

Tuberøs sklerose årsmøde 2023

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Center for Sjældne Sygdomme



- Kompleks multi-organ med behov for højt specialiseret opfølgning
- Udredning og opfølgning af patienter fra hhv vest- og øst-Danmark
- Behandling
- Koordination
 - mellem alle sygehusspecialer
 - Koordination med lokalt sygehus omkring opfølgning og udredning
- Videnscentre

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Tuberøs sklerose

- Tuberous sclerosis complex (TSC)
- Billede i hudbog år 1835
- Bourneville 1880
 - Tuber: knold
 - Skleros: hård
- 1:6000 dvs 1000 i DK



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Hvornår har man TS ?



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Diagnostiske kriterier

• **Hovedkriterier**

- Hypomelanotiske maculae
- Angiofibromer (min 1)
- Unguale fibromer (min 1)
- Shagreen plet
- Multiple retinale hamartomer
- Multiple Corticale tuber
- Subependymale noduli (min 2)
- Subependymale kæmpecelle astrocytomer (SEGA)
- Kardielle rhabdomyomer
- Lymphangiomiomatomer
- Renale angiomyolipomer

• **Bikriterier**

- Konfetti læsioner
- Dentale pits (min 3)
- Orale fibromer (min 2)
- Retinal hypopigmentering
- Multiple renale cyster
- Nonrenale hamartomer
- Scleroserende knogle læsioner

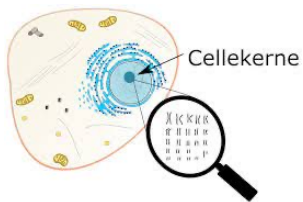
Sikker diagnose
2 hovedkriterier *eller*
1 hovedkriterie og >1 Genetik

Mulig diagnose
1 hovedkriterie *eller*
>1 bikriterier

Northrup et al. Updated International Tuberous Sclerosis Complex Diagnostic Criteria. Pediatr Neurol 2022

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Genetik



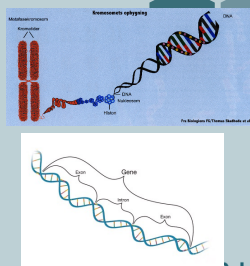
Mio celler
Cellekerne
Arvemateriale

6

Genetik

- Kromosomer og gener

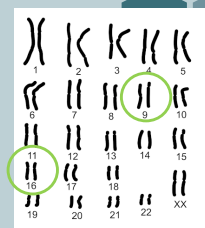
Pige	Dreng
1	1
2	2
3	3
4	4
5	5
6	6
7	7
8	8
9	9
10	10
11	11
12	12
13	13
14	14
15	15
16	16
17	17
18	18
19	19
20	20
21	21
22	22
23	23



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Genetik TS

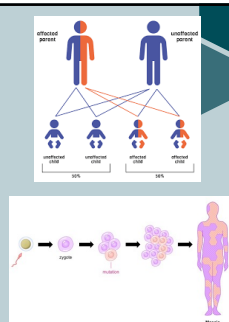
- TSC1 kromosom 9 (hamartin)
- TSC2 kromosom 16 (tuberin)
- Sidste 5-8 ?
- 2/3 nyopståede



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Arvegang

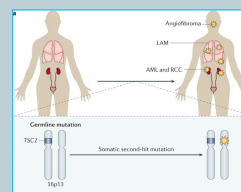
- Autosomt dominant
- Mosaik



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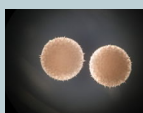
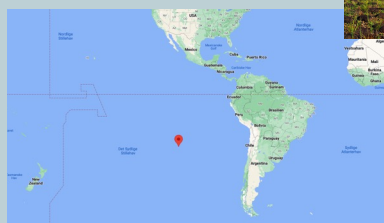
Men det bliver mere indviklet..

