UNIVERSITY OF KWAZULU-NATAL ™

INYUVESI YAKWAZULU-NATALI

Tuberous Sclerosis Complex

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9/4/2025

Outline

- Introduction
- Epidemiology
- History of TSC
- Genetics and molecular pathophysiology
- Clinical manifestations
  - Case1
  - Case 2
- Management
  - Surveillance
- Research Protocol
- Conclusion
- References

Tuberous Sclerosis Complex (TSC)

- Rare neurocutaneous disorder
- Mutations on TSC1 and TSC2 genes
- Dysregulation of the mTOR pathway
- Multiple organ systems involvement
- Variety of manifestations causing severe morbidity and even life-threatening complications
- Early diagnosis, along with lifelong surveillance and appropriate management, is essential

Epidemiology of TSC

- Autosomal dominant inheritance
- Incidence worldwide between 1:6000 and 1:10,000 live births.

❑United Kingdom→ the incidence at 1:5800 live births *(1991, J.P. Osborne, A. Fryer)*

❑Germany→ incidence rate from 1:6760 to 1:13,520 live births *(2025, JH. Driedger, J. Schröter)*

❖Epidemiological data from Africa, including South African (SA) populations, lacking!

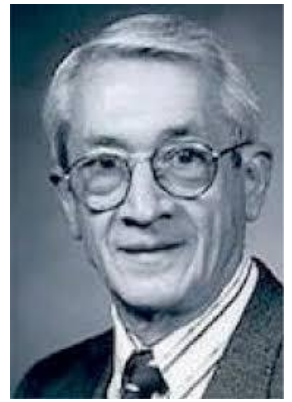
❖Estimated that 5000 – 10000 people with TSC in SA *(2017, P J de Vries, L Leclezio)*

❖This gap expresses the need for more research to accurately assess the burden of TSC in African population.

Natural History

Giants in Our Midst

- 1880 - First description of TSC by the French neurologist Bourneville.
- 1979 - Diagnostic criteria- 1st documented
- 20th century Manuel Rodriguez Gomez formalised diagnostic criteria and awareness of multisystem nature: Vogt triad of TSC (seizure, ID and facial angiofibromas)
- 1993 and 1997 - the *TSC1* and the *TSC2* gene were identified
- Between 2012 – 2015 TAND checklist was developed
- "Natural clusters" of TAND phenomena was hypothesized by Leclezio and de Vries
- 2018 - De Vries described the concept of "6 Natural TAND clusters"



Manuel Rodriguez Gomez

Prof Petrus J. de Vries

European Journal of Human Genetics (2005) 13, 731–741

www.nature.com/ejhg

ARTICLE

Mutational analysis of the *TSC1* and *TSC2* genes in a diagnostic setting: genotype – phenotype correlations and comparison of diagnostic DNA techniques in Tuberous Sclerosis Complex

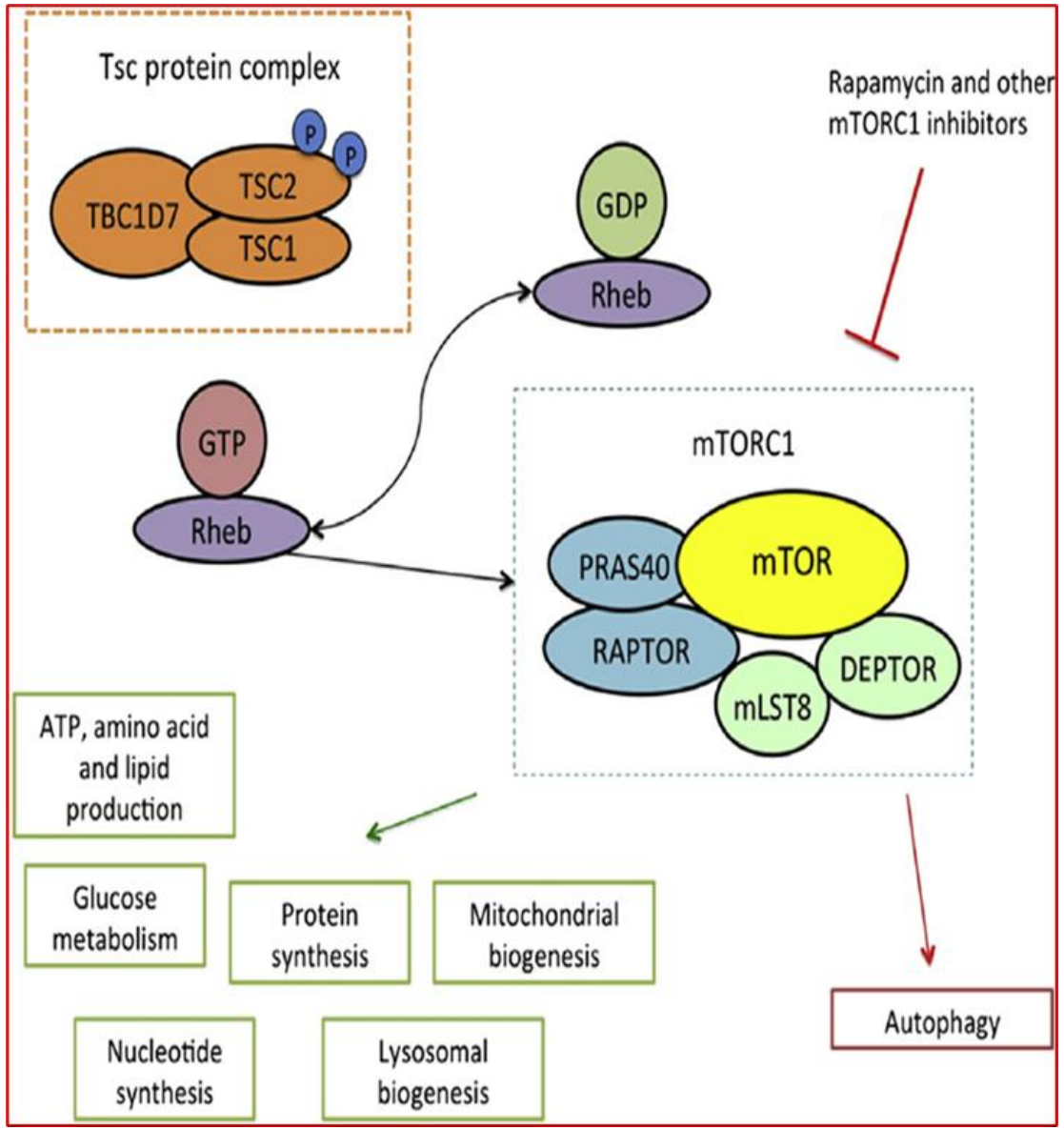
- Two-thirds of all TSC mutations - sporadic
  - De novo mutations + second somatic hit → disease
- High spontaneous mutation rate
- 100% penetrance with a wide phenotypic variability
- Routine genetic testing- identifies 85-90% of mutations
- 10% -15% of patients- no mutation on TSC1/TSC2 gene
- Mosaic or intronic mutations identified on DNA next generation sequencing (NGS)
- **In most centres in our setting- use clinical criteria for diagnosis**

