, if tolerated. Weekly seizure frequencies, percent change in seizure frequencies, and responder rates were calculated during the 2nd, 3rd, 6th, 9th, and 12th month of treatment with CBD.

Results

- The median weekly seizure frequency during the baseline period was 22.0 (interquartile range [IQR] 14.8–57.4), which decreased to 13.3 (IQR 5.1–22.1) after 3 months of treatment with cannabidiol. The median percent change in total weekly seizure frequency was −48.8% (IQR −69.1% to −11.1%) after 3 months of treatment. The 50% responder rates over the course of the study were 50%, 50%, 38.9%, 50%, and 50% after 2, 3, 6, 9, and 12 months of treatment with CBD, respectively. In patients taking clobazam concurrently with CBD (n = 12), the responder rate after 3 months of treatment was 58.3%, compared to 33.3% in patients not taking clobazam (n = 6). Twelve (66.7%) of 18 patients in this study experienced at least one adverse event thought possibly related to CBD; the most common adverse events were drowsiness (n = 8, 44.4%), ataxia (n = 5, 27.8%), and diarrhea (n = 4, 22.2%).

Significance

- Although double-blind, placebo-controlled trials are still necessary, these findings suggest that cannabidiol may be an effective and well-tolerated treatment option for patients with refractory seizures in TSC.

Important: CBD interacts with mTOR inhibitors!

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Cannabidiol in TSC-Associated Epilpsy (GWEP1521 Study)

- Key inclusion criteria:
  - Patients aged 1–65 years with TSC
  - ≥8 TSC-associated seizures (countable focal or generalised) during the 4-week baseline period,
    with ≥1 seizure per week in ≥3 out of 4 weeks
  - Taking ≥1 antiepileptic drug (AED)
- Patients received 25 or 50 mg/kg/day of plant-derived highly purified CBD medicine (Epidyolex®;
  100 mg/mL oral solution) or placebo for 16 weeks

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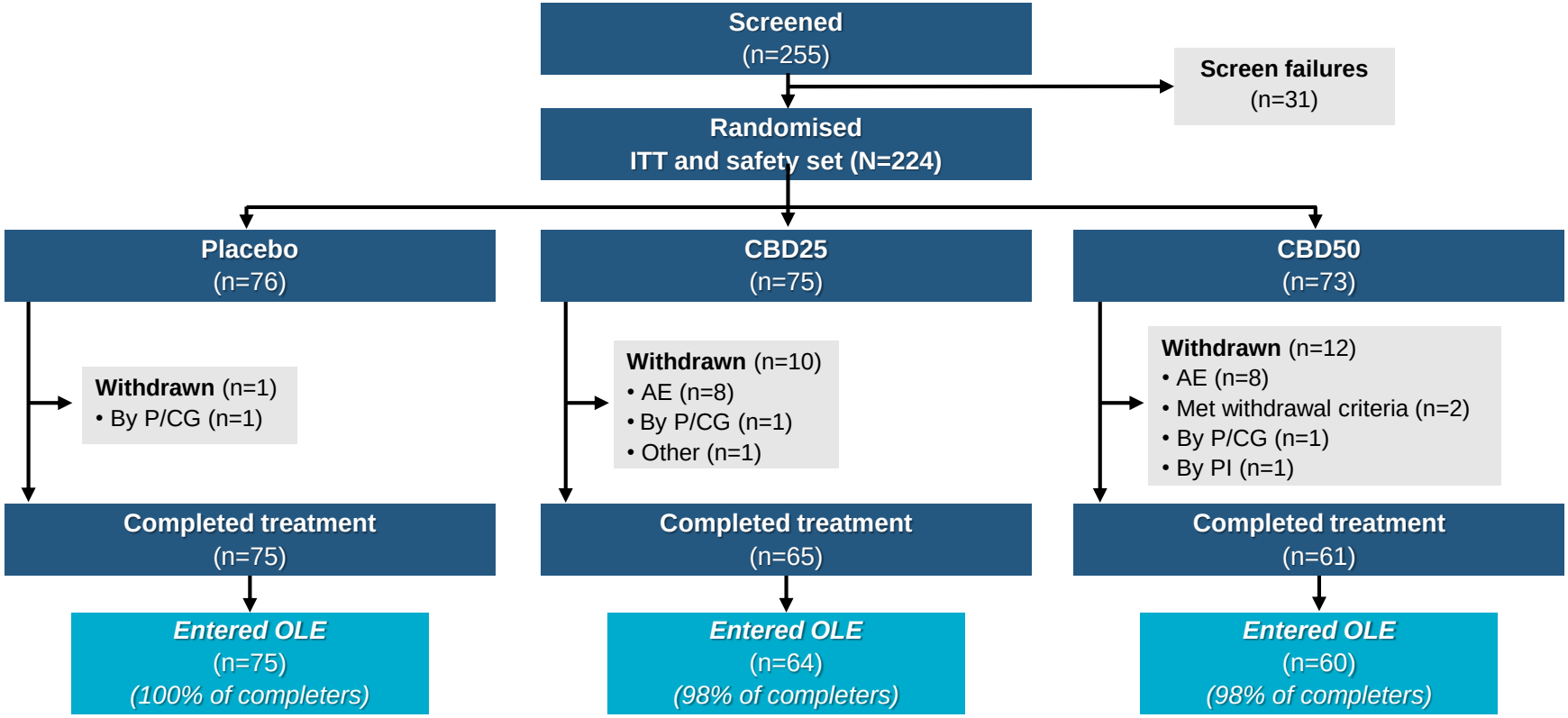
CBD is approved as Epidyolex® in the EU for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, in conjunction with clobazam, in patients ≥2 years of age.

