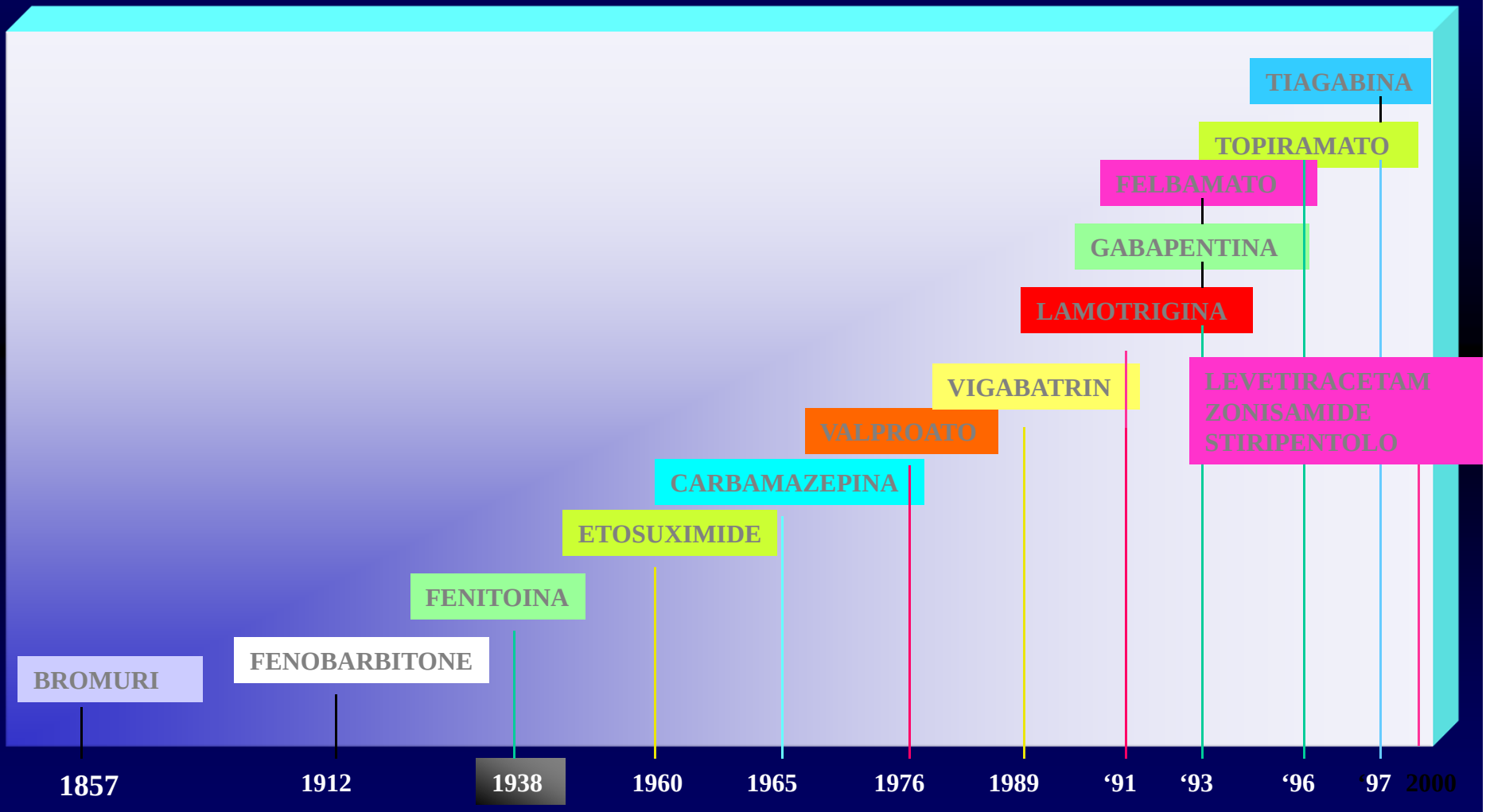
EVOLUZIONE NEL TEMPO DEL TRATTAMENTO CON ANTIEPILETTICI



Perché i nuovi farmaci antiepilettici?

- 30% dei pazienti non controllati con i "vecchi farmaci"
- Tentare di ridurre gli effetti collaterali dei vecchi farmaci

Terapia farmacologica

- Vecchi AEDs
- Acido valproico
- Carbamazepina
- Fenitoina
- Fenobarbital
- Etosuccimide
- Clonazapam
- Clobazam

- Nuovi AEDs
- Vigabatrin
- Lamotrigina
- Topiramato
- Levetiracetam
- Gabapentina
- Tiagabina
- Zonisamide
- Felbamato

Fenobarbital

- PB, Gardenale, Luminale
- Attivo in tutte le forme di epilessia, tranne le assenze tipiche
- Efficace→ crisi convulsive primariamente generalizzate o secondariamente generalizzate
- Basso costo→ antiepilettico più prescritto nel mondo
- Emivita→ lunga (una sola dose quotidiana)
- Efficacia→ valutata solo > 3-4 settimane
- Induttore enzimatico
- Paesi industrializzati→ PB non più di 1° scelta

Fenobarbital

Effetti collaterali

- Inizio trattamento
- Eruzioni cutanee allergiche
- Sedazione (adulto)
- Eccitazione (bambino)

- In cronico
- Riduzione vivacità intellettuale e capacità di concentrazione
- Aumento tempi di reazione
- Osteopenia/osteoporosi
- Sindromi algodistrofiche e m. di Dupuytren
- Sospensione brusca→ rischio ricomparsa crisi

Fenitoina

- PHT, Dintoina
- Crisi parziali e secondariamente generalizzate
- No→ assenze tipiche
- I.V.→ terapia stato di male
- Farmacocinetica non lineare→ possibili neurotossicosi

Fenitoina

Effetti collaterali

- A medio termine

- Ipertrofia gengivale
- Ingrossamento tratti del volto
- Irsutismo
- Seborrea
- Acne

- A lungo termine

- Alterazioni funzioni cerebellari
- Osteopenia/osteoporosi

Carbamazepina

- CBZ, Tegretol, Tegretol CR
- Crisi parziali e secondariamente generalizzate
- No→ forme generalizzate idiopatiche
- Farmaco di scelta nelle E. Parziali
- Buona efficacia e tollerabilità clinica
- Farmaco di 1° scelta

Carbamazepina

Effetti collaterali

- Fasi iniziali

- Vertigini
- Diplopia
- Atassia
- Difficoltà cognitive
- Allergia cutanea
- Mielodepressione

- A lungo termine

- Modesti disturbi funzioni cognitive
- Osteopenia

Acido valproico

- VPA, Depakin, Depakin Chrono
- Valproato di sodio o di magnesio
- Ampio spettro, attivo su tutti i tipi di crisi
- Efficace→ epilessie generalizzate idiopatiche, ma anche parziali
- Tollerabilità→ più delle volte eccellente
- Funzioni cognitive→ poco compromesse

Acido valproico

- Fasi iniziali

- Gastralgia
- Tremori
- Sonnolenza

- **In cronico**

- Incremento di peso (aumento appetito)
- Tremori di attitudine (dose-dipendenti)
- Epatopatie gravi (eccezionali)
- Iperammoniemia moderata
- Osteopenia/osteoporosi

Osteopenia/osteoporosi

- Fenobarbital, Fenitoina (Andress et al., Arch Neurol, 2002)
- Carbamazepina (Verrotti et al., Epilepsia, 2002)
- Acido valproico (Sheth et al., J. Pediatr.,1995; Sato et al., Neurology, 2001)
- AEDs in pz. < 50 anni→ 40% osteopenici, 10% osteoporotici (Pack e Morrell, Seizure, 2002)
- Nuovi AEDs-→ minori effetti negativi sul metabolismo osseo?

Altri "vecchi" farmaci

- Etosuccimide (ESM, Zarontin)
- assenze tipiche, atipiche, mioclonie

- Primidone (PRM, Mysoline)
- simile al PB

- Acetazolamide (Diamox)

Antiepilettici di complemento

- Benzodiazepine
- Diazepam (Valium, Ansiolin, Tranquirit, Noan)
- E.V.→ terapia d'urgenza delle crisi e stato di male
- E.R.→ Micronoan 5 e 10 mg
- Clobazam (Frisium, Urbanyl)→ add-on epilessie resistenti
- Nitrazepam (Mogadon)

Nuovi farmaci antiepilettici

- Indicazioni principali:
- - nei pazienti in cui i farmaci "vecchi"" sono poco efficaci o mal tollerati
- - sempre più spesso come prima scelta in monoterapia (LTG, TPM, LEV)

Nuovi farmaci antiepilettici

- Tali molecole:
- - in genere hanno una buona tollerabilità
- - rispettano maggiormente le funzioni cognitive
- - presentano meno o nessuna interazione farmacologica
- - costo elevato (solo nei paesi industrializzati)

Nuovi farmaci antiepilettici

- Studi di efficacia:

- - soprattutto come farmaci aggiunti

- - in monoterapia

Nuovi farmaci antiepilettici

- Vigabatrin
- Felbamato
- Gabapentina
- tiagabina

- Lamotrigina
- Topiramato
- Levetiracetam
- Oxcarbazepina

Vigabatrin

- GVG, Sabril
- Indicazioni→ molto ridimensionate dopo l'individuazione di deficit concentrico del campo visivo in soggetti trattati a lungo termine (35-40%)
- -S. di West (spasmi infantili)→ sopr. Sclerosi tuberosa
- E. parziali farmacoresistenti agli altri AEDs
- In genere è ben tollerato
- Possibili psicosi acuta irreversibile sopr. in pazienti predisposti

Felbamato

- FBM, Taloxa
- E. parziali, Sindrome di Lennox-Gastaut, spasmi infantili resistenti

- Problema→ epatiti tossiche e aplasie midollari talvolta letali

Gabapentina

- GBP, Neurontin, Aclonium
- Come AED aggiunto→ Epilessie parziali
- Efficacia→ scarsa

Lamotrigina

- LTG, Lamictal
- Indicazioni→ epilessie generalizzate o parziali refrattarie
- Come farmaco aggiunto o in monoterapia
- Ben tollerato (possibile rash cutaneo, vertigine)
- Effetto psicotropo favorevole

Topiramato

- TPM, Topamax
- Epilessie parziali e secondariamente generalizzate; e. generalizzate cripto/sintomatiche
- Tollerabilità→ spesso buona
  ma attenzione alle funzioni cognitive (linguaggio, apprendimento)
- Altri effetti collaterali: calcolosi renale
  riduzione appetito (calo ponderale)

Levetiracetam

- LEV, Keppra
- Epilessie sia parziali che generalizzate
- In genere ben tollerato
- Possibile→ irritabilità, tremori, sonnolenza
- Sia come farmaco aggiunto che in monoterapia

Pregi e difetti dei vecchi e nuovi farmaci

- **Vecchi:**
- - efficacia sicuramente ben nota (la loro disponibilità è senz'altro "rassicurante")
- - PB e PHT→ si cerca senz'altro di non usarli come 1° scelta e, se possibile, neanche come 2° scelta!
- - VPA e CBZ→ sono ancora di 1° scelta nelle forme parziali del bambino e generalizzate (VPA)

Pregi e difetti dei vecchi e nuovi farmaci

- **Nuovi:**
- - come farmaci aggiunti possono determinare il controllo o una marcata riduzione delle crisi
- (es. VPA+LTG nella assenze
- CBZ+TPM o LEV nelle crisi parziali
- Come monoterapia:
- 1° scelta (possibile per LTG, TPM, LEV)
- viraggio in monoterapia

Pregi e difetti dei vecchi e nuovi farmaci

Nuovi farmaci:

- - LTG → ottima tollerabilità
- - LEV→ ottima tollerabilità
- - TPM→ -++
- Efficacia come monoterapia→ da verificare anche se esistono dati che equiparano la loro efficacia ai vecchi farmaci

Pregi e difetti dei vecchi e nuovi farmaci

- Funzioni cognitive→ importantissime
- Migliori AEDs
- Vecchi
- VPA
- CBZ

Nuovi

LTG
LEV
TPM

Efficacia dei farmaci in relazione ad alcuni quadri sindromici

- Sclerosi tuberosa→ GVG
- Sindrome di Lennox-Gastaut→ VPA-LTG-FBM-TPM-GVG
- Spasmi infantili→ GVG
- Assenze→ VPA o LTG
- VPA+LTG VPA+ESM
- Crisi tonico-cloniche→ VPA
- VPA+LTG
- VPA+TPM
- Sindrome di Angelman→ VPA-ESM-LTG-Clobazam
- LEV

