Lo stato di male epilettico: principi di terapia

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Disclosures

Roberto Michelucci

Ha ricevuto negli ultimi 2 anni fees per interventi come relatore e/o moderatore a eventi scientifici e/o advisory boards da EISAI, SANDOZ, SANOFI, UCB

Neurologo e trattamento dello stato di male: obiettivi

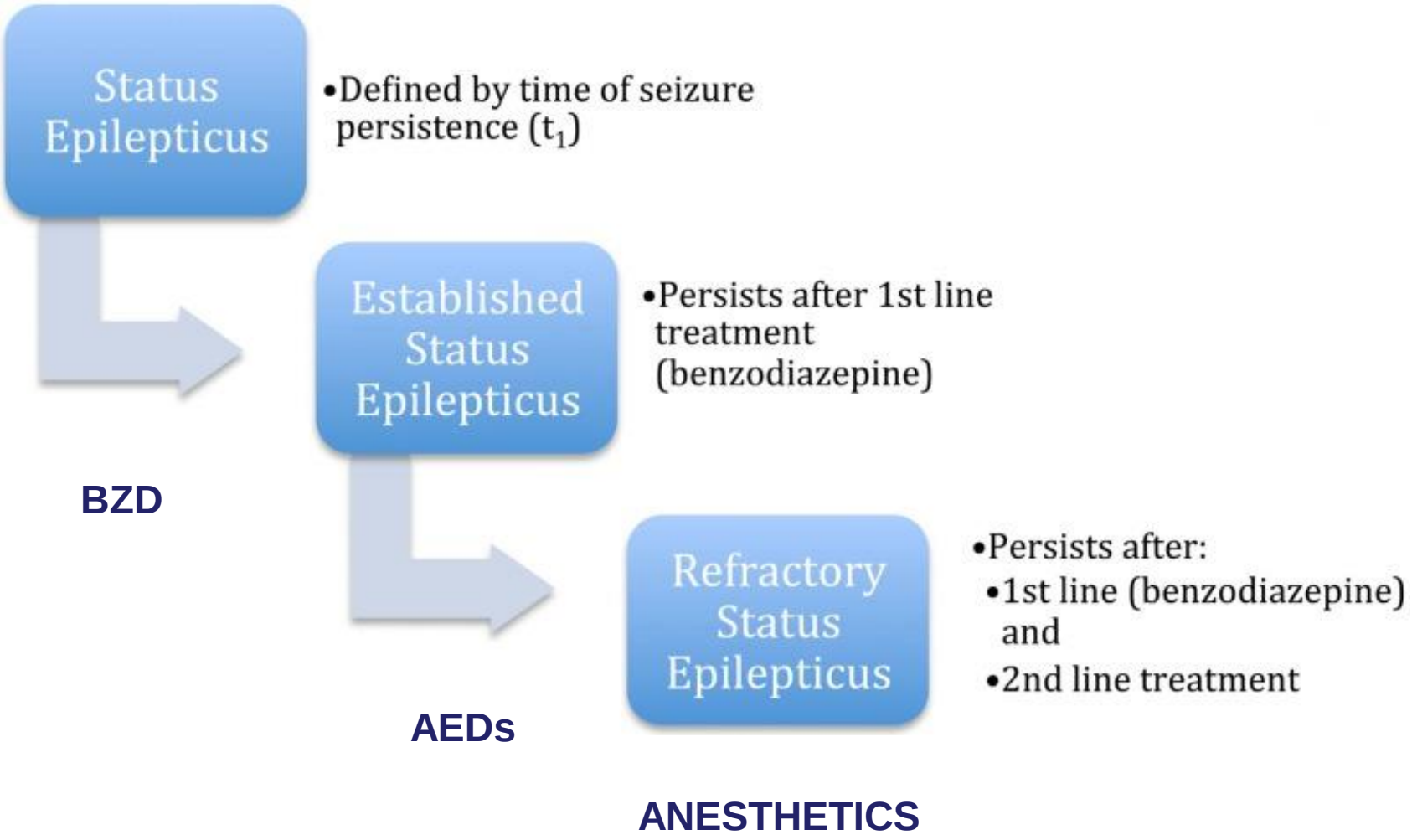
- ✓ **Prima di iniziare la terapia** ⇒ effettuare la diagnosi di status!
- ✓ **Al momento di iniziare la terapia** ⇒ scegliere il trattamento *più appropriato* in relazione alla fase, al tipo di status e al contesto eziologico *nel più breve tempo possibile*
- ✓ **Durante la terapia** ⇒ monitorarne l'efficacia

  valutare il ricorso alla Terapia Intensiva
- ✓ **Dopo la risoluzione dello status** ⇒ prevenire la ricorrenza di crisi

Quale trattamento scegliere?