Genetics and molecular pathophysiology

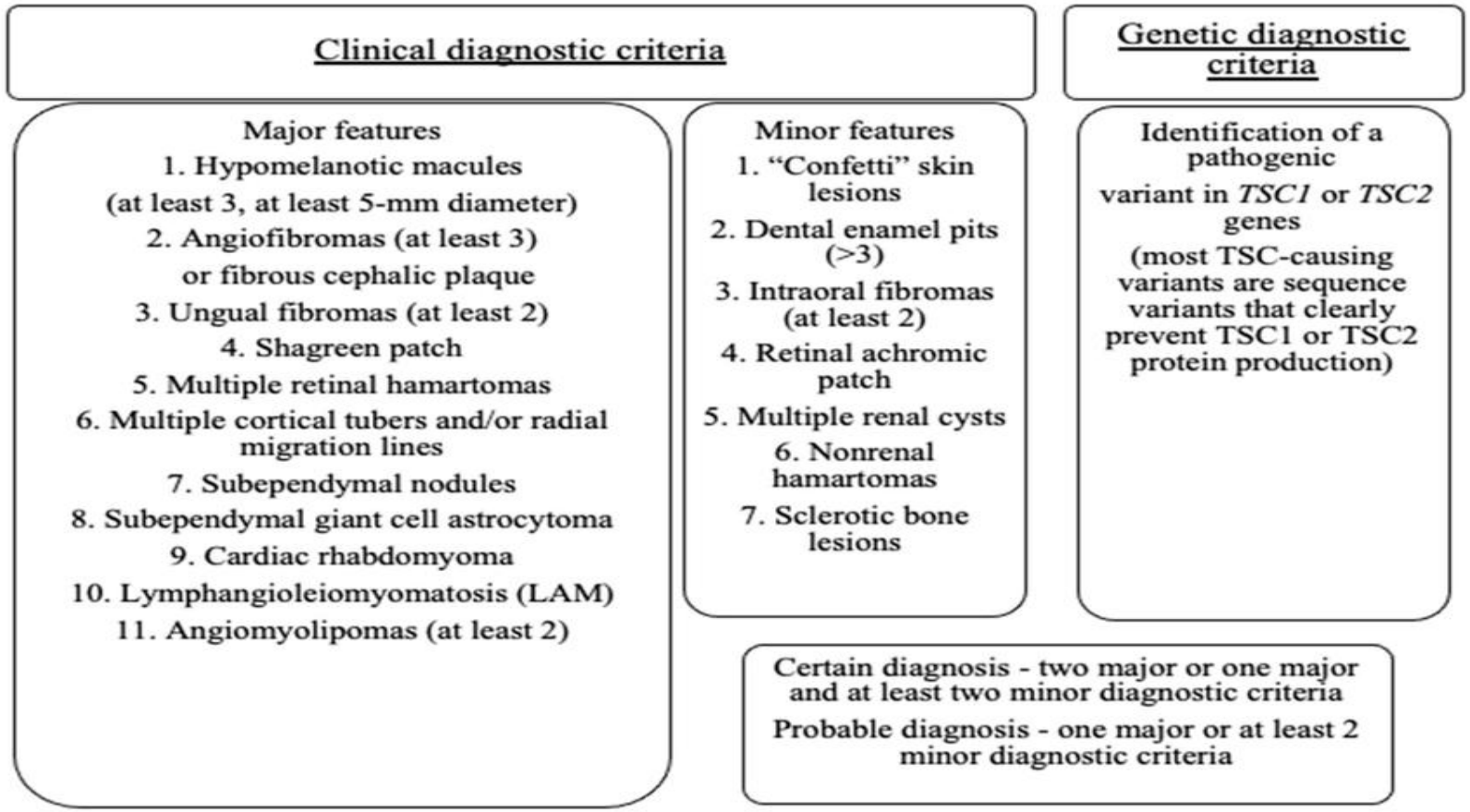
- Genes → chromosome 9q34 (TSC1) encoding protein hamartin

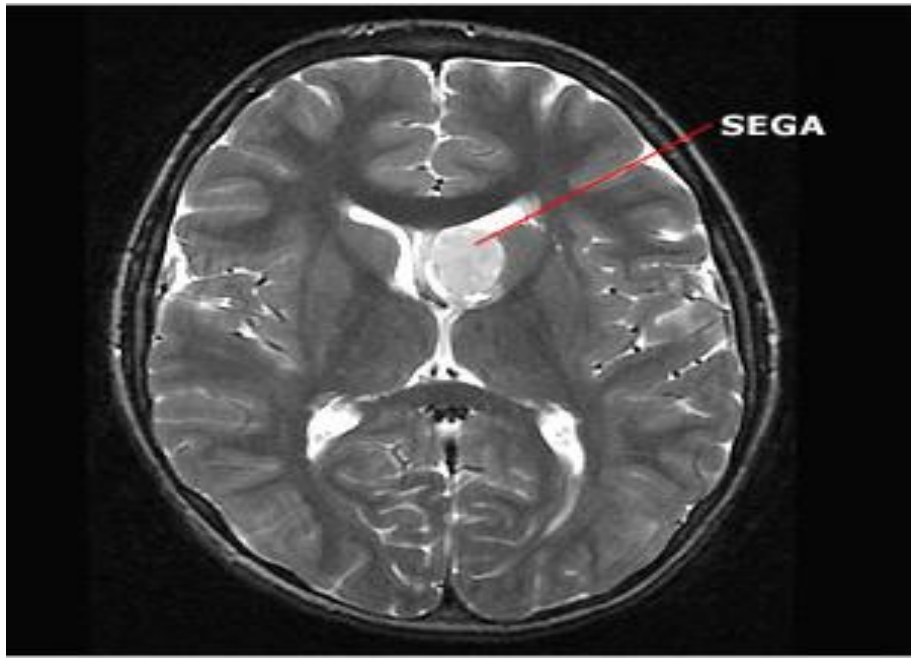
  → chromosome 16p13.3 (TSC2) encoding the protein tuberin
- TSC 1& 2 proteins → tumour suppressor genes → coiled-coin domain → negative effector of mTOR signalling pathways
- Inactivation → overactivation of the mTOR signaling (involving different organ system)
- **Abnormal:-** Neuronal migration
  - Cellular differentiation
  - Cellular proliferation
  - Protein synthesis