Sindrome di Angelman

- **Poco indicati**

- Carbamazepina
- Fenitoina
- Fenobarbital

- **Più efficaci**

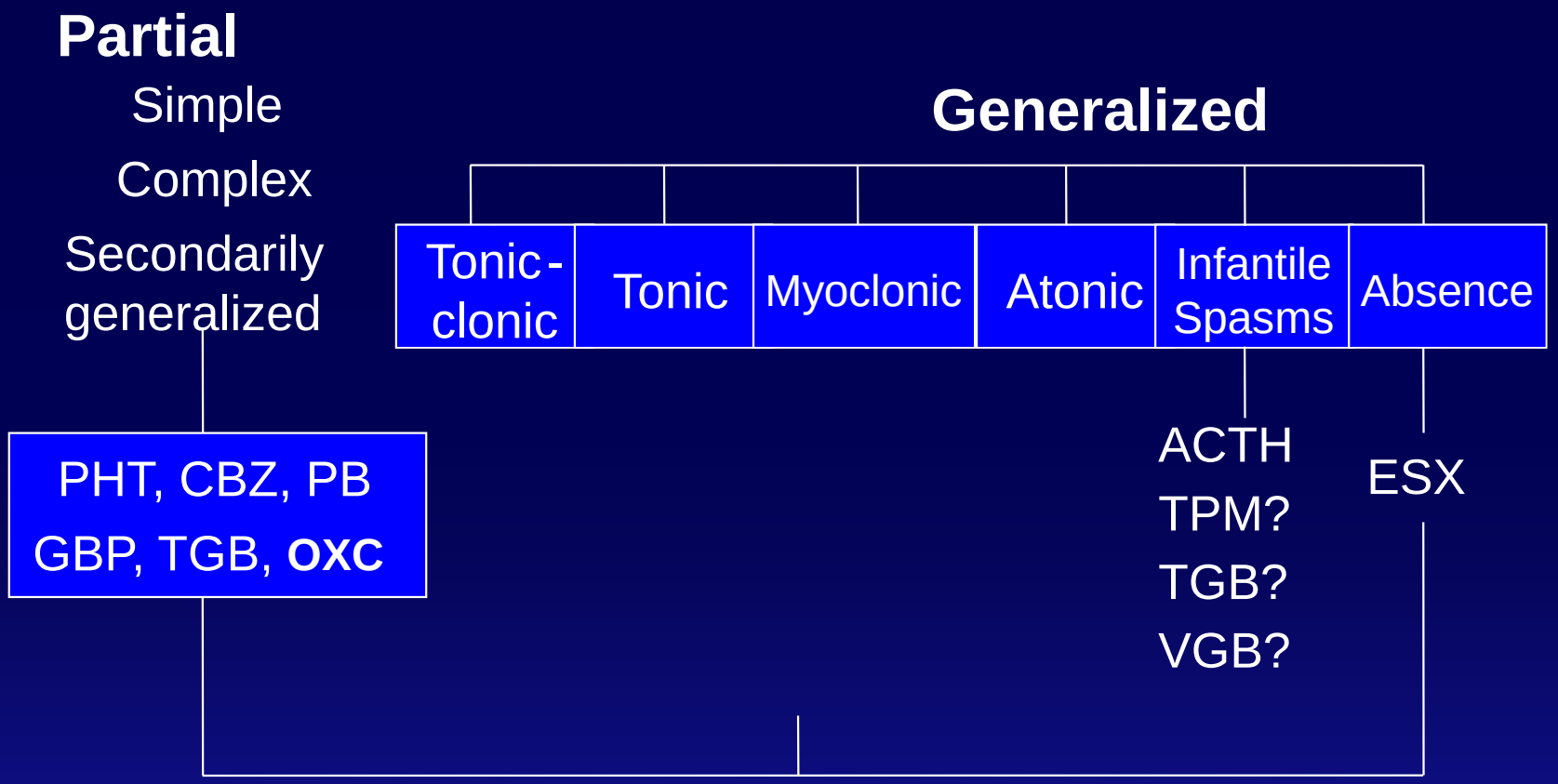
- Acido valproico
- Etosuccimide
- Lamotrigina
- Levetiracetam
- Clobazam
- Clonazepam
- Topiramato
- Piracetam

Proposed therapeuthic scheme for the treatment of symptomatic or cryptogenic partial seizures in childhood

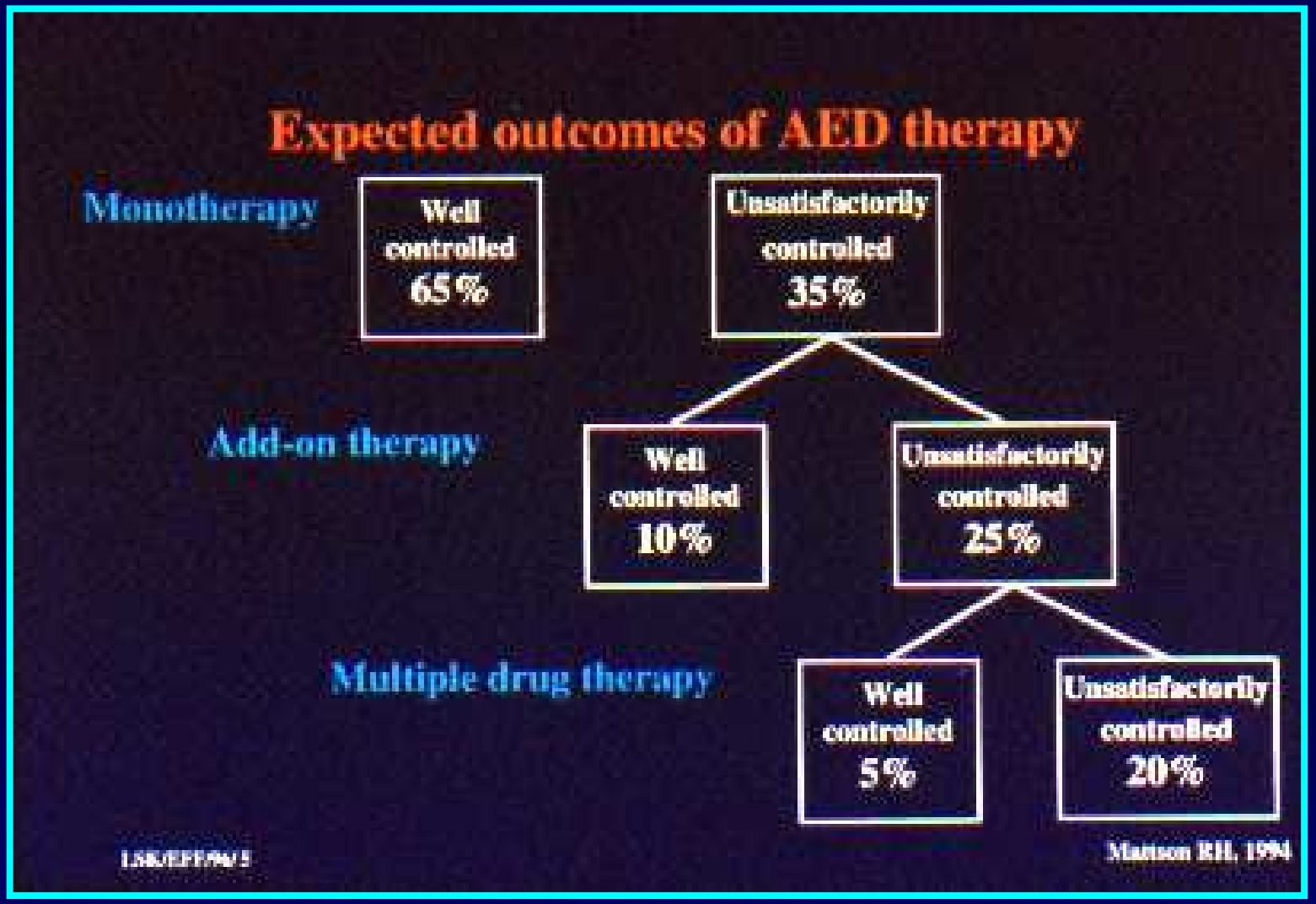
Usually used first-line therapy	Alternative monotherapy or add-on therapy	Possible monotherapy or add-on therapy	Possible add-on therapy in selected patients with refractory seizures
CBZ, VPA	OXC, TPM, GBP, LTG	LEV, PHT, PB, TGB, ZNS, CLB	FBM, KD, VNS