- 2-hit hypotesen
- Generationsforskelle
- Forskellig fordeling
 - Sjældent i tubera i hjernen



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Rapanui - Påskeøerne

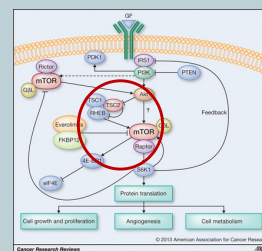


Streptomyces hygroscopicus

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mTOR kaskaden

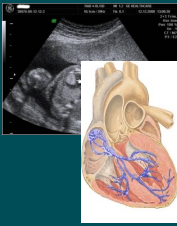
- Rapanui – Rapamycin
- Mammalian target of Rapamycin
- Rapamycin = Sirolimus
- Medvirker til hjernens udvikling
 - Nerveceller
 - Hjernens støtteceller



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Tidlige symptomer

- Knuder i hjertet
- Oftest uden symptomer
- Rytmeforstyrrelse
- Forsvinder oftest med tid



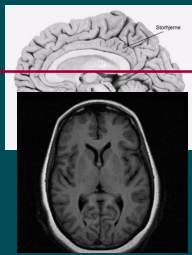
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Epilepsi

- Udgår fra hjernebarken
- Dysfunktion i kommunikation
- 90%
- Kan ændre sig
- Ofte fokale



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Fokalt anfald fra start	Generaliseret anfald fra start	Anfald med ukendt start
Uden bevidstheds-påvirkning		
Med bevidstheds-påvirkning		
Motorisk start	Motorisk: - Tonisk-klonisk - Anden motorik	Motorisk: - Tonisk-klonisk - Anden motorik
Ikke-motorisk start	Ikke-motorisk: - Absence	Ikke-motorisk
Fokalt til bilateralt tonisk-klonisk		Uklassificerbart