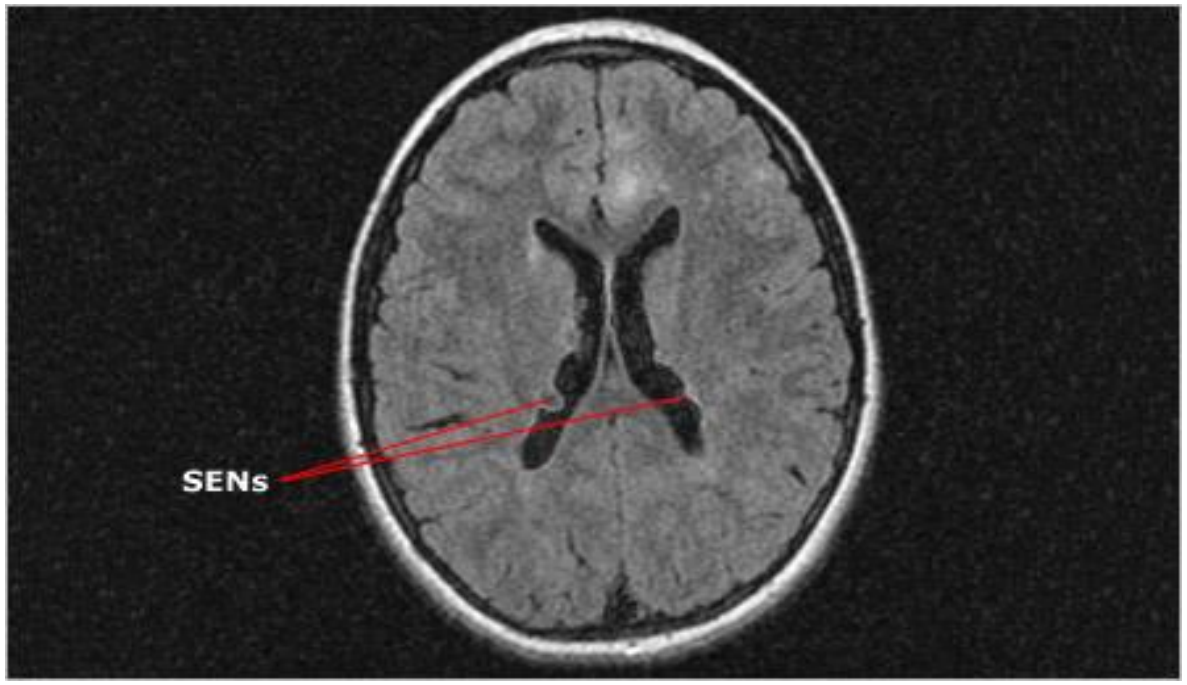
Pathophysiology of the mTOR pathway

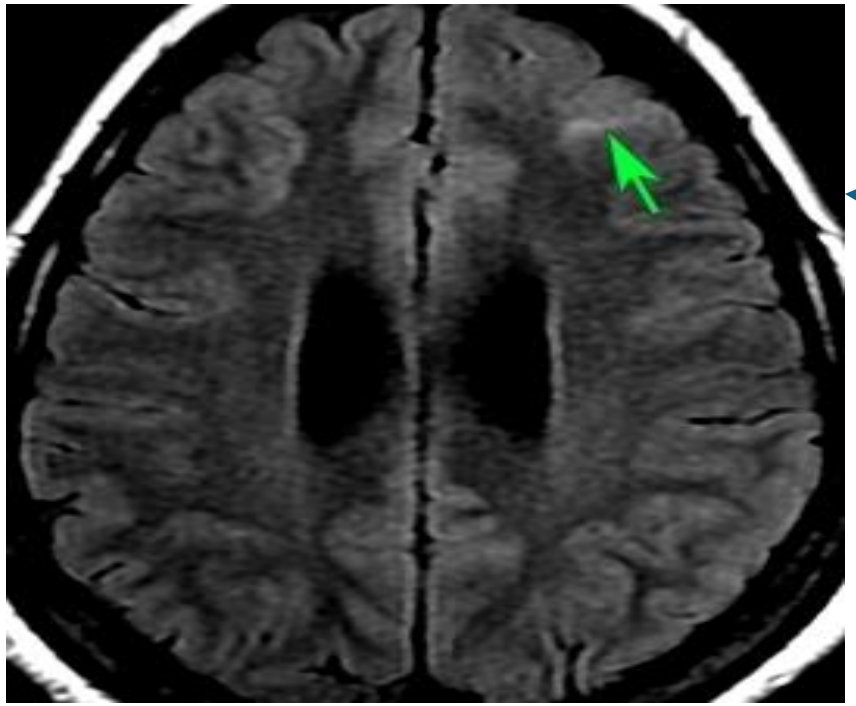


TSC: Updated Diagnostic Criteria (2021)









Radial bands

Case 1

- **8 yr old boy presented with Epilepsy**
- TSC stigmata: facial angiofibromas, CALMs
- No family history of NCTL
- No neurological deficits
- **Genetic: TSC2 positive**
  - TSC 2 gene cDNA :c.4912_4914de/AAG
  - Aminoacid p.Lys1638de
- Rx: Valproate Cr 200 mg bd po – remission
- EEG – multifocal SWS activity
- CT Brain: SEN
- MRI brain: cortical tubers, SEN
- USS abdomen: kidneys normal, pancreatic tumour nodule

- MRI Abdomen

Solid lesion in the body of the pancreas measuring 1.8cm x 2.28cm. In view of the history of TSC the primary consideration will be neuroendocrine lesion.

- Histology

- Well differentiated pancreatic neuroendocrine tumour (WHO grade 1)
- Showed thin fibrous capsule suggestive of complete enucleation

Frequency , Progression and Current Management: Report of 16 New Cases of Nonfunctional PNET in TSC and Comparison With Previous Reports. *Mowrey K et al. Front Neurol. 2021*

- Pancreatic neuroendocrine neoplasias (PNEN) : based on degree of cellular differentiation
  - PNET and Poorly differentiated Pancreatic Neuroendocrine carcinoma (PNEC)
- **Classification** : Functional: abnormal hormonal production and Non-functional: asymptomatic, with local invasion
- **Prevalence:** 0.003% general population and 4% - 9% in patients with TSC
- Younger patients (<40 yrs)
- Transformation from NFT to FT has been reported
- **Management:** limited data on outcomes
- Surgical resection → functional PNET or non-functional > 2cm
- mTOR inhibitors used – growth slower with RX

Kidney involvement in paediatric TSC

(Limavady A. et. Al, Pediatric Nephrology, 2024)

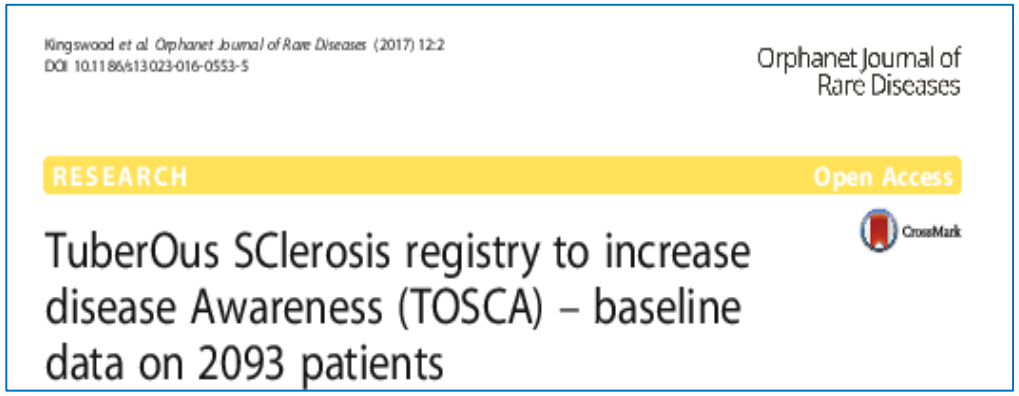
Table 5 Kidney abnormalities and management

Parameters	Overall	
	n	%
Hyperfiltration (eGFR ≥ 140 mL/min/1.73 m^2)[a]	39/81	48.1
Nephromegaly (> 2 SD)[b]	28/85	32.9
Hypertension (≥ 95th centile)[c]	31/125	24.8
Chronic kidney disease (eGFR < 90 mL/min/1.73 m^2)	10/81	12.3
Kidney AMLs ≥ 3 cm (high-risk)	13/145	9.0
On antihypertensives	9/125	7.2
On everolimus	13/182	7.1
Kidney interventions	3/182	1.6

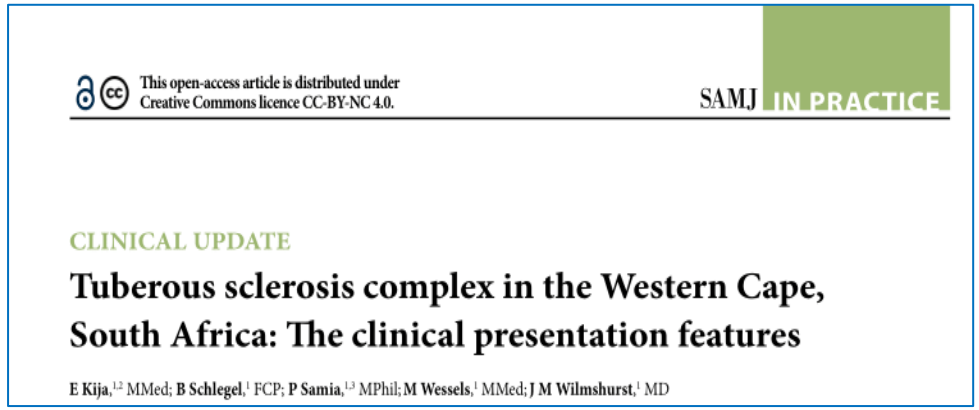
- Cysts were more common than AMLs in children < 5yrs
- >40% of children < 5yrs had cysts
- 25% with AMLs
- Kidney AMLs are relatively infrequent in children < 2yrs,
  - due to their slow growth and small size (often missed on imaging)

Incidence of clinical manifestations

- TOSCA registry -large international data base of TSC patients
- South Africa was part of this study
- Reported on was the incidence of clinical manifestations
- South African study describing local cohort of patients from the Western Cape