Coppola , CNS Drugs, 2004

Treatment Options



EXPECTED OUTCOMES OF AED THERAPY

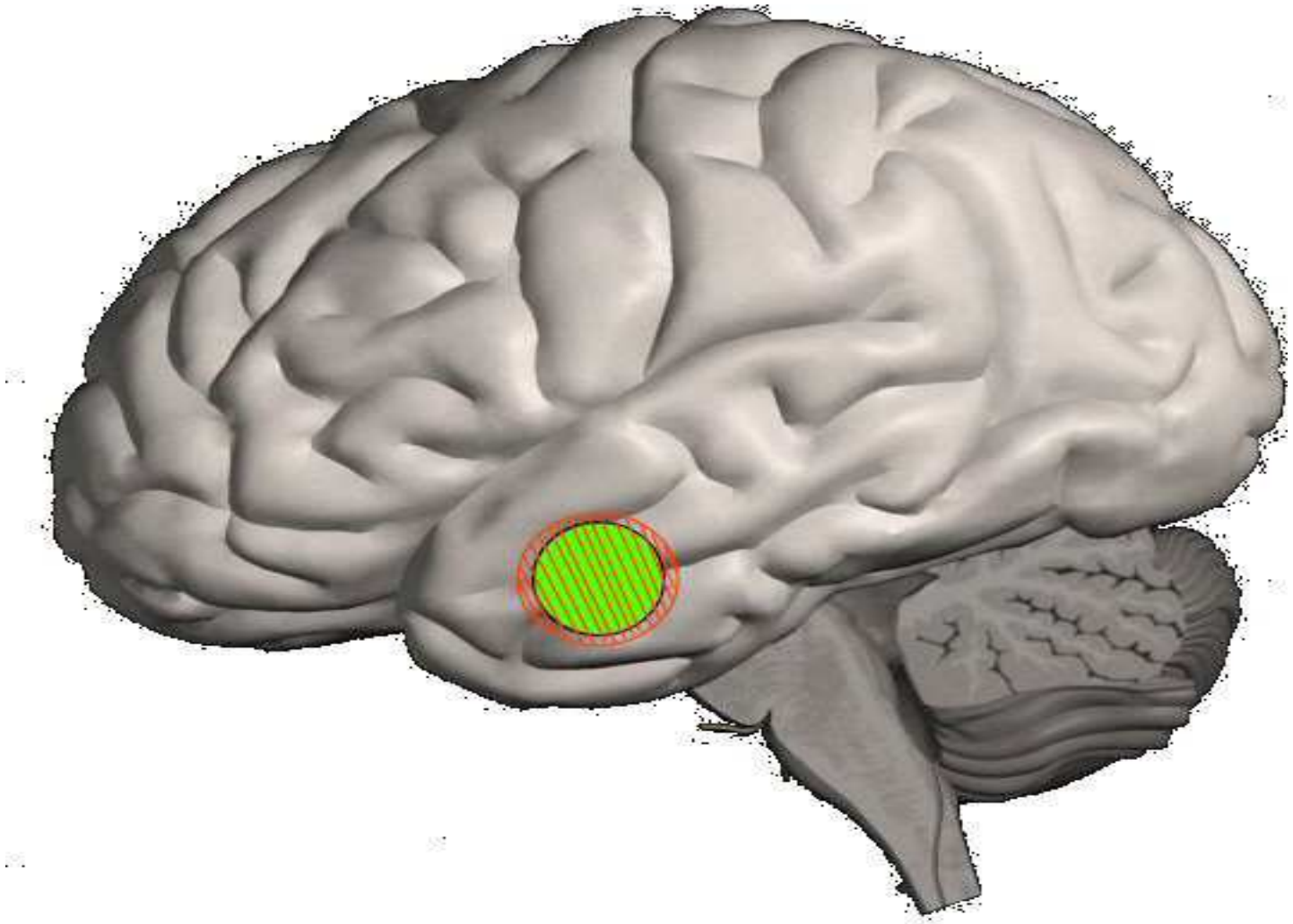


CHILDHOOD EPILEPSY: NEW TREATMENTS

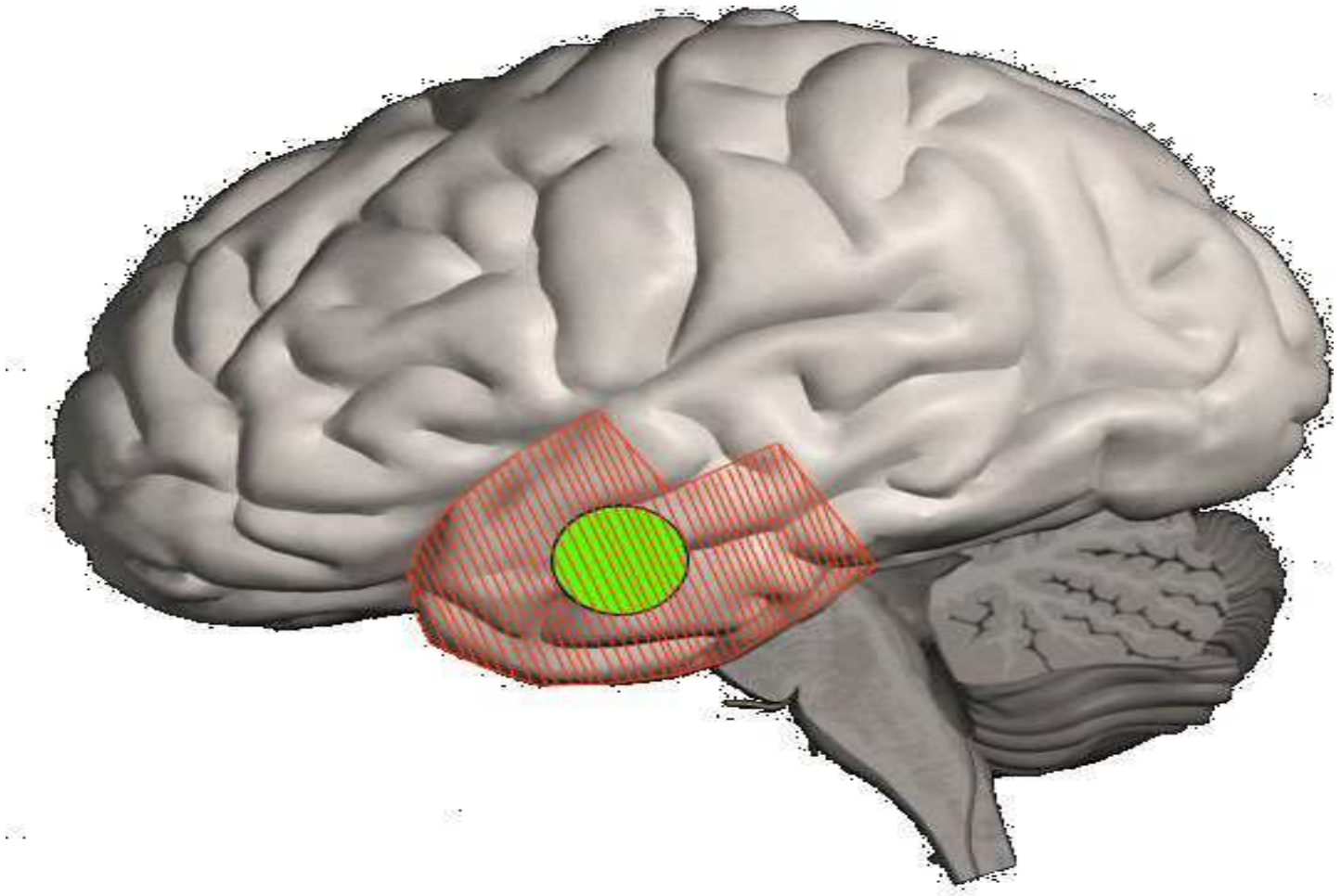
- DRUGS (NEW)

- NON-DRUG THERAPIES
- Surgical therapy
- Radiosurgery
- Left vagus nerve stimulation
- Ketogenic diet
- Deep brain stimulation
- Magnetic transcranial stimulation

CHILDHOOD EPILEPSY: NEW TREATMENTS



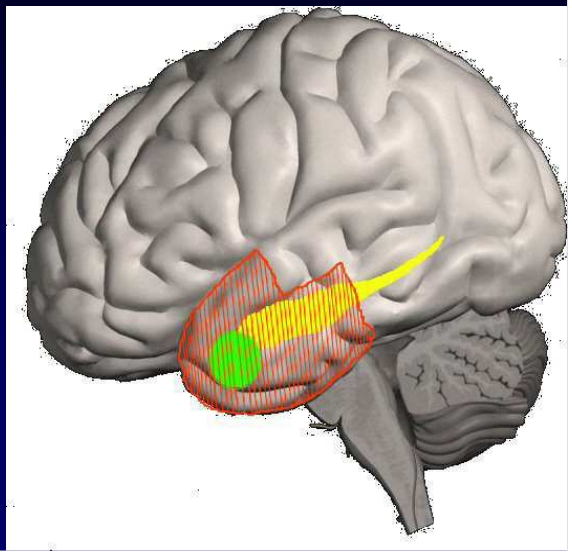
CHILDHOOD EPILEPSY: NEW TREATMENTS



CHILDHOOD EPILEPSY: NEW TREATMENTS

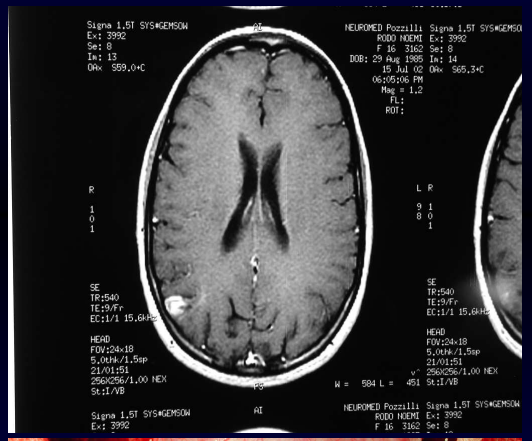
- **Analysis of different types of resections for pediatric patients with temporal lobe epilepsy (Clusmann et al., Neurosurgery, 2004)(1)**

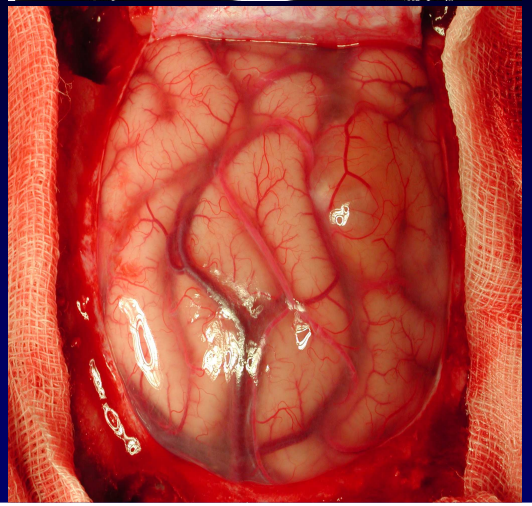
- 89 children
- TLE
- 1- anterior temporal lobectomies
- 2- resections “tailored” to the lesion and presumed epileptogenic area
- Results→ mean follow-up 46 months (14-118)
- 87% → Engel class I (82%) and II (5%)
- 13%→ Engel class III-IV
- Anterior temporal lobectomies→ 94% good outome
- Amigdalohyppocampectomy → 74%
- Lesionectomy plus hyppocampectomy→ 77%



CHILDHOOD EPILEPSY: NEW TREATMENTS

- Extratemporal resections for childhood epilepsy (Sinclair et al., Pediatr Neurol 2004)(2)
- Pathology→ FCD (8)
- brain tumors (6)
- neurocutaneous syndrome (7)
- Rasmussen's encephalitis (2)
- porencephalic cysts (4)
- hypothalamic hcmartoma (1)
- non specific gliosis (6)
- Outcome→ 68.5% Engel class I
- 11% Engel class III
- Improved behavior and psychosocial function after
- surgery in many children.



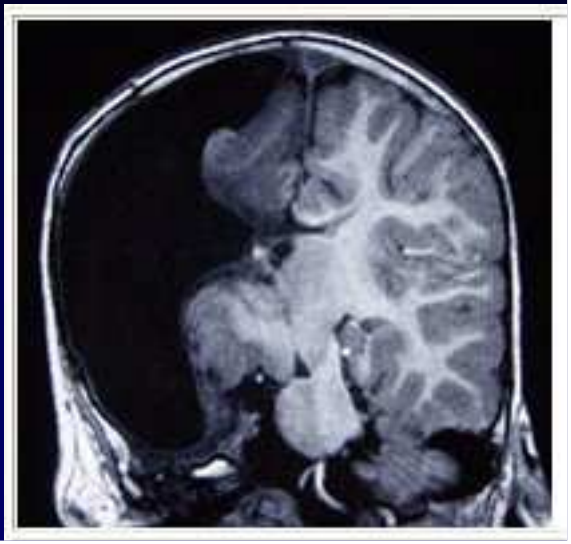


CHILDHOOD EPILEPSY: NEW TREATMENTS

- Hemispherectomy in pediatric populations Vining et al., 1997
- 27 Rasmussen syndrome→ 89% seizure-free
- 24 CD/hemimegalencephaly→ 67% seizure-free

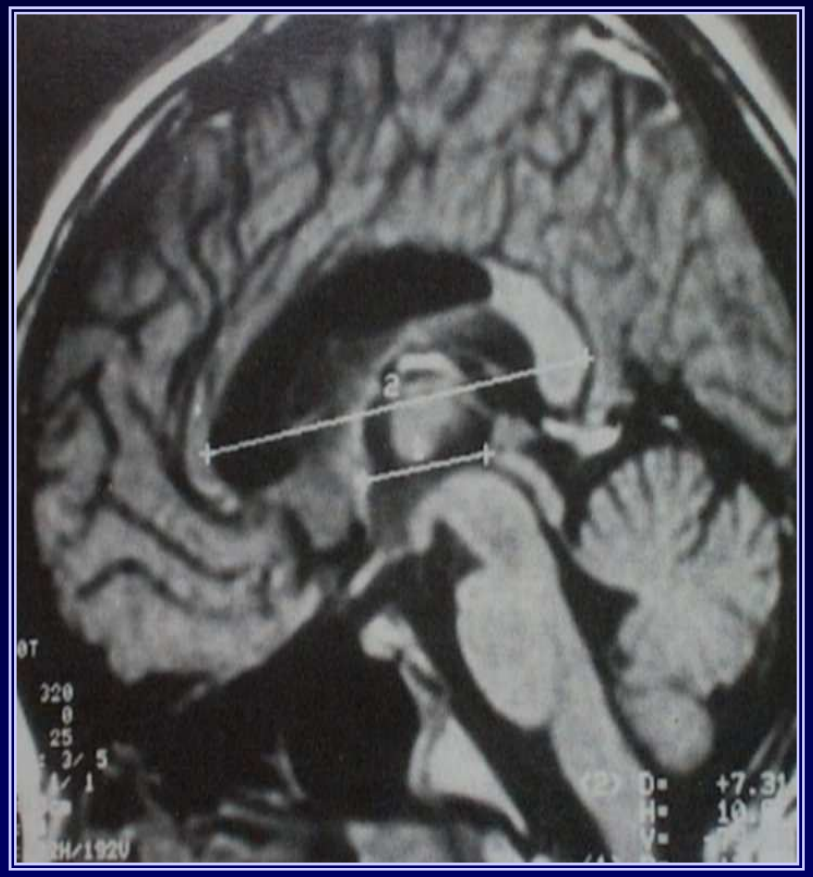
- Kossoff et al. 2002 32 Sturge-Weber syndrome→ 81% seizure-free

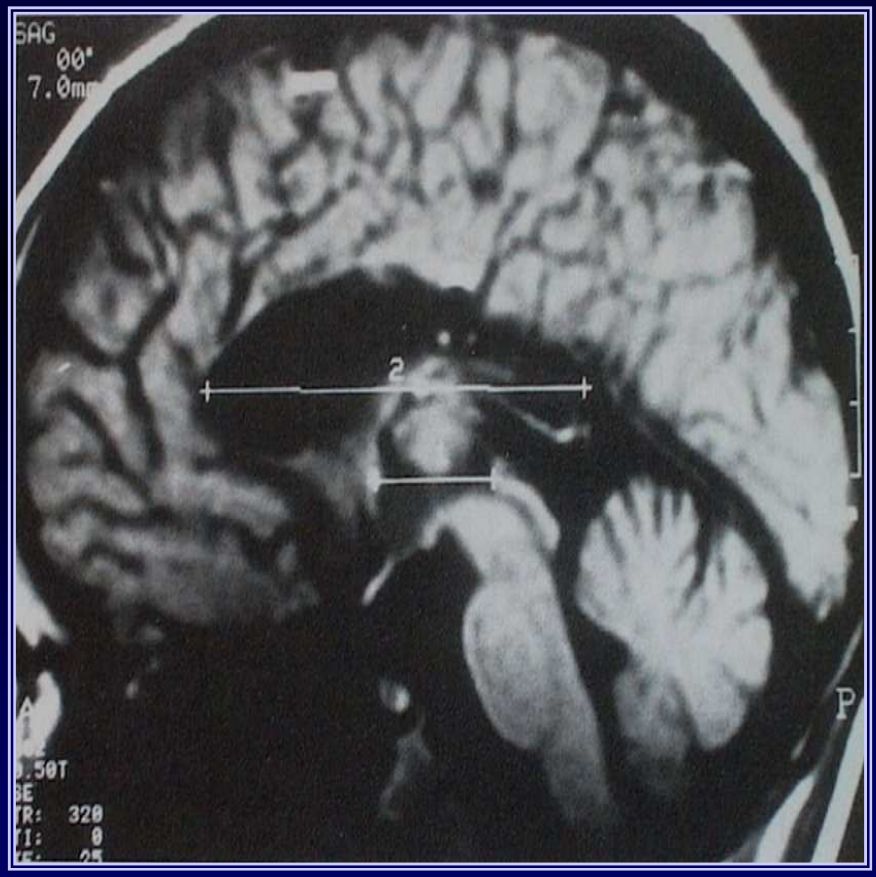
- Pulsifer et al. 2004 71 children-→ 65% seizure-free
- Rasmussen sydnrome, CD, vascular malformations
  Mean age at surgery: 7.2 years
  Follow-up (avarage 5.4 years)