PATIENT DISPOSITION



ITT, intention to treat; OLE, open-label extension; P/CG patient/caregiver; PI, principal investigator

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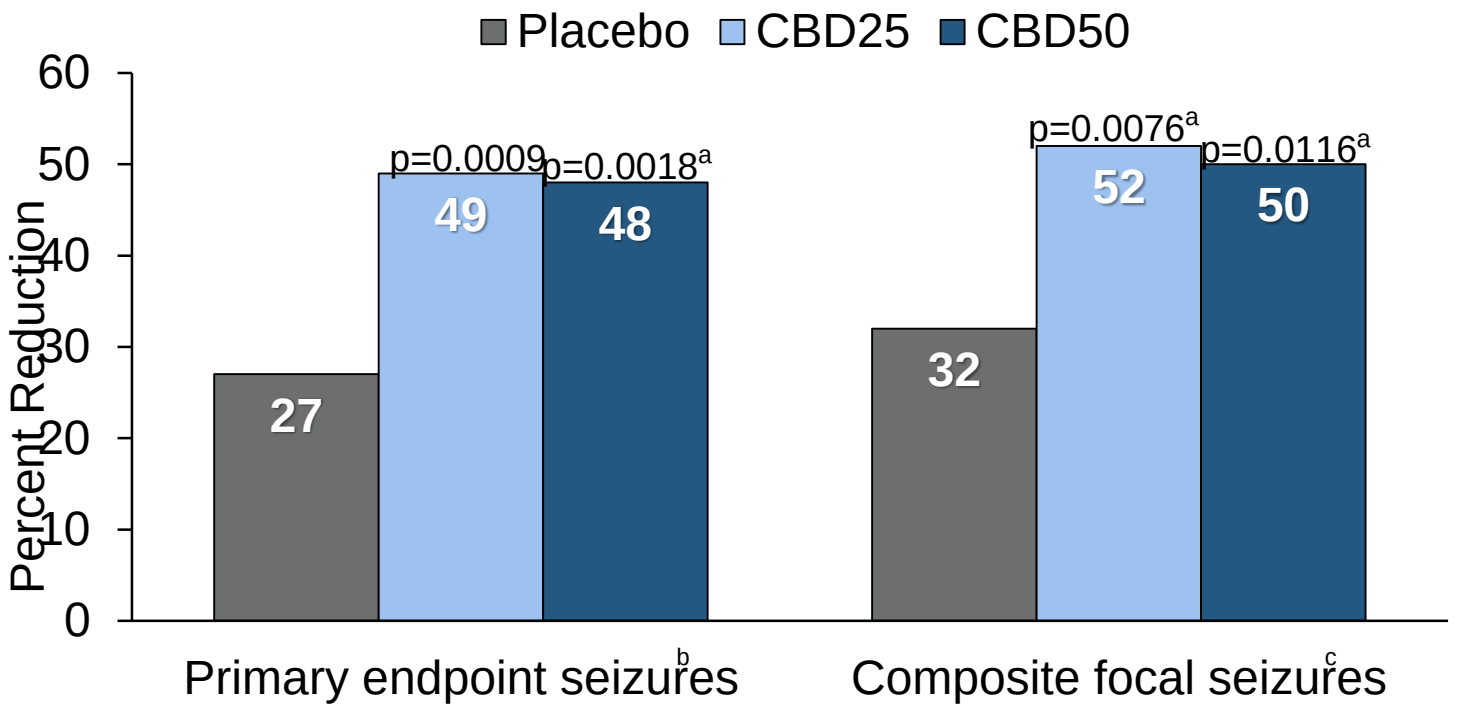
Reduction from baseline in seizures during the treatment period



[a]Nominal p value. [b]The primary seizure endpoint included all countable TSC-associated seizures as follows: focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, focal seizures evolving to bilateral generalised convulsive seizures, and generalised seizures (tonic-clonic, clonic, or atonic) in the context of an epileptic encephalopathy. It excluded absence, myoclonic, focal sensory, and infantile/epileptic spasms. [c]Composite focal seizures included all focal seizures included in primary endpoint.