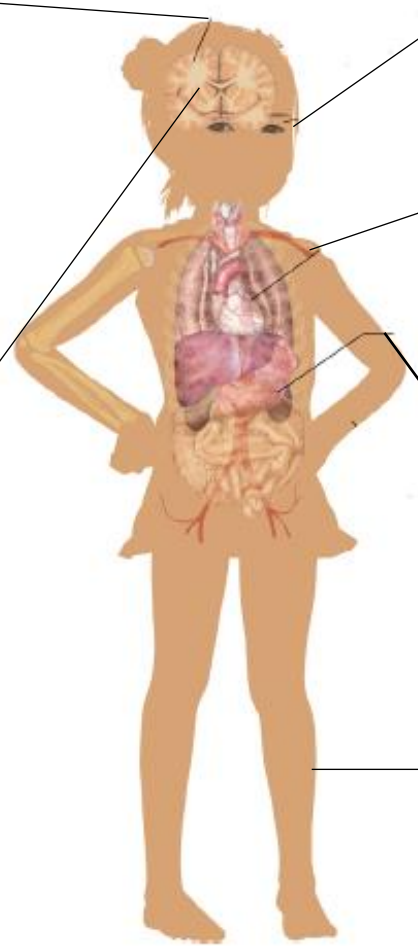
VS



Clinical manifestations: TOSCA vs SA (WC)

	TOSCA (%)	SA (%)
Median age	13	16
Epilepsy	83.5	87
- Focal epilepsy	66.9	54
- Epileptic spasm	38.8	18
SEGA	24.4	26
Cortical tubers	82.2	79
Subependymal nodules	78.2	92
Cerebral whitematter radial migration lines	20.5	

	TOSCA%	SA-WC %
TAND	39.2	57.8
-Behavioural	35.6	
-Psychiatric		
- ASD	20.7	
- ADHD	19.6	
- Anxiety	9.1	
- Depression	6.1	24.4
- ID	54.9	59
- Academic	57.8	
- Neuropsychological	55	



Eyes	TOSCA%
Retinal harmatomas	14

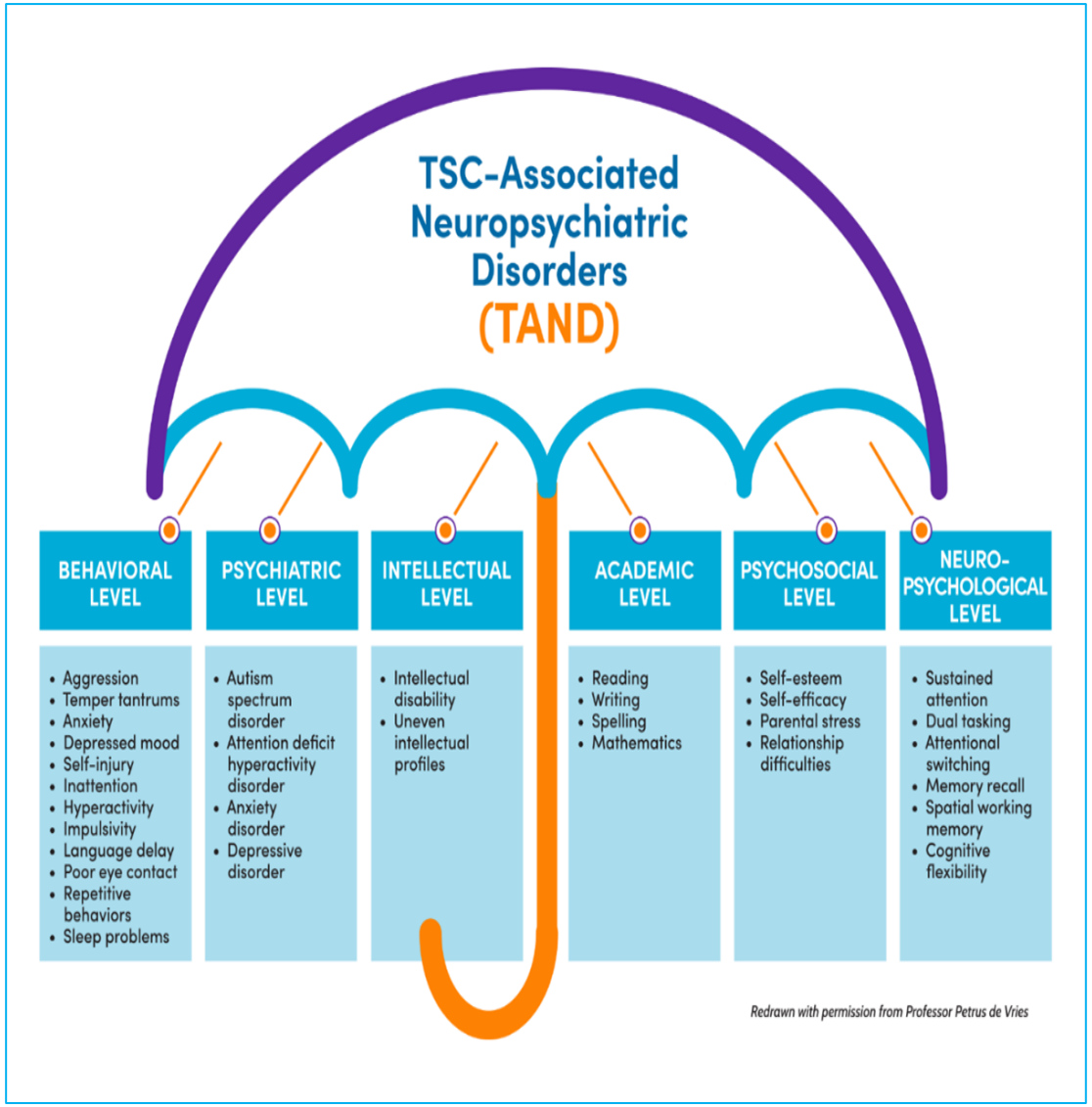
Cardiac	TOSCA%	SA-WC%
Cardiac rhabdomyoma	34.3	20

Lungs	TOSCA%
LAM	6.9

Renal	TOSCA%	SA-WC%
Angiomyolipoma	47.2	44
Multiple renal cyst	22.8	
Polycystic kidneys	3.5	
Renal malignancy	1.1	

Skin	TOSCA%	SA-WC%
Facial angiofibroma	57.3	49
>3 hypomelanotic macules	66.8	69
Shagreen patch	27.4	28
Ungual & periungual fibroma	16.7	0.02

TAND (TSC-Associated Neuropsychiatric Disorder)



10 core principles

1. Everyone with TSC is at risk of TAND
2. Everyone with TSC needs lifelong monitoring for the emergence of TAND
3. Screen at least annually and follow up with appropriate action
4. The goal is early identification and early intervention
5. TAND clusters cluster together
6. Always consider the impact of physical health problems + medications on TAND
7. Work with families and caregivers as lived experts in TSC and TAND
8. Generate a “bio-psycho-social” “whole-system” plan for intervention
9. Be evidence-based and evidence-informed
10. Strive for optimal functional outcomes and quality of life

Brain malformations in TSC

- TSC genes are involved in cell body size, dendritic arborization, axonal outgrowth and targeting, neuronal migration, cortical lamination, spine formation and vascular abnormalities
- Subependymal nodules(SEN) → Walls of the lateral ventricles
  - CT/MRI appear as small calcified nodules
  - Can be precursors to SEGA's
- White matter changes→ linear or radial migration lines extending from ventricles to the cortex

Case 2

10 yr male

-Clinically confirmed TSC

-Fetal sonar: suspicion of the diagnosis

-Uneventful delivery

Postnatal: skin lesions compatible with TSC

- **Echo** → Confirmed Multiple Rhabdomyomas
- **Renal U/S** → Polycystic kidney disease
- **MRI Brain** → Multiple tubers, SEN with a SEGA (no active hydrocephalus
- **Ophthalmology** → Left subretinal astrocytoma

Ongoing Surveillance and Management

- **Neurology**: Seizure onset @ 1yr of age, now in remission since 2017
- TAND: ADHD @ 4 yrs, learning disabilities