CHILDHOOD EPILEPSY: NEW TREATMENTS

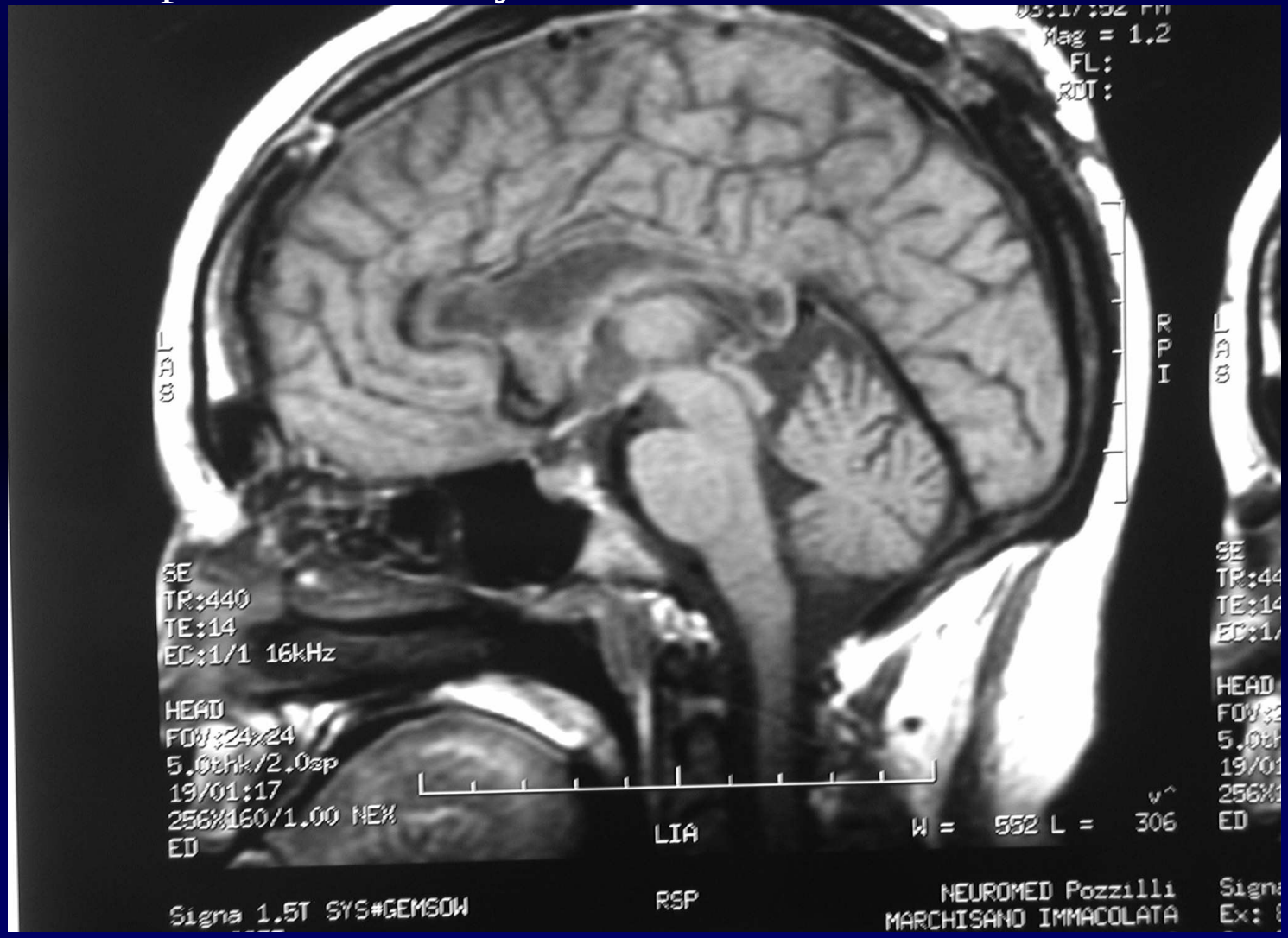
Corpus callosotomy





CHILDHOOD EPILEPSY: NEW TREATMENTS

Corpus callosotomy



CHILDHOOD EPILEPSY: NEW TREATMENTS

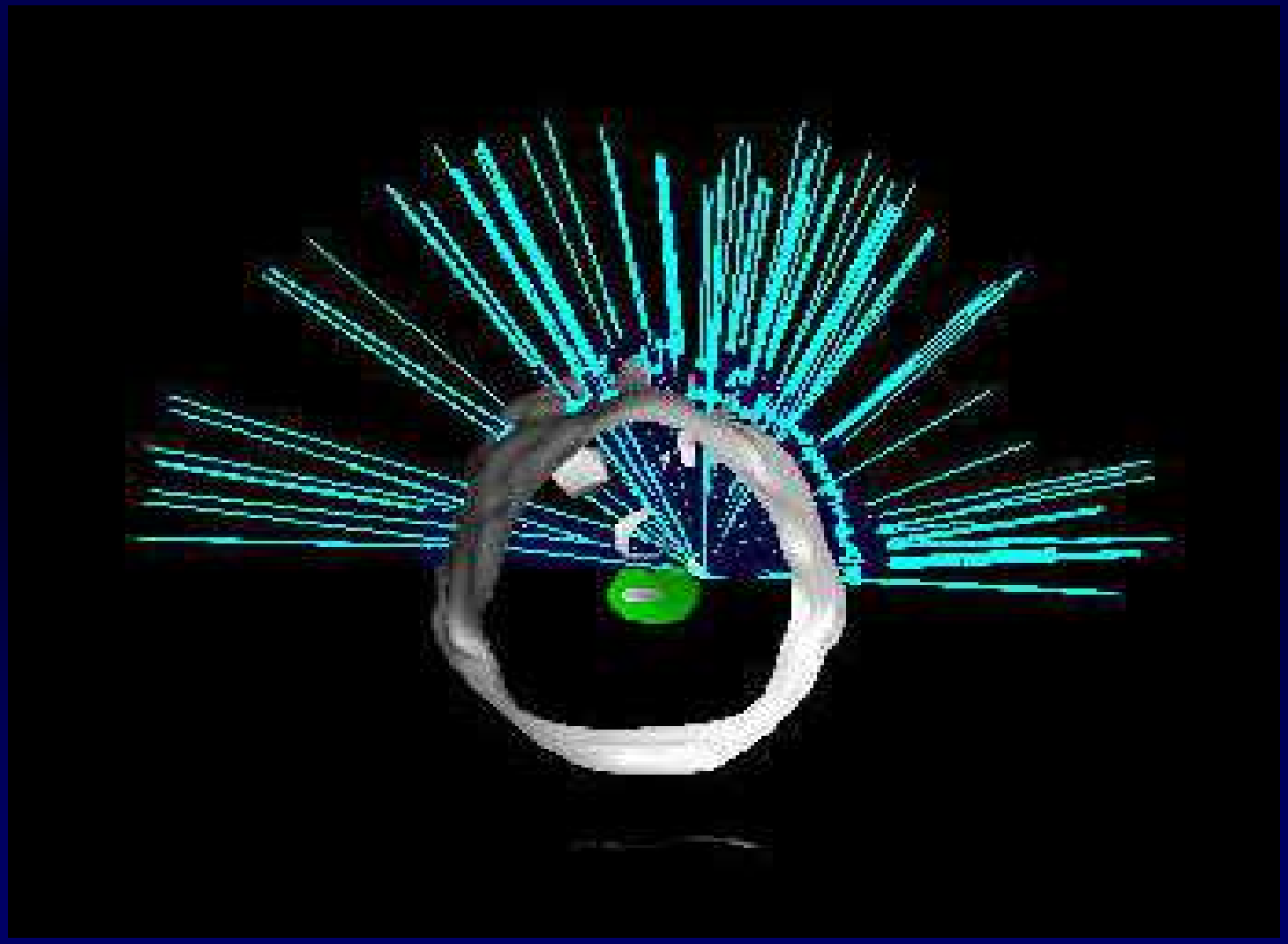
- NON-DRUG THERAPIES
- Surgical therapy
- Radiosurgery
- Left vagus nerve stimulation
- Ketogenic diet

- Magnetic transcranial stimulation (?)
- Deep brain stimulation (?)