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Anfald med fokalt start

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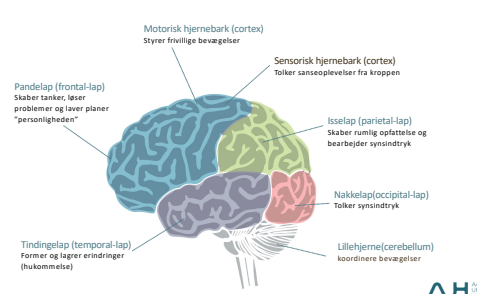
graph TD
    A[Anfald med fokalt start] --> B[Med bevidsthed]
    A --> C[Uden bevidsthed]
    B --> D[Motorisk start]
    B --> E[Ikke-motorisk start]
    C --> F[Motorisk start]
    C --> G[Ikke-motorisk start]
  
```

Alle kan udvikle sig til fokalt til bilateralt tonisk-klonisk anfald

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Motorisk hjernebark (cortex)
Styrer frivillige bevægelser

Sensorisk hjernebark (cortex)
Tolker sansoplevelser fra kroppen

Pandelap (frontal-lap)
Skaber tanker, løser problemer og laver planer "personligheden"

Tisselap (parietal-lap)
Skaber rumlig opfattelse og bearbejder synsindtryk

Nakkelap (occipital-lap)
Tolker synsindtryk

Tindingelap (temporal-lap)
Former og lagrer erindringer (hukommelse)

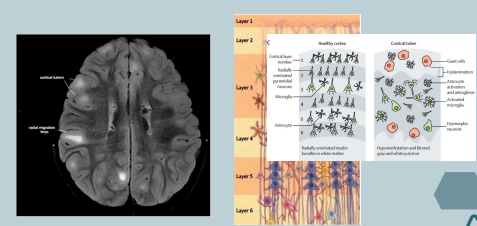
Lillehjerne (cerebellum)
Koordinere bevægelser

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Lidt mere hjerneanatomi



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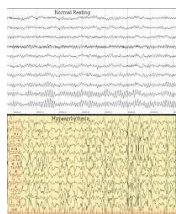
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Infantile spasmer



[video infantile spasmer](#)



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Udredning epilepsi



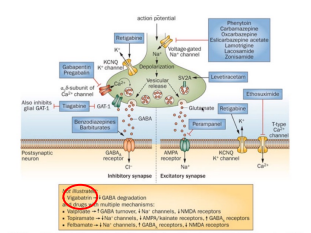
- Anfaldsbeskrivelse/video
- EEG
 - Søvn
 - Video
 - provokation
- MR
- genetik

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Behandling



- Sabrilex
- Behandling før anfald
- Ketogen diæt
- Epi-kirurgi
- m-TOR inhibitors
- Nervus vagus stimulator

"National behandlings- og vejledningsvejledning for epilepsi 2022"

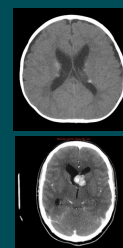
- ☐ Om behandlings- og vejledningsvejledningen
- ☐ Download vejledningen
- ☐ Skriv og print sammenfatning

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- Andre knuder i hjernen
 - Subependymale noduli (SEN)
 - Forkalkninger
 - Kæmpecelle tumorer
 - SEGA
- Barne/unge alder
- Everolimus/kirurgi



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Andre hjerneproblemer

- Høj risiko
 - TSC2
 - Stort tuber volumen
 - Tidlige anfald
- adfærdsforstyrrelser
- autisme
- ADHD
- Børnepsykiatrisk udredning

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ADHD

- Attention deficit fx kan ikke fastholde opmærksomheden
- Hyperactivity fx løber omkring på utilpasset måde
- Flere underpunkter
- Mindst 6 mdr
- tilstede fra barnealder
- Flere situationer
- Medføre vanskeligheder
- Skyldes ikke andet fx depression



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Autisme

- Flere undertyper
 - Infantil
 - Atypisk
 - Asperger
- Opfylde flere kriterier
 - Sprog
 - Socialt samspil
 - Funktionel leg
 - Repetitive og stereotype adfærd- og interessenemønstre
- Øjenkontakt, mimik
- Empati, situationsfølelse
- Sansemæssig sensitivitet

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TSC-Associated Neuropsychiatric Disorders (TAND)

Neurological Level: Epilepsy, Migraine, Headaches, Seizures, Sleep problems, etc.

Psychological Level: Anxiety, Depression, Attention deficit hyperactivity disorder, etc.

Intellectual Level: Intellectual disability, Learning difficulties, etc.

Academic Level: Reading, Writing, Spelling, etc.

Psychosocial Level: Self-esteem, Peer relations, etc.

Neuro-psychological Level: Functional disability, etc.

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Barne/unge år

- Nyrer
- AML mm
- Scannes regelmæssigt
- Biopsi
- Scleroterapi
- everolimus

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Lunger

- voksne
- Kvinder
- Lungefunktion og CT
- Obs østrogen (p-piller)

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Andre organer

- Lever
 - Ofte TSC2
 - Ca 1/3
 - Ofte godartet
- knogler
 - Ofte asymptomatisk

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Multiorgan – brug for netværk

Brain: 90% epilepsy, 50-60% SEN, 10-15% SEGA, 90% TAND, 50% intellectual disability, 40% autism spectrum disorder.

Heart: 90% cardiac rhabdomyoma. Adults: 20% cardiac rhabdomyoma.

Kidney: 70% angiomyolipoma, 35% simple multiple cysts, 5% polycystic kidney disease, 2-3% renal cell carcinoma.

Other: 50% oral fibromas, 50% retinal astrocytic hamartomas.

Lung: Women: 80% asymptomatic LAM, 5-10% symptomatic LAM can lead to respiratory failure. Men and women: 10% MAPH.