Started on Sirolimus Nov 2022

SEGA – **(see next slide)**

Skin: Facial angiofibromas→ improved Sirolimus gel

Cardiac: Rhabdomyoma but resolved in 2024

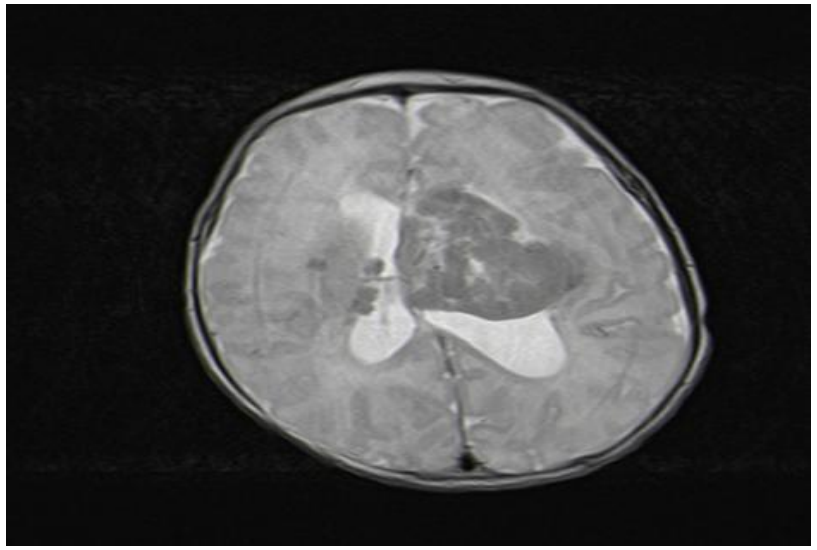
Ophthalmology: Astrocytoma – debulking (4/12 of age)

Nephrology: Serial u/s

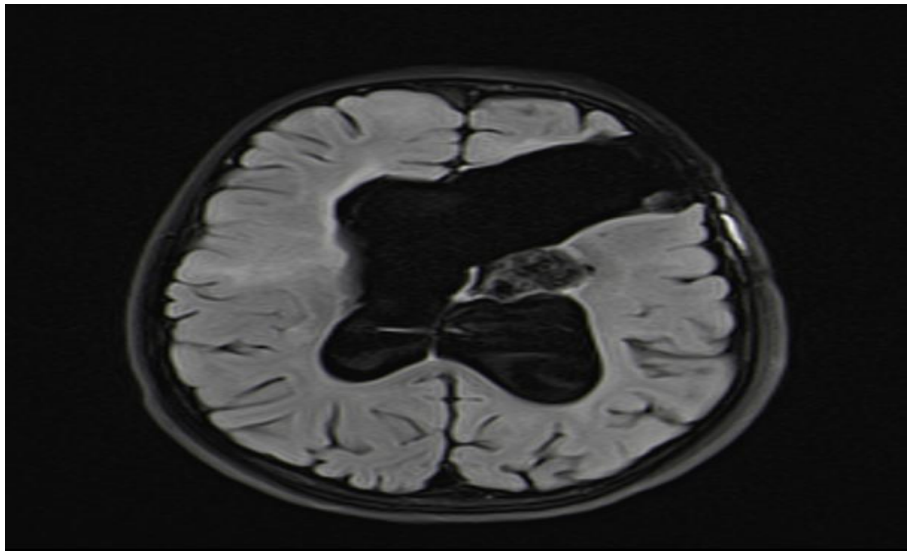
2018 (4yrs)→ progressive disease, reduced GFR and HPT

CT Abdomen : bilateral polycystic kidneys

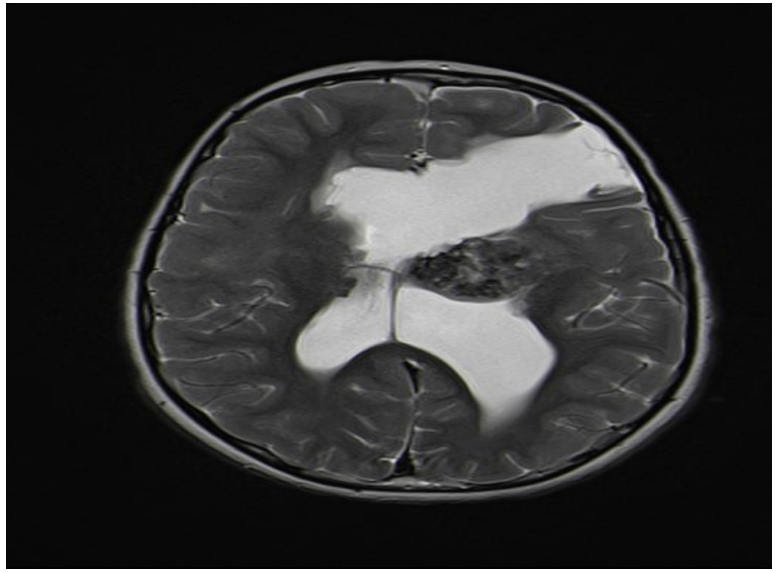
U/S 2024: no increase in size of the cysts



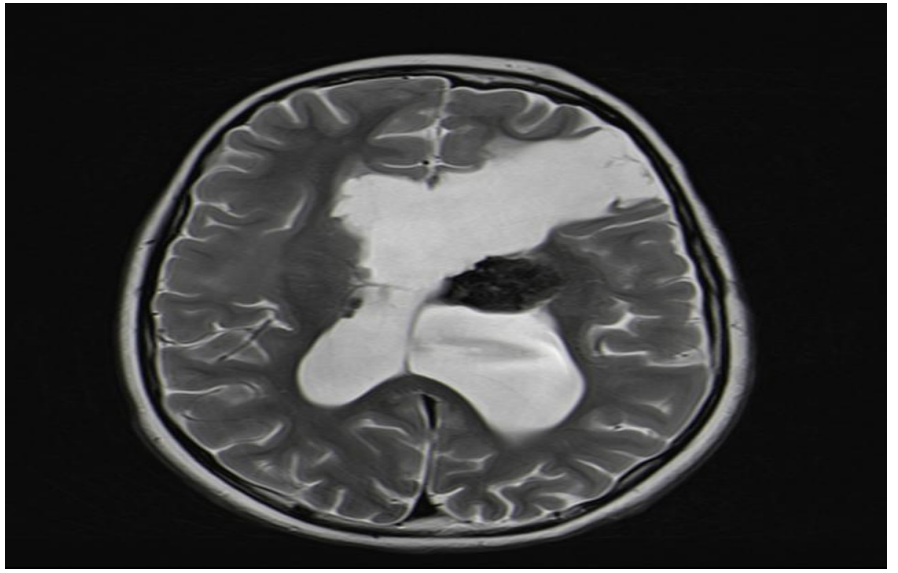
15/12/2015



2018



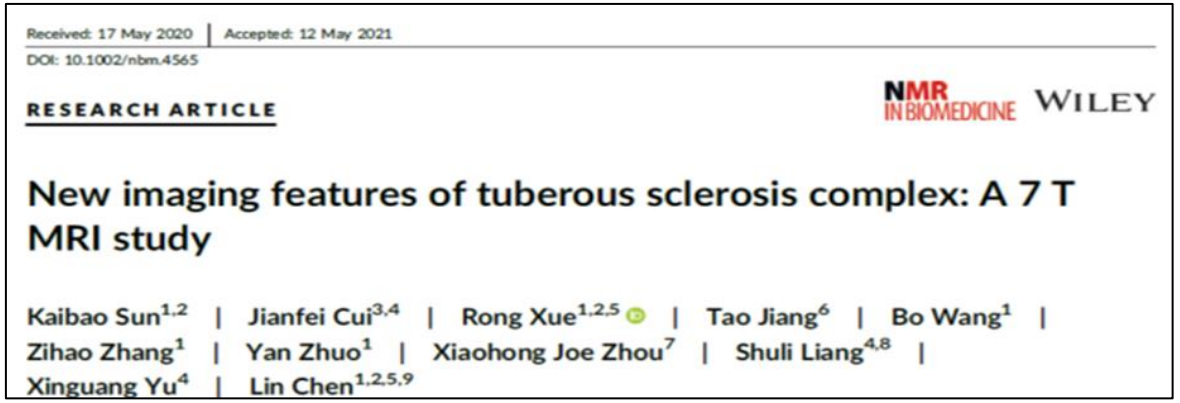
2022



2024

Brain malformations in TSC

- Cortical tubers → commonest
- Boundary of grey and white matter
- Tend to not increase in size/ number over time
- Chinese study-using MRI image:
- - 91.3% of cortical tubers exhibited venous involvement
- - venous structures and iron deposition may play a role in the development and characteristics of TSC lesions