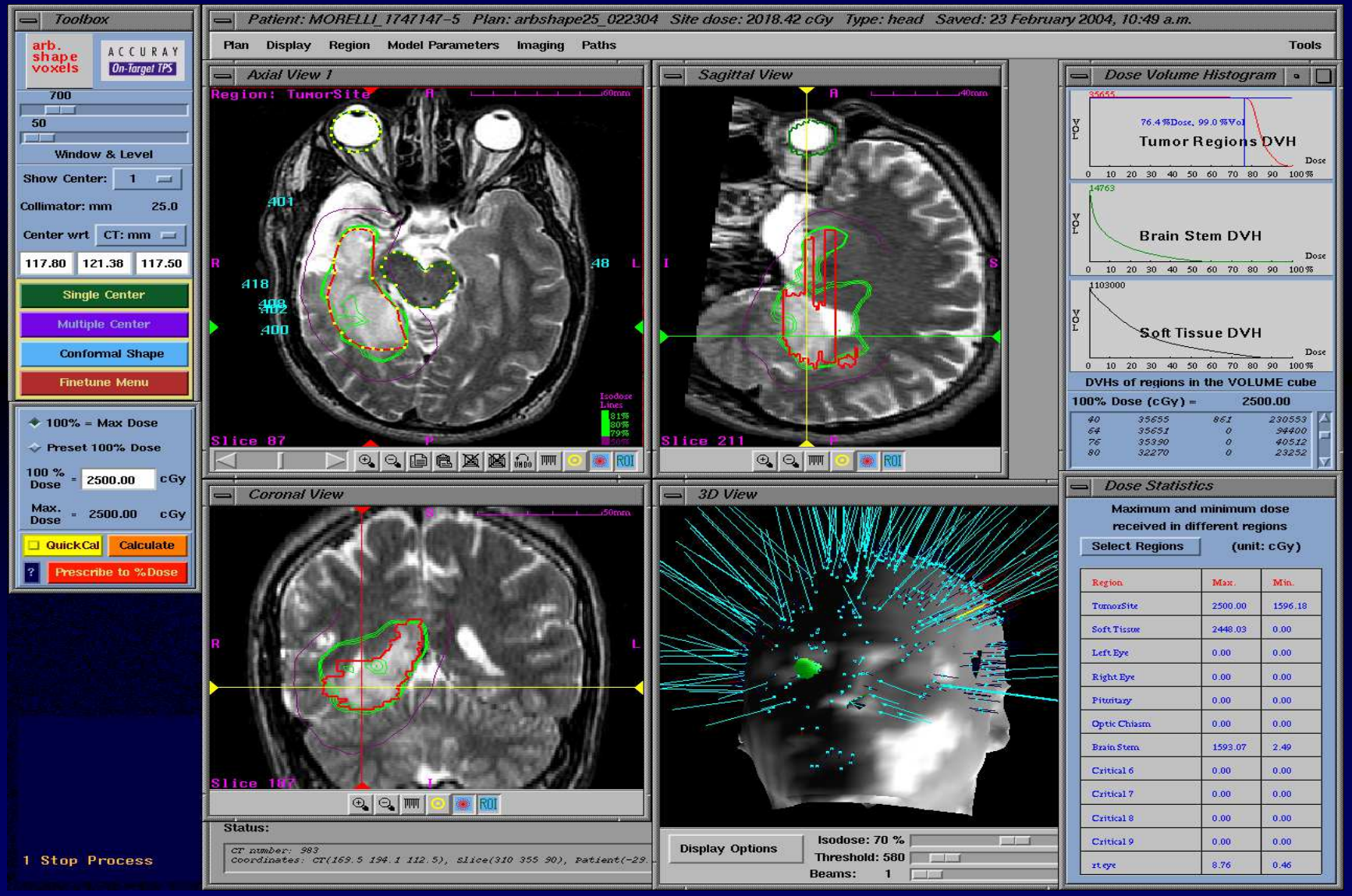
CHILDHOOD EPILEPSY: NEW TREATMENTS

Cyber-knife

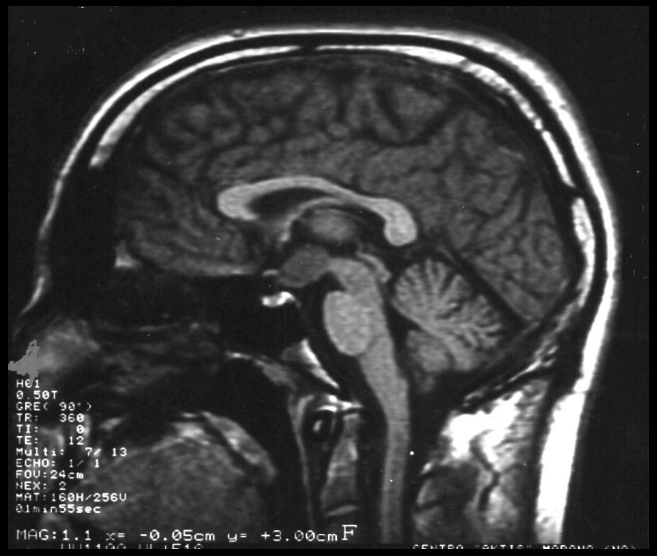
CHILDHOOD EPILEPSY: NEW TREATMENTS

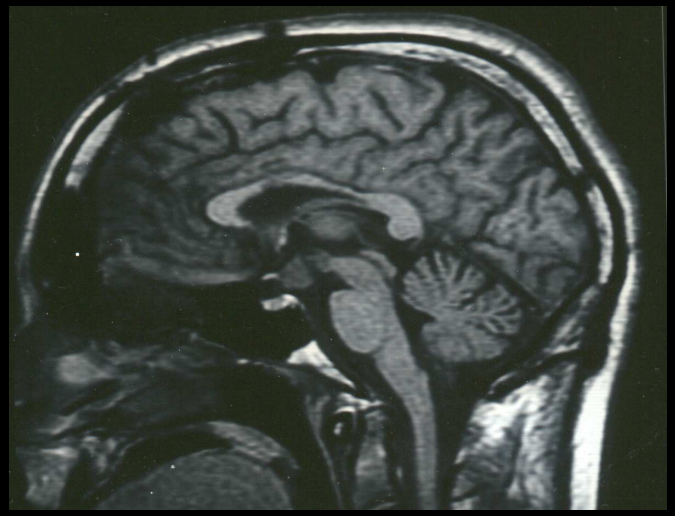


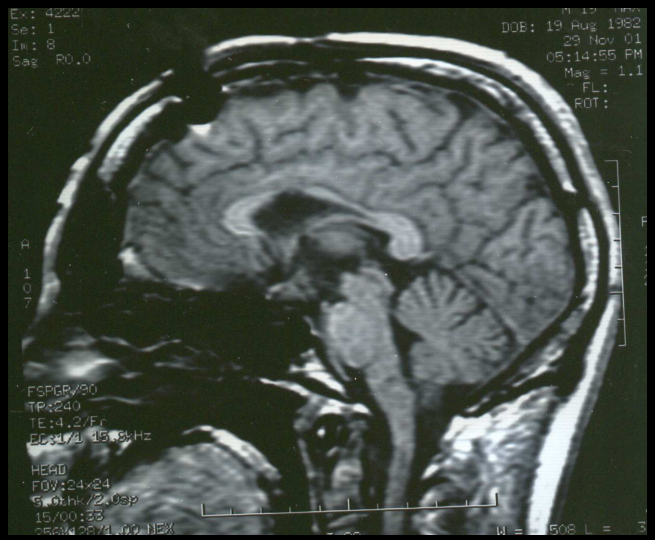
CHILDHOOD EPILEPSY: NEW TREATMENTS

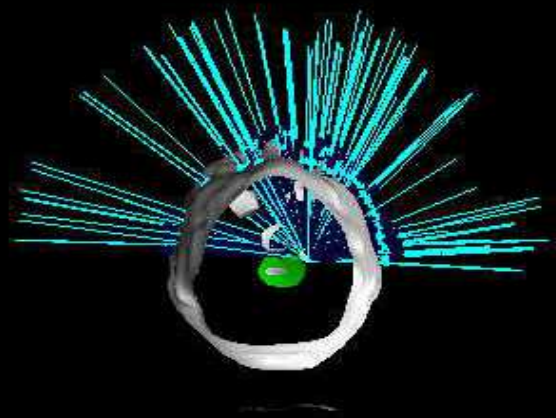


Hypothalamic hamartoma









CHILDHOOD EPILEPSY: NEW TREATMENTS

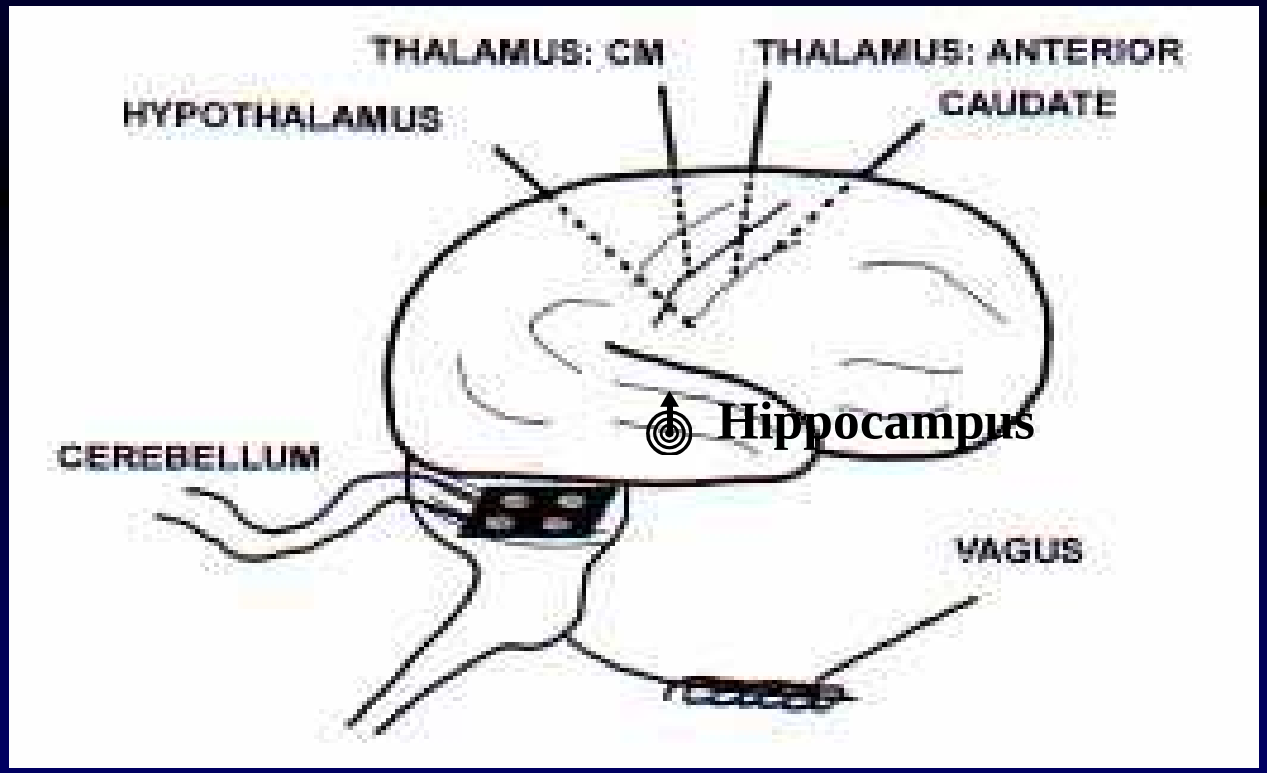
- DRUGS (NEW)

- NON-DRUG THERAPIES
- Surgical therapy
- Radiosurgery
- Left vagus nerve stimulation
- Ketogenic diet

- Magnetic transcranial stimulation (?)
- Deep brain stimulation (?)

CHILDHOOD EPILEPSY: NEW TREATMENTS

Brain stimulations



CHILDHOOD EPILEPSY: NEW TREATMENTS

- DRUGS (NEW)

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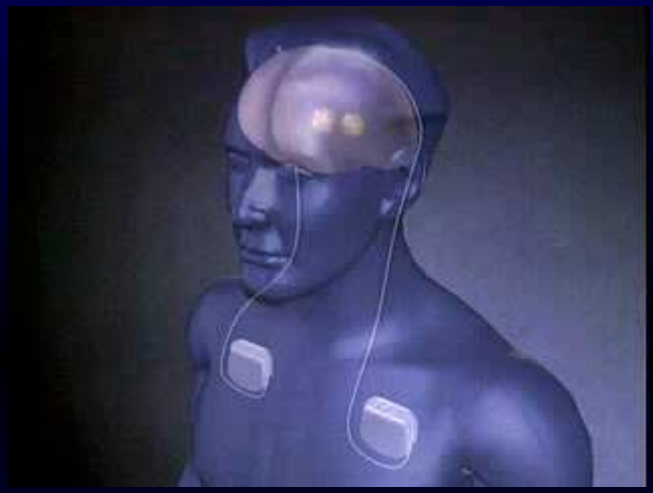
- Magnetic transcranial stimulation (?)
- Deep brain stimulation (?)

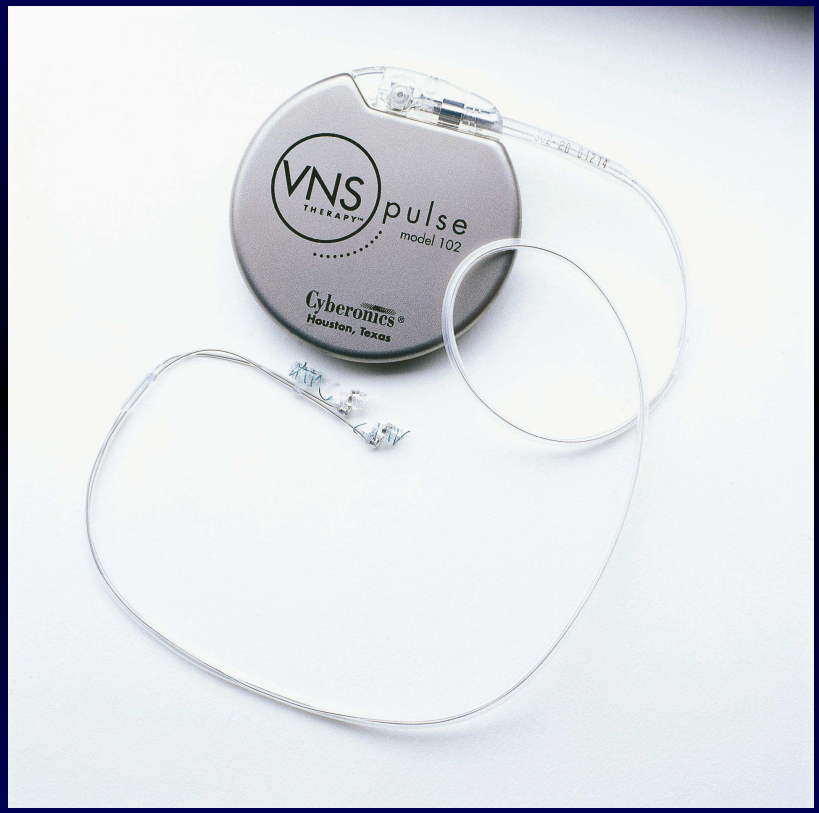
VNS Therapy

- Implantable pulse generator and lead
- Mild electrical pulses applied to the left vagus nerve in the neck send signals to the brain
- Automatic intermittent stimulation
- Magnet use allows patient/caregiver
  - On-demand stimulation
  - On-demand side effect control
- Simple in-office programming
- Assured compliance