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CONCLUSIONS:

- TSC is associated with 90% risk of epilepsy, in majority developing in infants
- TSC is increasingly diagnosed early, well before seizures
- In TSC, EEG can be used as a biomarker to identify TSC infants at risk for developing seizures
- Preventive/disease modifying strategies are emerging
- Vigabatrin should be used as a first line treatment for IS and focal seizures in infants with TSC
- In drug-resistant epilepsy in TSC, therapeutic options include AEDs,mTOR inhibitors, resective surgery, VNS, other surgical procedures, and ketogenic diet
- Early treatment is associated with better epilepsy and neurocognitive outcome

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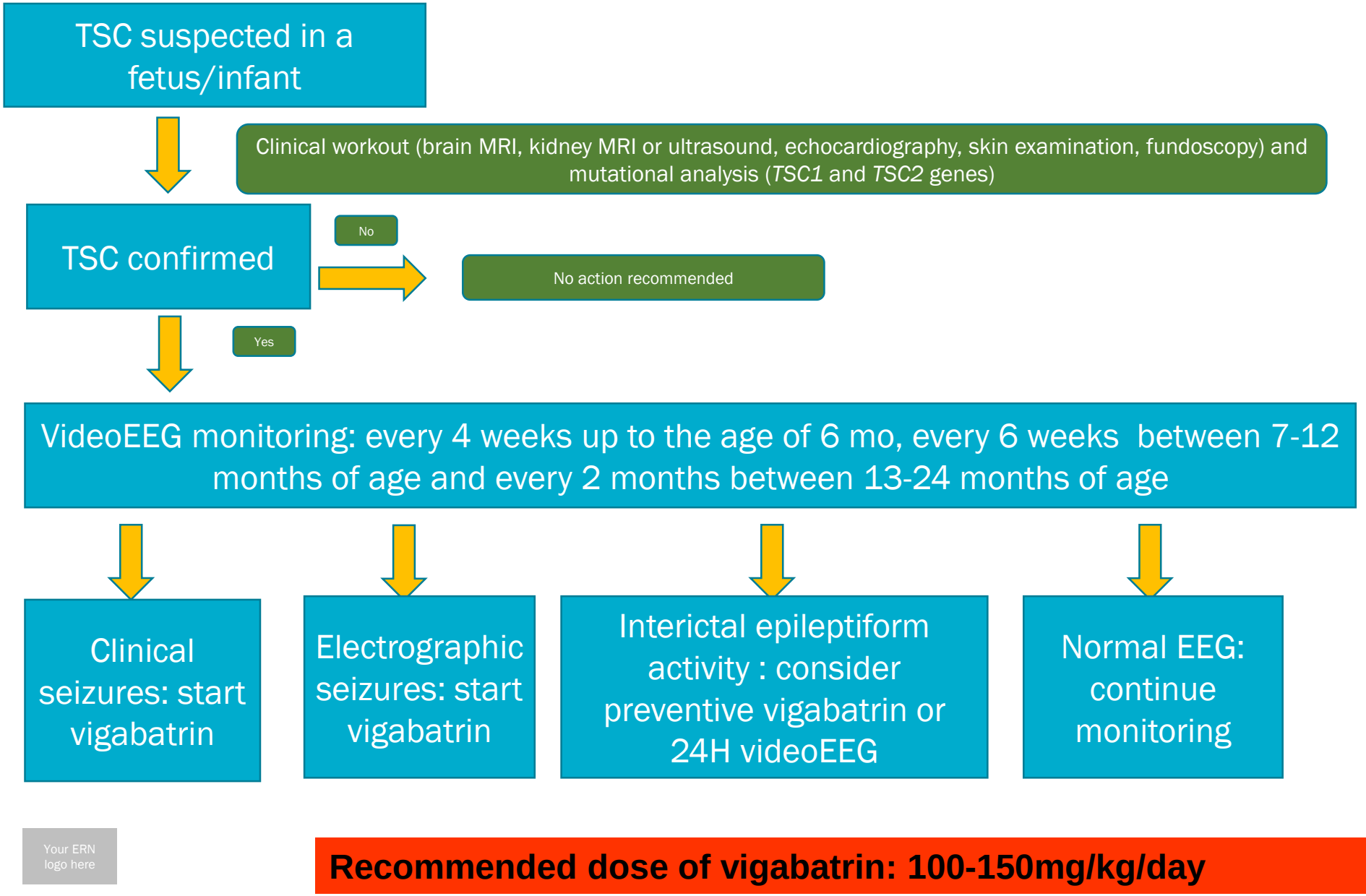
Recommended management of epilepsy in TSC infants



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Recommended dose of vigabatrin: 100-150mg/kg/day

Treatment options in TSC – associated epilepsy

Focal seizures:	**First choice in infants: vigabatrin** **First choice in older children and adults: vigabatrin or other AEDs**
Infantile spasms:	**First choice: vigabatrin** **Other options: ACTH, other AEDs, ketogenic diet, surgery**
Drug-resistant epilepsy:	**Antiepileptic drugs** **mTOR inhibitors** **Cannabidiol** **Ketogenic diet** **Resective surgery** **VNS** **Other surgical procedures**

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THANK YOU!

Questions?

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