Received: 17 May 2020 | Accepted: 12 May 2021
DOI: 10.1002/nbm.4565

RESEARCH ARTICLE

NMR IN BIOMEDICINE WILEY

New imaging features of tuberous sclerosis complex: A 7 T MRI study

Kaibao Sun[1,2] | Jianfei Cui[3,4] | Rong Xue[1,2,5] | Tao Jiang[6] | Bo Wang[1] | Zihao Zhang[1] | Yan Zhuo[1] | Xiaohong Joe Zhou[7] | Shuli Liang[4,8] | Xinguang Yu[4] | Lin Chen[1,2,5,9]

Subependymal Giant Cell Astrocytoma(SEGA)

- Slow-growth tumours (WHO Grade I)
  - 25% of mortality rate associated with TSC (50% if complicated)
- Complicated SEGA: - raised ICP, visual loss (35%), epilepsy (86.8%)
- SEN's Vs SEGA's
  - No contrast enhancement
  - Diameter is less than 13 mm
  - Rarely cause hydrocephalus
- Management of SEGA's

surgical & mTOR inhibitor vs mTOR inhibitor only:

  - Size and / rapid growth/ mTOR inhibitor resistance/ intolerance
  - Inoperable and surgery is a high risk

Child's Nervous System (2020) 36:951–960
https://doi.org/10.1007/s00381-019-04449-w

ORIGINAL ARTICLE

Neurosurgical treatment of subependymal giant cell astrocytomas in tuberous sclerosis complex: a series of 44 surgical procedures in 31 patients

Flavio Giordano[1] · Carla Moscheo[2] · Matteo Lenge[1,3] · Roberto Biagiotti[4] · Francesco Mari[3] · Iacopo Sardi[2] · Anna Maria Buccoliero[5] · Lorenzo Mongardi[6] · Eleonora Aronica[7,8] · Renzo Guerrini[3] · Lorenzo Genitori[1]

Outcome

- No evidence of SEGA progression over 5 yrs (90%)
- Gross total removal (GTR) (81%)
- Subtotal removal (STR) (19%)
- Recurrence 30% - associated with STR > GTR
- mTOR usage 18% → reduce & stabilising tumour
- Morbidity (22%) and mortality 2%)

Surgical approach, combined with mTOR inhibitors, is a valid option for the treatment of SEGAs.

Management in TSC

It is essential that the treatment is holistic and individualised

It is multidisciplinary:

Neurologist
Dermatologist
Nephrologist
Cardiologist
Neurosurgeon
Neurodevelopmental specialist and/or psychiatrist for TAND,
Applied behaviour analysis for autism spectrum disorder, consideration of

It is important to do surveillance of all complications of TSC to improve quality of life for both patient and parent.

It will also be cost effective for the hospital avoiding haphazard use of resources.

mTOR inhibitors and EXIST Trials

- Everolimus or rapalog, an mTOR- greater oral bioavailability and favourable pharmacokinetics.
- **EXIST-1** : examined safety/efficacy of TSC-related SEGA.
- **EXIST-2**: effect on AMLs and improvement in the burden of facial angiofibromas.
- **EXIST-3:** reduction of treatment- resistant seizures associated with TSC
- South Africa: Sirolimus authorised for use in Tertiary/Quaternary centres (financial difficulties in the public sector it has recently been unavailable)

Table 25: Subependymal Giant Cell Astrocytoma Response Rate in TSC-Associated SEGA in EXIST-1

	AFINITOR N = 78	Placebo N = 39	p-value
Primary analysis			
SEGA response rate[a] - (%)	**35**	**0**	**< 0.0001**
95% CI	24, 46	0, 9	

[a]Per independent central radiology review.

Patients randomized to placebo were permitted to receive AFINITOR at the time of SEGA progression or after the primary analysis, whichever occurred first. After the primary analysis, patients treated with AFINITOR underwent additional follow-up MRI scans to

Table 26: Percentage Reduction in Seizure Frequency and Response Rate in TSC-Associated Partial-Onset Seizures in EXIST-3

	AFINITOR DISPERZ Target of 3-7 ng/mL N = 117	AFINITOR DISPERZ Target of 9-15 ng/mL N = 130	Placebo N = 119
Seizures per week			
Median at Baseline (Min, Max)	8.6 (1.4, 192.9)	9.5 (0.3, 218.4)	10.5 (1.3, 231.7)
Median at Core phase[a] (Min, Max)	6.8 (0.0, 193.5)	4.9 (0.0, 133.7)	8.5 (0.0, 217.7)
Percentage reduction from Baseline to Core phase (Maintenance[a])			
Median	29.3	39.6	14.9
95% CI[b]	18.8, 41.9	35.0, 48.7	0.1, 21.7
p-value[c]	0.003	< 0.001	
Response rate			
Responders, n (%)	28.2	40	15.1
95% CI[d]	20.3, 37.3	31.5, 49.0	9.2, 22.8

Preventantive treatment of TSC with Sirolimus: Phase 1 safety and efficacy results

CapalcJK. et al. Annals of the Child Neurology Society.2024

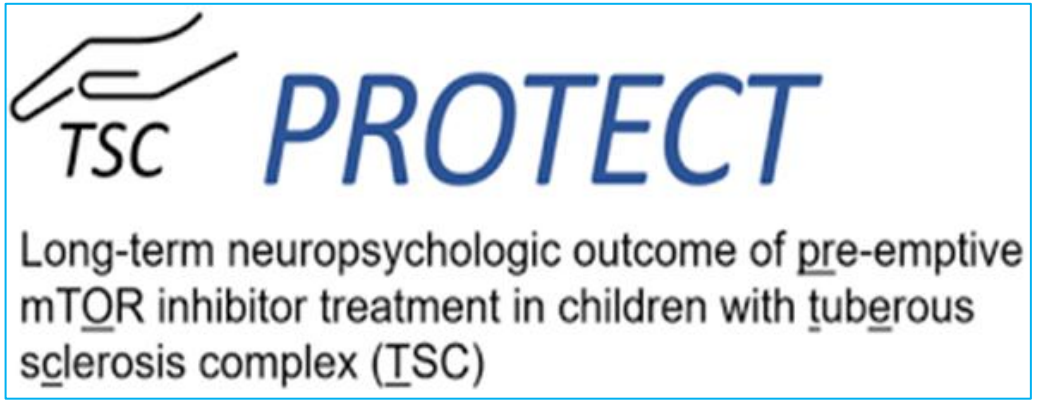
- 5 infants < 6/12 with
  - No prior seizures/ Sirolimus indication
  - Sirolimus over a 1 yr period
- Safety & Tolerability:
  - 92 A/E were reported (34 – related to Sirolimus)
    - All A/E → resolved by 24/12
- Sirolimus blood levels:
  - 94% - within the target range

- Seizure Development and Neurodevelopmental outcomes by 2yrs
  - 3 infants → had developed seizures
  - 4 infants → normal cognitive development for their age
  - 1 infant → diagnosed with possible ASD

Conclusion

- Sirolimus is safe and well-tolerated in infants with TSC during their first year of life.
- Preliminary efficacy data indicate a favorable profile compared to previous TSC cohorts not exposed to early sirolimus treatment.
- These findings support further investigation of sirolimus as a preventive treatment in TSC, leading to the initiation of a prospective Phase 2 clinical trial (TSC-STEPS)

Ongoing trials on early intervention in infants with TSC using mTOR inhibitors



- **TSC-STEPS (Sirolimus TSC Epilepsy Prevention Study)**
- **Phase:** Phase 1/2 clinical trial
- **Objective:** To evaluate the safety and efficacy of sirolimus in preventing or delaying the onset of seizures in infants diagnosed with TSC who have not yet experienced seizures.
- **Design:** Multicenter study involving sites in the United States and Australia, enrolling infants under six months of age with a confirmed TSC diagnosis.