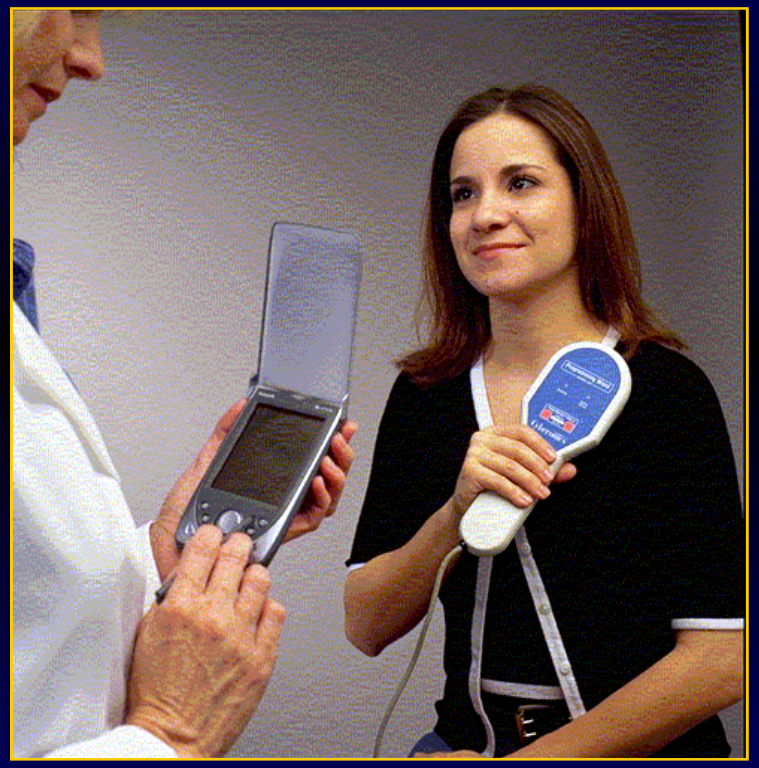


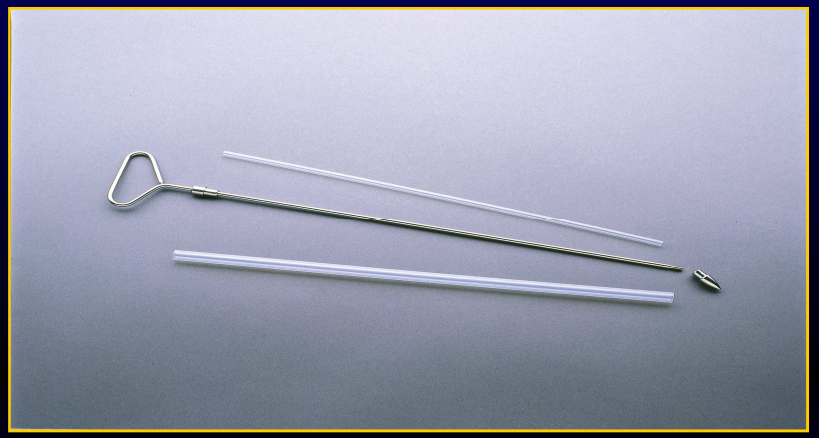
VNS Therapy System: Implanted Components

- Implanted in more than 20,000 patients
- Model 102 Pacemaker-like pulse generator
  - 6.9 mm thick
  - 25 grams
  - 6- to 11-year battery life depending on stimulation parameters



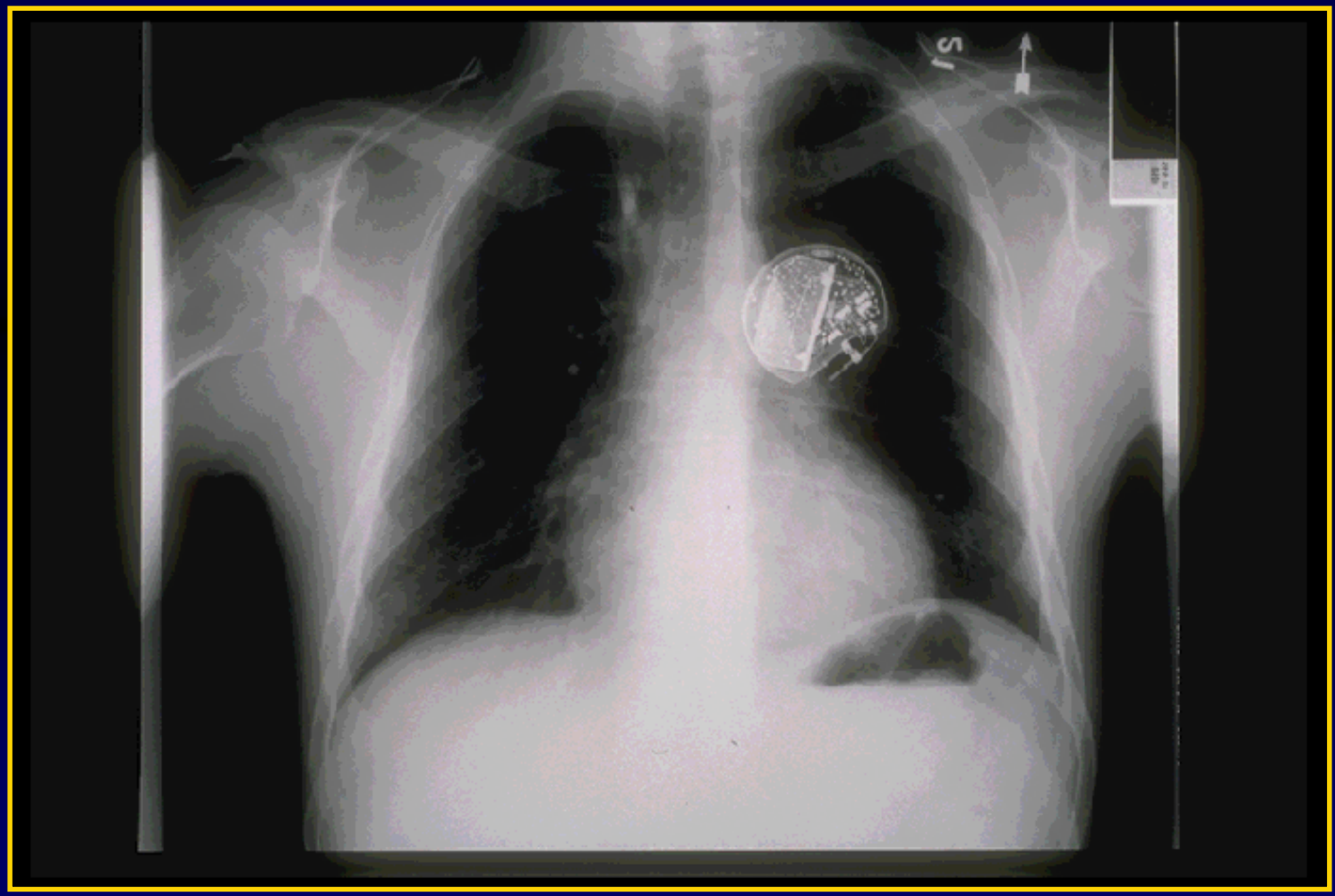
VNS Therapy System: Non-Implanted Components