Skin: 75% angiokerioma, 20-50% ungual fibroma, 25% fibrous cephalic plaques, >50% shagreen patches, 90% focal hypopigmentation.

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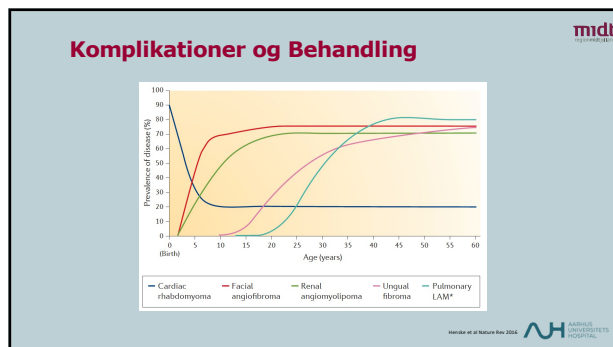
Multiorgan – brug for netværk

FIGUR 1
Koordineret indsats for børn (A) og voksne (B) med tuberose sklerosekompleks (TSC)

KOMPMAN
Publiceret på [Ugeskriftet.dk](https://www.ugeskriftet.dk) 4. november 2019
Udredning, opfølgning og behandling af tuberose sklerose-kompleks

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Komplikationer og Behandling

Clinical manifestation	Diagnosis and monitoring	Management options
Infantile spasms and seizures	• EEG • vEEG	• Steroids • Antiepileptics • Clonazepam • Vigabatrin • Ketogenic diet • Vagus nerve stimulation • Surgical resection
SEGAs	• MRI	• Everolimus • Surgical resection
TANDs	• Periodic screening	• Special educational programmes • Neuropsychiatric evaluation and treatment
LAM	• High-resolution CT scan • Pulmonary function testing • Diffusion capacity • Oxygen monitoring during exercise	• Sirolimus
AMLs	• MRI (preferred) • Renal function tests • CT scan	• Percutaneous embolization • Everolimus • Nephron-sparing surgical resection (avoid if possible) • Ablation by carbon dioxide • Pulse laser dye • Sun protection • Topical squaric acid
Skin lesions	• Periodic examination	

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EXIST studierne

- EXIST-1 Everolimus mod SEGA

THE LANCET
Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial

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EXIST studierne

- EXIST-2 Everolimus mod AML

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EXIST-3 Everolimus mod epilepsi

- Dobbelt-blindt, placebo-kontrolleret fase 3 studie
- Tillægsbehandling ved behandlings refraktær epilepsi ved TS
- 366 patienter (2-65 år)
- 6 uger titrering + 12 uger vedligehold
- Median anfaldsreduktion

Placebo 14,9 %
Lav dosis 29,3 %
Høj dosis 39,6 %

- Få bivirkninger

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Extension Study

Open label (361/366)

Median anfaldsreduktion

- 18 uger 32%
- 1 år 47%
- 2 år 57%

13% holdte pga bivirkninger

- Pneumoni, stomatitis
- 2 dødsfald (pneumoni, sepsis)

Neurology Clinical Practice

Everolimus for treatment-refractory seizures in TSC

Extension of a randomised controlled trial

Adjunctive everolimus for children and adolescents with treatment-refractory seizures associated with tuberous sclerosis complex: post-hoc analysis of the phase 3 EXOS-3 trial

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Protokolleret behandling med everolimus i Danmark

- Everolimus mod behandlingsrefraktær epilepsi ved TS
- RH, AUH (Filadelfia)
- Opstart aug 2017
- Evaluering af behandlingseffekten efter 4 og 12 måneders behandling

Starting criteria

- TSC diagnosis (clinical or genetic criteria)
- Medically refractory epilepsy
- NVSI ketogenic diet considered
- Frequent seizures with great impact on daily life (≥ weekly seizures)
- No contraindications to everolimus
- Expected good compliance

Stop criteria

- Seizure reduction < 33% after 6 months of adequate p-everolimus levels
- Seizure reduction < 50% after 12 months of adequate p-everolimus levels
- Intolerable side effects

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Everolimus bivirkninger

Mange blodprøver
Åben indlæggelse (infektion)
Behandlingsjustering ved AE
Grad 1 – se an
Grad 2-3 – reducer dosis eller pause

Adverse event (all patients)	EXOS1 n=100 44 events/100 patients	EXOS2 n=100 44 events/100 patients
Headache	32	18
Diarrhoea	21	48
Stomatitis	20	1
Fatigue	22	1
Nausea/vomiting	18	24
Weighting	17	13
Upper respiratory tract infection	15	18
Cough	14	18
Congest	13	28
Stomach	13	13
Head	12	1
Arthralgia	10	1
Myalgia	10	1
Acute rise in liver enzymes	1	1
Headache	1	1
Diarrhoea	1	1
Stomatitis	1	1
Weighting	1	1
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Diarrhoea	1	1
Stomatitis	1	1
Weighting	1	1
Upper respiratory tract infection	1	1
Arthralgia	1	1
Myalgia	1	1
Acute rise in liver enzymes	1	1
Headache	1	1
Diarrhoea	1	1
Stomatitis	1	1
Weighting	1	1
Upper respiratory tract infection	1	1
Arthralgia	1	1
Myalgia	1	1
Acute rise in liver enzymes	1	1
Headache	1	1
Diarrhoea	1	1
Stomatitis	1	1
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