- **PROTECT (Long-term Neuropsychologic Outcome of Pre-emptive mTOR Inhibitor Treatment in Children with TSC):**
- **Phase:** Phase IIb national multicenter clinical trial
- **Objective:** To investigate the long-term neuropsychological outcomes of preemptive mTOR inhibitor treatment in children diagnosed with TSC under four months of age.
- **Design:** Aims to enroll 60 participants, randomized in a 1:1 ratio, with the primary endpoint being the neuropsychological outcome assessed by the cognitive scale of the Bayley Scales of Infant and Toddler Development III at 24 months of age.

Updated clinical recommendations for the management of TSC associated Epilepsy

Speechio N. et al. European Journal of Paediatric Neurology 47 (2023) 25–34

ASM's

- Vigabatrin→ 1st line monotherapy

  → presymptomatic
- ACTH &Prednisolone→ 2nd line
- ASM's combination therapy→ Vigabatrin & steroid therapy has failed

mTOR inhibitors: Everolimus & Sirolimus

- Everolimus→ adjunct in ≥2yrs (refractory focal seizures, with/without evolution to bilateral)

  → DRE
- Sirolimus→ favourable safety & efficacy

Surgery:- Greater probability of seizure freedom

→ early surgery

→ resection beyond tuber margins

Ketogenic diet → patients not for surgical intervention

- Vigabatrin/ other ASM's failure

VNS → DRE

Canabidiol → Drug-drug interaction with Everolimus

Epilepsy & TAND

- TAND manifestations are highly prevalent and demonstrate a strong association with early onset epilepsy and severity in this population

RESEARCH ARTICLE

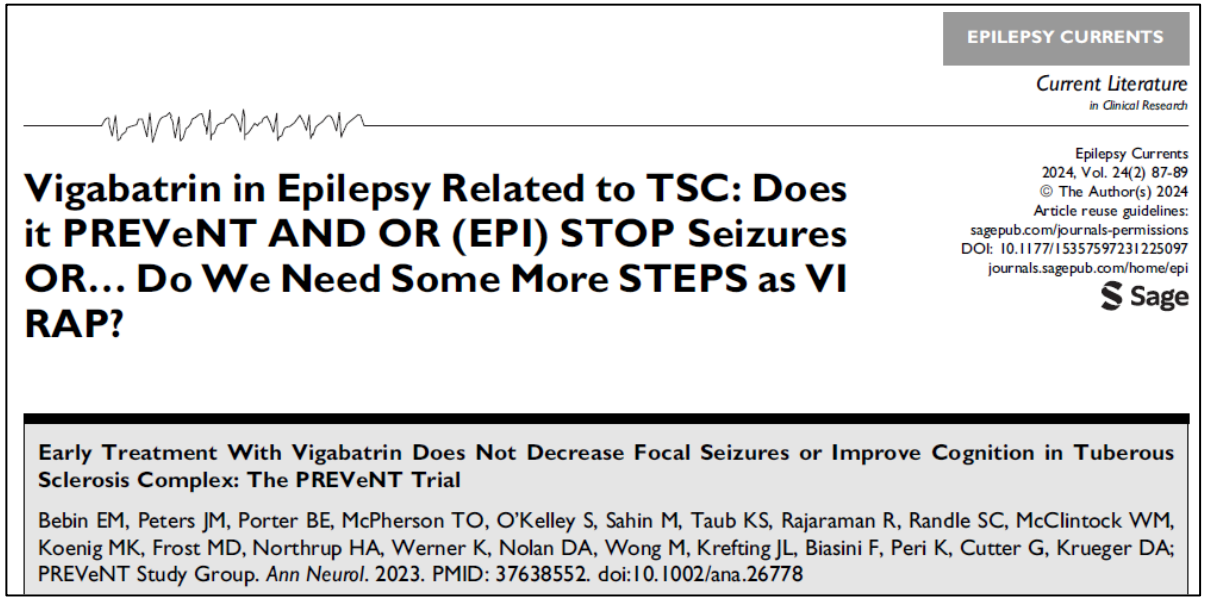
Early Treatment with Vigabatrin Does Not Decrease Focal Seizures or Improve Cognition in Tuberous Sclerosis Complex: The PREVeNT Trial

VS

RESEARCH ARTICLE

Prevention of Epilepsy in Infants with Tuberous Sclerosis Complex in the EPISTOP Trial

VS



EPILEPSY CURRENTS

Current Literature in Clinical Research

Vigabatrin in Epilepsy Related to TSC: Does it PREVeNT AND OR (EPI) STOP Seizures OR… Do We Need Some More STEPS as VI RAP?

Epilepsy Currents
2024, Vol. 24(2) 87-89

DOI: 10.1177/15357597231225097
journals.sagepub.com/home/epi
Sage

Early Treatment With Vigabatrin Does Not Decrease Focal Seizures or Improve Cognition in Tuberous Sclerosis Complex: The PREVeNT Trial

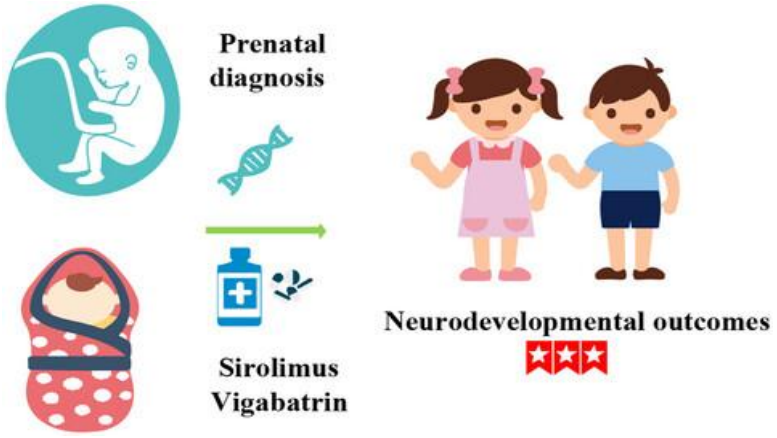
Bebin EM, Peters JM, Porter BE, McPherson TO, O'Kelley S, Sahin M, Taub KS, Rajaraman R, Randle SC, McClintock WM, Koenig MK, Frost MD, Northrup HA, Werner K, Nolan DA, Wong M, Krefting JL, Biasini F, Peri K, Cutter G, Krueger DA; PREVeNT Study Group. *Ann Neurol*. 2023. PMID: 37638552. doi:10.1002/ana.26778

Prenatal diagnosis and intervention improve developmental outcomes and epilepsy prognosis in children with TSC (Wang X. et.al, Dev Med Child Neurol. © 2022 Mac Keith Press. 2022)

TABLE 2 Effects of preventive intervention on epilepsy and developmental outcomes in individuals diagnosed prenatally

	Preventive intervention (*n*)	No preventive intervention (*n*)	RR (95% CI)	*p*
Demographic characteristic				
n	18	13	NA	–
Gestational week at diagnosis, median (IQR)	30.50 (25.98–34.03)	32.00 (29.55–34.05)	NA	0.253
Male	8	7	NA	0.605
Reason for encounter (cardiac rhabdomyoma, intracranial lesion)	15:3	8:5	NA	0.171
Age at epilepsy onset in months, median (IQR)	6.00 (4.00–17.00)	6.00 (5.00–19.00)	NA	0.661
TSC1, *TSC2*, unknown[a]	3, 13, 2	4, 7, 2	NA	0.558
Clinical outcome				
Epilepsy	7	11	0.41 (0.23–0.75)	0.003[b]
Spasms	2	6	0.47 (0.15–1.43)	0.183
Drug-refractory epilepsy	1	5	0.26 (0.36–1.92)	0.187
Development (normal, borderline, delay)				
Cognitive	14, 3, 1	3, 8, 2	0.31 (0.12–0.77)	0.022[b]
Language	13, 4, 1	3, 8, 2	0.37 (0.17–0.82)	0.039[b]
Motor	13, 4, 1	5, 8, 0	0.36 (0.14–0.96)	0.138

- Prenatal diagnosis and early intervention may Improve developmental outcomes in children with tuberous sclerosis complex (TSC)
- **Prophylactic intervention with sirolimus and vigabatrin may reduce the incidence of epilepsy**
- Cardiac and/or intracranial lesions combined with genetic testing can be used to diagnose TSC prenatally



Epilepsy surgery in TSC (Lesion network mapping)

Though there may be multiple cortical tubers, however, seizure focus may be from one cortical tuber

Lesion network mapping helps:

identify which tuber is causing the seizures

target surgery or treatment (like brain stimulation or medicine)

predict developmental delays or behaviour challenges based on which networks are affected.