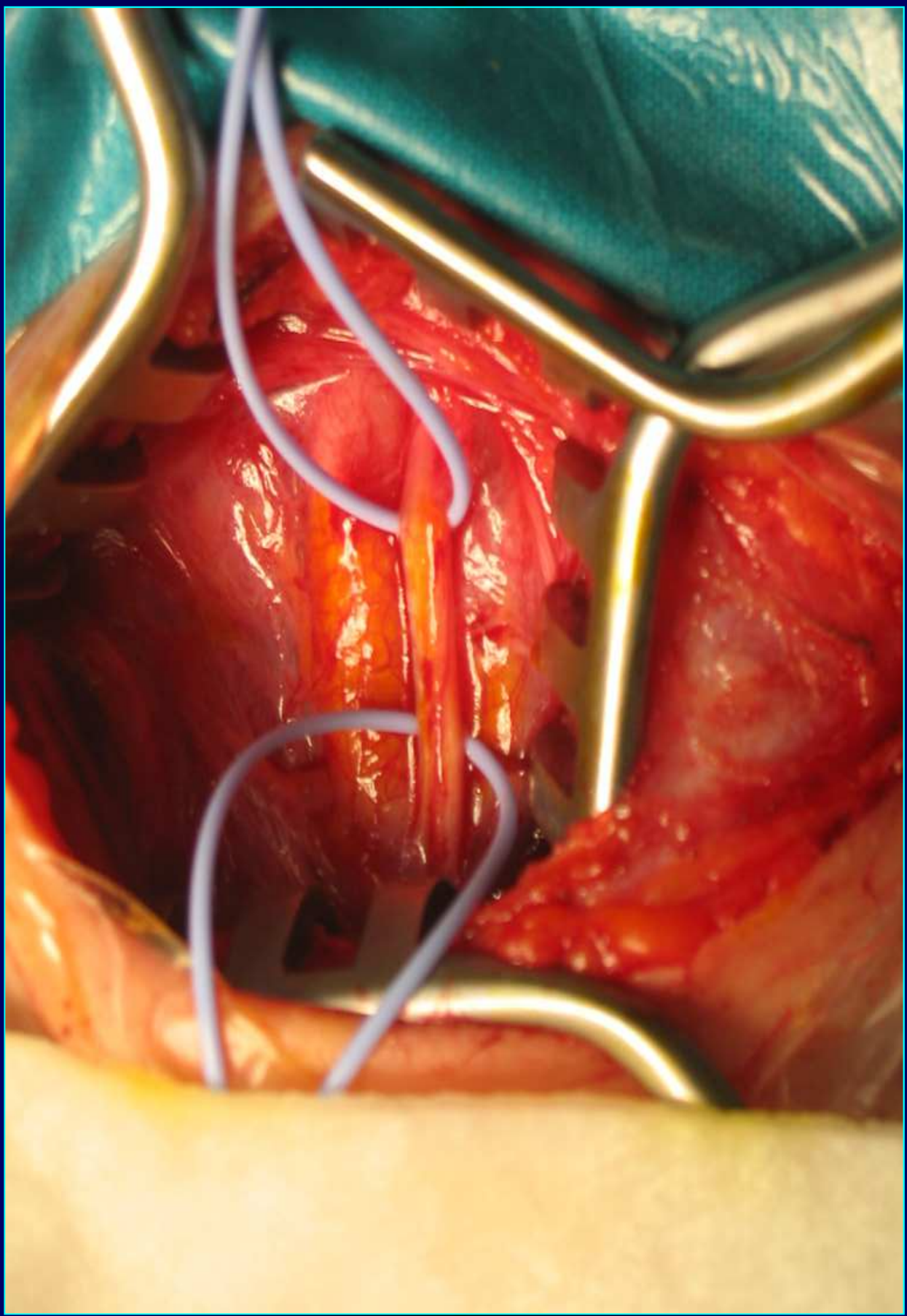


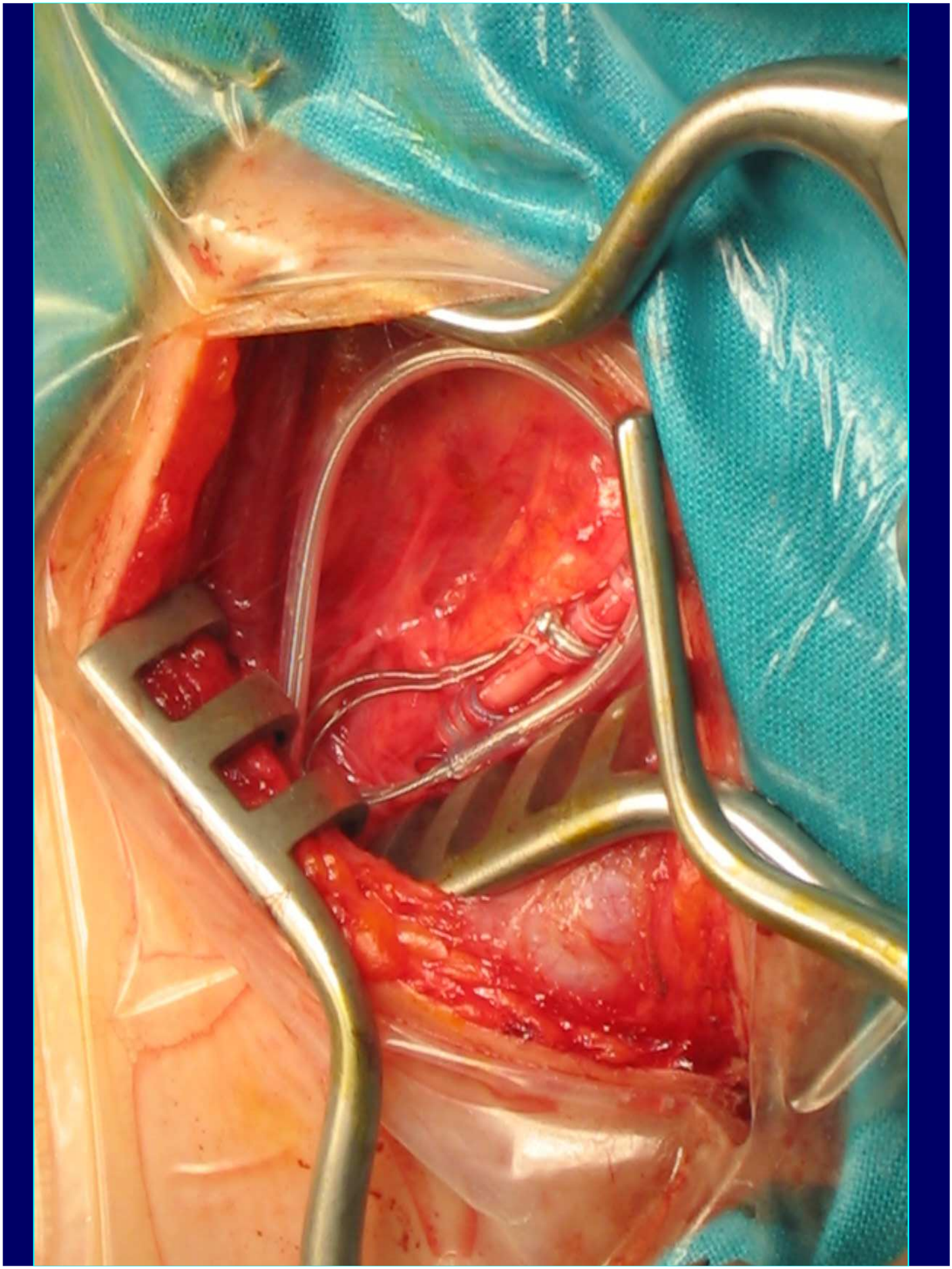


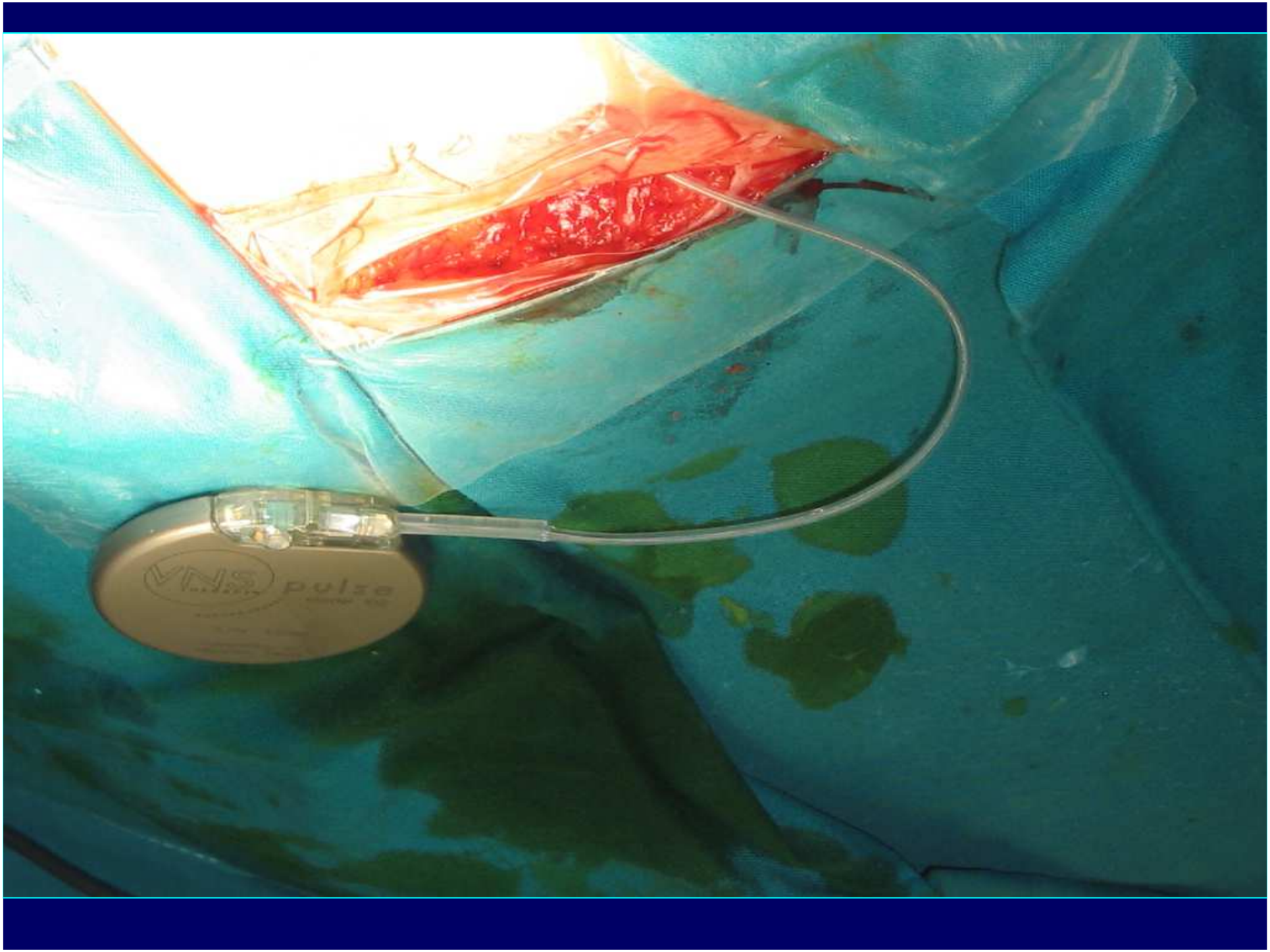
VNS: OPTIMIZING STIMULATION

VNS Therapy








VNS pulse

CHILDHOOD EPILEPSY: NEW TREATMENTS

- **Vagus nerve stimulation in pediatric patients**
- (Murphy et al. Arch Pediatr Adolesc Med, 2003)

- 100 consecutive children
- Avarage age 10.4 years
- 45%→ 50% seizure reduction
- Outcome indipendent of epilepsy duration and age (>=< 12 years)
- 3 pts→ generator infection

STIMOLAZIONE DEL NERVO VAGO

- SVANTAGGI

- NON BEN DEFINITI I CRITERI DI SELEZIONE DEI PAZIENTI.
- COSTOSO
- INVASIVO
- SOSTITUZIONE BATTERIA >3-5 ANNI
- INEFFICACE SE USATO COME MONOTERAPIA

CHILDHOOD EPILEPSY: NEW TREATMENTS

- DRUGS (NEW)

- NON-DRUG THERAPIES
- Surgical therapy
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- Left vagus nerve stimulation
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THE KETOGENIC DIET IN CHILDHOOD REFRACTORY EPILEPSY

- THE KETOGENIC DIET IS AN INDIVIDUALLY CALCULATED AND RIGIDLY CONTROLLED, HIGH-FAT, LOW- PROTEIN, LOW-CARBOHYDRATE DIET USED FOR THE TREATMENT OF DIFFICULT-TO-CONTROL SEIZURES.

- ORIGINALLY DEVELOPED IN THE 1920S, THIS DIET WAS DESIGNED TO MIMIC THE BIOCHEMICAL CHANGES ASSOCIATED WITH STARVATION.

- THREE TYPES OF KD: “CLASSICAL”, “ MCT DIET”,“ “MODIFIED MCT”.

Ketogenic diet

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Short Communication

The ketogenic diet in children, adolescents and young adults with refractory epilepsy: an Italian multicentric experience

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Abstract

Purpose: This collaborative study by three Italian groups of child neuropsychiatrists was carried on to evaluate the efficacy and safety of the classic 4:1 ketogenic diet as add-on treatment in refractory partial or generalized epilepsy in children, adolescents and young adults. *Methods:* We performed a prospective add-on study in 56 refractory epilepsy young patients (age 1–23 years, mean 10.4 years), all with both symptomatic and cryptogenic, generalized or partial epilepsies. Child neuropsychiatrists worked with nutritional team for sample selection and patients management. The ketogenic diet was added to the baseline antiepileptic drugs and the efficacy was rated according to seizure type and frequency. During treatment, seizure frequency, side effects, urine and blood ketone levels and other parameters were systematically evaluated. *Results:* Patients have been treated for 1–18 months (mean 5 months). A >50% reduction in seizure frequency was gained in 37.5 and 26.8% of patients after 3 and 6 months, respectively, at 12 months, this number fell by 8.9%. No significant relationship between diet efficacy and seizure or epilepsy type, age at diet onset, sex and etiology of epilepsy was noted. Nevertheless, it seems noteworthy that 64% of our patients with neuronal migration disorders improved on this diet. Adverse effects occurred, mainly in the first weeks of treatment, in 32 patients (57.1%), but were generally mild and transient. In seven patients (12.5%) it was possible to withdraw one to two AED after 3–4 months on ketogenic diet. *Conclusion:* This initial experience with the ketogenic diet was effective in difficult-to-treat patients with partial and generalized epilepsies, though its efficacy dropped significantly by 9–12 months. © 2001 Published by Elsevier Science B.V.

Keywords: Refractory epilepsy; Ketogenic diet; Children, adolescents and young adults

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Fig.1 Distribution of age at ketogenic diet onset

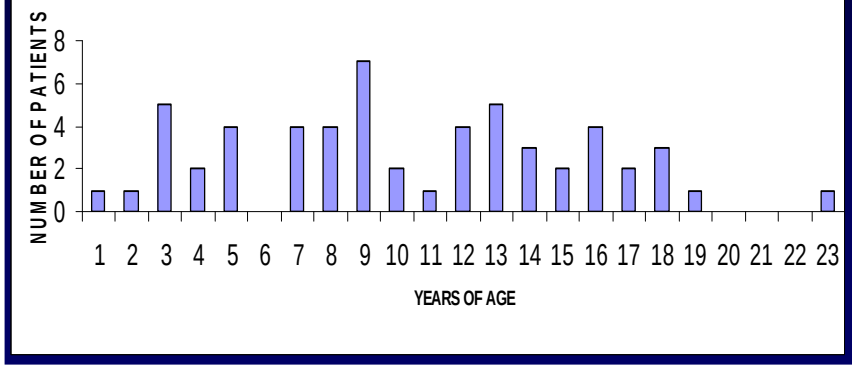
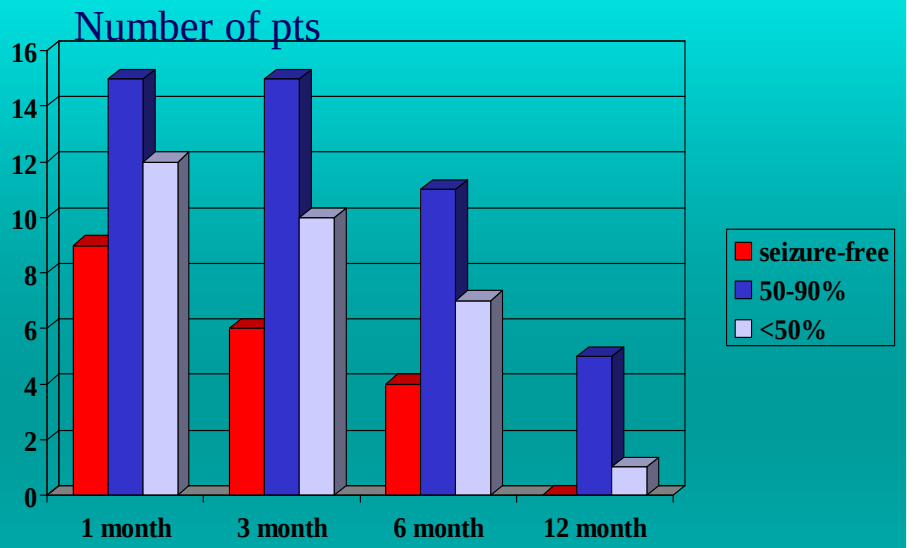


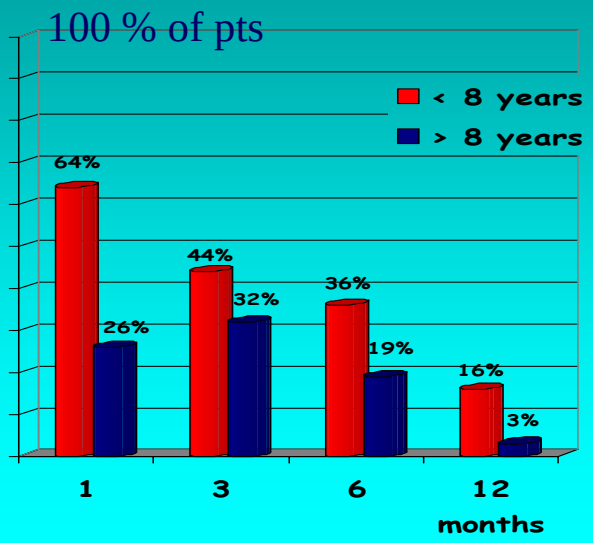
Table 1
Epilepsy type and etiology in our patients ($n = 56$)

Epilepsy type	Number of patients	Etiology
Symptomatic partial (multifocal)	18 (12)	Nine pre-perinatal hypoxi-ischemic One tuberous sclerosis Two postvaccinal encephalitis
Cryptogenic partial	2	
Symptomatic generalized	16	
Epileptogenic encephalopathy	(11)	10 migration disorders One Rett syndrome
Lennox–Gastaut syndrome	(5)	Pre-perinatal hypoxic-ischemic damage
Cryptogenic generalized	14	
Epileptogenic encephalopathy	(9)	
Lennox–Gastaut syndrome	(4)	
Astathic –myoclonic syndrome	1	
Severe myoclonic epilepsy in infancy	5	
Continuous spike-wave status of slow sleep	1	

THE KETOGENIC DIET IN CHILDHOOD REFRACTORY EPILEPSY

- Conclusions (1):
- the ketogenic diet, in the short-term at least , showed itself effective both in partial and generalized seizures
- in our experience 43% (24 pts) benefited substantially from the ketogenic diet treatment and seven out of them (12.5%) were seizure-free.





THE KETOGENIC DIET IN CHILDHOOD REFRACTORY EPILEPSY

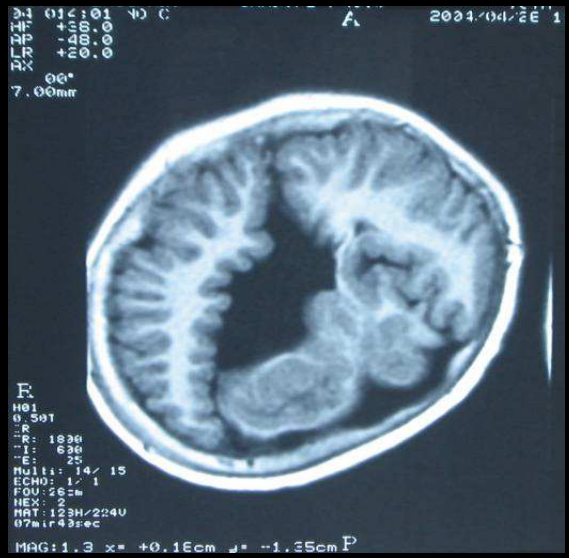
- Conclusions (2)

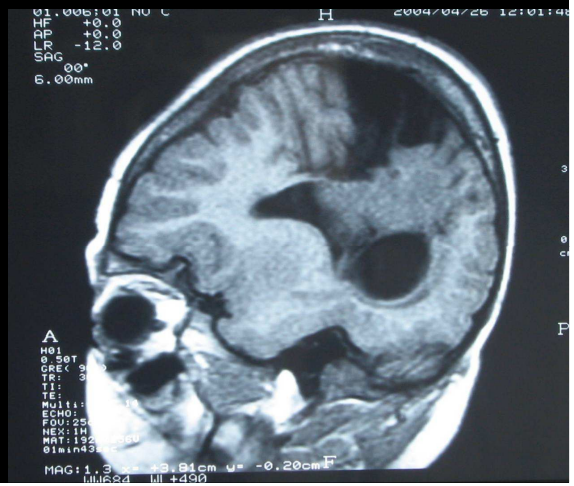
- kd resulted poorly effective in multifocal encephalopathies associated with spams and tonic seizures

- kd lost its efficacy 9-12 months after it was started in most of our patients

- kd must be considered in a therapeutic strategy in selected patients

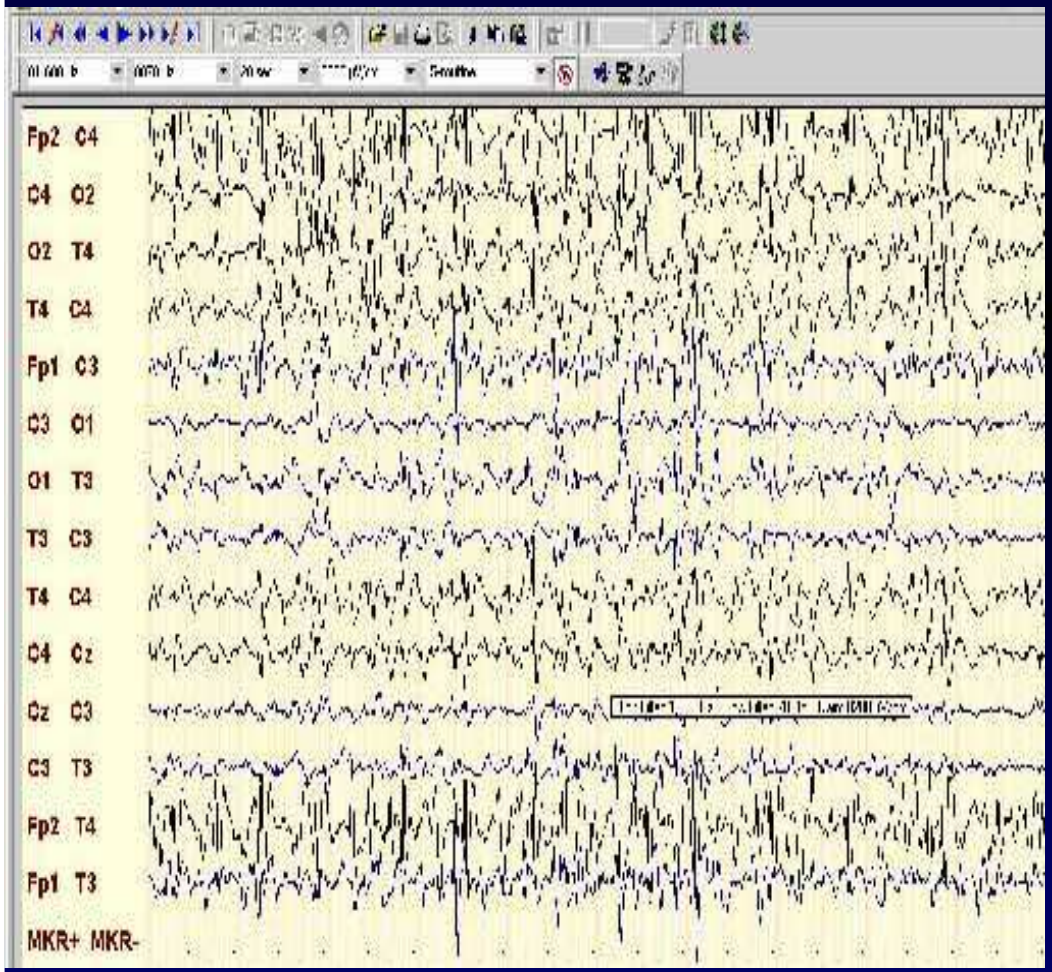
- possible indications: early epileptic encephalopathy, lennox-gastaut s.at onset, acute encephalities with epileptic status, migrating partial epilepsy, refractory patients waiting for or after surgical treatment, migration disorders

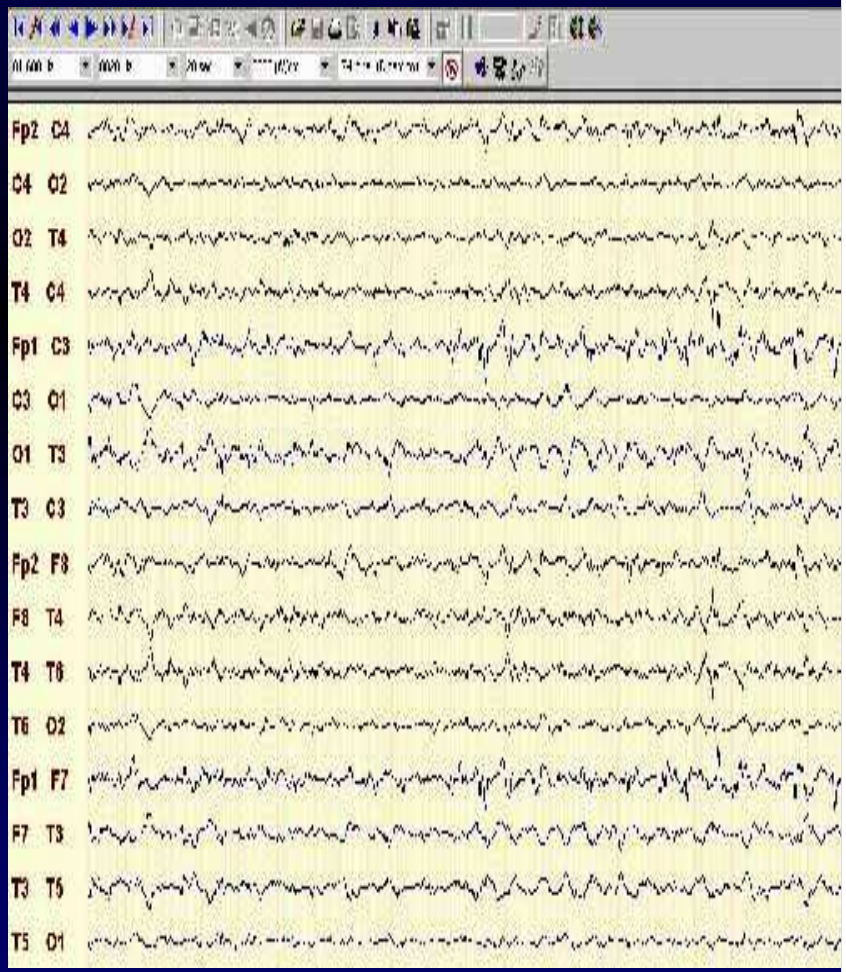




Wake EEG before KD

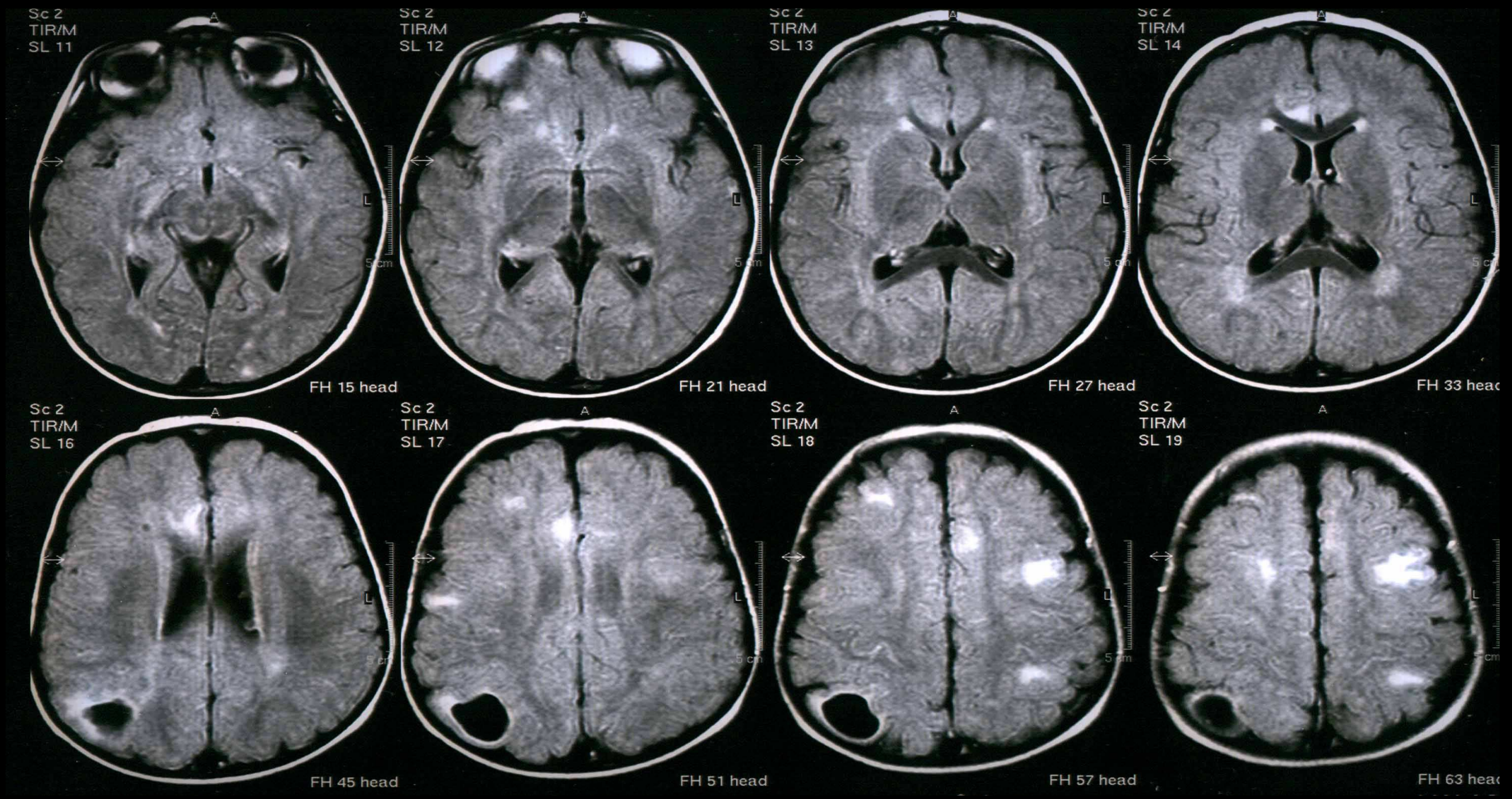
(C.F.male, 9-year-old)





CHILDHOOD EPILEPSY: NEW TREATMENTS

Tuberous sclerosis; refractory partial seizures;male 26 months



Catastrophic encephalopathies

What is the main goal of treatment?

↓

Seizure control (crucial)

↓

The real target must be an “as good as possible” psychomotor development