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Epilepsia

RESEARCH ARTICLE

Prognostic application of lesion network mapping to epilepsy surgery outcomes in pediatric tuberous sclerosis complex

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- Lesion network mapping was performed to determine the association between cortical networks connected to the resection zone and postoperative outcome in children with TSC

Outcome:

- Application of LNM →better outcomes when the resection zone is connected to certain networks, including the default mode and motor networks, that may support sustainment of seizures in kids with TSC.

Diagnosis, monitoring and treatment of TSC: A SA consensus response to international guidelines (De Vries et.al, SAMJ, 2017)

Organ System	Treatment	Surveillance
Genetics	-Genetic assessment & counselling -First degree relatives – clinical assessment	-Individual with TSC or first degree relative→ Antenatal referral
Brain	-Symptomatic SEGA→ Surgical resection, VP shunt -Asymptomatic, Growing SEGA→ Surgical resection/ mTOR inhibitor -Epileptic spasm→ Vigabatrin, ACTH -Other seizure types→ ASM's -DRE→ Epilepsy surgery, VNS, Ketogenic diet, mTOR inhibitors	-Brain MRI 1 – 3yrs→ asymptomatic & < 25yrs -MRI scans > frequently -May continue as adults to exclude any growing SEGA
TAND	-Based on the TAND profile of each patient -School aged→ AIDP -Sudden change in behaviour→ medical/ clinical evaluation	-Annually→ TAND Checklist -Formal evaluation→ 5 key developmental time points: - infancy (0 - 3 years)/ preschool (3 - 6 years)/ middle school years (6 - 9 years)/ in adolescence (12 - 16 years)/ in early adulthood (18 - 25 years), and as required after that -This includes:- detailed neurodevelopmental/ behavioural/ psychiatric/ learning/ neuropsychological/ and psychosocial assessment
Kidneys	-Acute haemorrhage→ embolization ff by corticosteroids -Asymptomatic, growing angiomyolipomas >3 cm→ 1st line mTOR inhibitor/ 2nd line Selective embolisation or kidney-sparing resection (Nephrotomy – avoided at all cost)	-MRI abdomen 1 – 3yrs from diagnosis throughout the lifespan for AML & renal cystic disease -Annual renal function assessment (GFR) & BP -Urinalysis (haematuria) at each clinic visit

Diagnosis, monitoring and treatment of TSC: A SA consensus response to international guidelines (De Vries et.al, SAMJ, 2017)

Organ system	Treatment	Surveillance
Lungs	-LAM→ mTOR inhibitor/ lung transplant	-LAM symptoms @ each clinic visit -HRCT every 5 – 10yrs in asymptomatic individuals at risk for LAM -Lung cysts @ baseline HRCT should have annual lung function tests & HRCT every 2 - 3 years
Skin	-If rapidly changing & disfiguring→ Surgical excision, mTOR topicals	-Annual detailed skin assessment
Teeth	-Symptomatic or deforming dental lesions, oral fibromas and bony jaw lesions→ surgical excision, curettage, or lasers -Dental pits→ restorative treatments	-Detailed dental assessment every 6 months -Panoramic radiograph by the age of 7 years, if not performed earlier
Heart	-Cconduction defects and rhythm disturbances such as Wolff-Parkinson-White syndrome→frequent monitoring & appropriate treatment	-Echocardiogram every 1 - 3 years in asymptomatic paediatric patients until regression of cardiac rhabdomyoma -Symptomatic → more frequent -ECG every 3 - 5 years in asymptomatic patients of all ages to monitor for conduction defects
Eyes	-Intervene as appropriate when clinical concern arise	-Annual ophthalmological examination in patients with previously identified eye lesions or vision symptoms -More frequent assessment(including individuals on Vigabatrin) → not recommended unless new clinical concerns arise

TSC: A Retrospective review

- To contribute to a better understanding of TSC in our province
- It will help raise awareness of the variable presentation of this condition
- Advocate for appropriate treatment for affected children
- A previous clinical audit on TSC in KZN focused primarily on epilepsy.
- This study aims to collect more data on TAND and systemic complications.

TSC: A Retrospective review

Title: The clinical spectrum and outcome of children with Tuberous Sclerosis Complex over a 10-year period at Inkosi Albert Luthuli Central Hospital, South Africa.

Aim of the study:

- To describe the clinical profile children with Tuberous Sclerosis Complex
- To assess the clinical, radiological and psychiatric influencing the outcomes and severity of disease in children with TSC.

Objectives

- To describe the clinical presentation, complications and progress of children with TSC complex presenting to a quaternary care hospital.
- To describe the radiological findings of this group of children.
- To describe the comorbid conditions in TSC: epilepsies, psychiatric and multiorgan complications.
- To assess the severity of the disease and its outcome.

Conceptual framework of the study of TSC outcome at Paeds Neurology Clinic of IALCH

Dependent variables

Skin/ Oral cavity

- Hypomelanotic macules
- Angiofibromas
- Fibrous cephalic plaque
- Ungual fibromas
- Shagreen patch
- Confetti skin lesions
- Dental enamel pits
- Intraoral fibromas

CNS

- Cortical tubers
- SEN
- SEGA
- Cerebral white matter radial migration lines
- Epilepsy
  - Seizure Semiology
- TAND – Behavioural
  - Psychiatric
  - Intellectual
  - Academic
  - Neuropsychological
  - Psychological

Other Organs: CVS/Renal/

Confounders

- Age at first presentation
- Compliance
- Socioeconomic status
- Family History of TSC

Independent variables

- Age
- Sex
- Antiseizure medication
- Non-Seizure medication
- Complications
- Surgical intervention
- Frequency of hospital admission

Methodology

Study Design

- The study will be an institution-based retrospective, descriptive study on children with a confirmed TSC-1.
- Describing the epidemiology, clinical profile, radiological characteristics, co-morbidities and outcomes of children with Tuberous Sclerosis Complex.
- Retrospective review of outpatients at a Paediatric Neurology Clinic and Inpatient medical records will be done using data from an existing IALCH database

Study site

- The study will be conducted at a level IV Tertiary/ Quartenary Hospital at Inkosi Albert Luthuli Central Hospital, Durban, South Africa

Population study

- The study will involve children of all ages less then 15yrs known to Paediatric Neurology Clinic at IALCH
- The study will involve both inpatients and outpatients

Inclusion/Exclusion criteria

Using the Updated Diagnostic Criteria of TSC (2021)

Patient selection

Exclusion criteria

- More than 15 years of age
- Patients not fulfilling the diagnostic criteria for TSC

Inclusion criteria

- TSC confirmed using a Updated Diagnostic Criteria of TSC (2021)
- All children less than 15 years of age

Sample size

- All patients with TSC presenting to the Paediatric Neurology Clinic
- As compared to previous similar studies with less sample size

Materials and Methods

- Patients with a confirmed diagnosis of TSC, in a 10-year period between January 2015 to December 2024 will be identified from the neurology patient registry.
- The demographic, baseline clinical and radiological features of the selected patients will be captured on a data sheet.
- Complications of the presenting features
- Intervention and response to treatment will be assessed
- Assess the relationship between TAND and epilepsy
- Variability of presenting clinical and radiological features between siblings
- Factors influencing outcome will be assessed

Conclusion

- TSC is a severe and debilitating neurocutaneous disease.
- TSC poses high economic burden on both the government and community.
- The level of screening, diagnosis, and treatment for patients with TSC lags behind in SA.
- There is paucity of epidemiological data in Africa.
- TAND clinical manifestations significantly impact the quality of life of the patient, their family and the broader community, highlighting the need for further research and increased awareness.
- Effective diagnosis and surveillance will greatly reduce the burden of the disease.

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THANK YOU