- Il tipo di trattamento è piuttosto standardizzabile e sostanzialmente analogo per i diversi tipi di status
- L'urgenza di intervento dipende in gran parte dal tipo di stato di male e contesto eziologico
  - ⇨ Convulsivo (con sintomi motori preminenti)
  - ⇨ Non-convulsivo (senza sintomi motori preminenti)
- Il trattamento eziologico deve andare di pari passo al trattamento sintomatico delle crisi

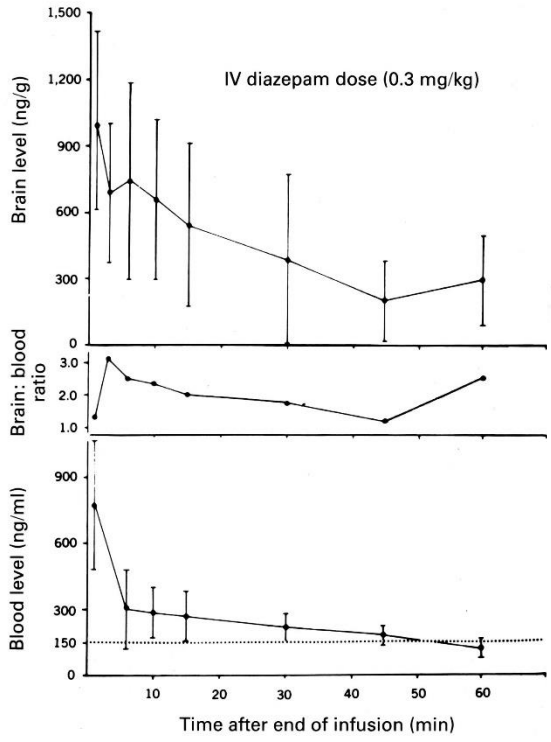
E quale trattamento scegliere in relazione alla fase dello status?



Proprietà di un AED ideale per la terapia dello Stato di Male

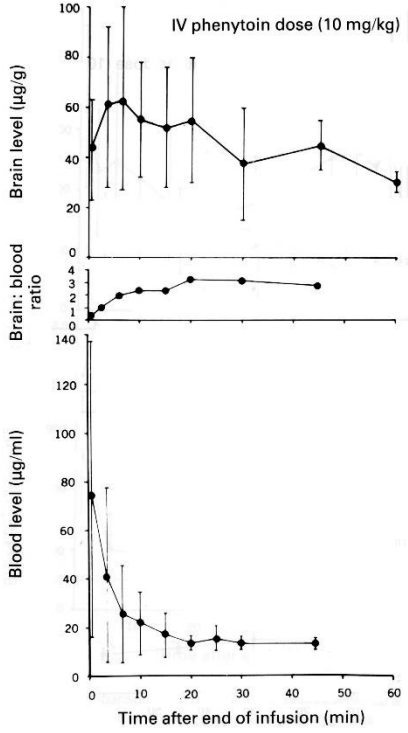
- Rapidamente efficace in tutti i tipi di stato di male
- Disponibile per la somministrazione e.v. e orale
- Sicuro (↯ depressione cardio-respiratoria e di coscienza)
- Rapido ingresso nel cervello
- Lunga emivita di distribuzione
- Breve emivita di eliminazione

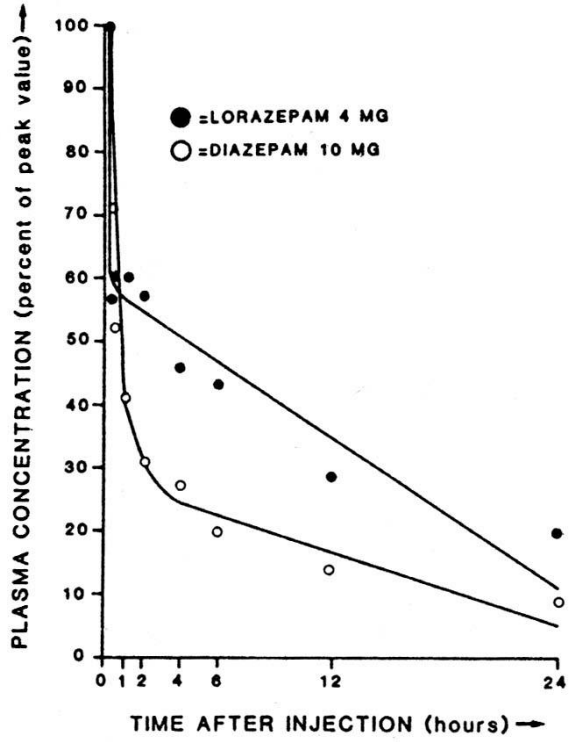
(*a*)



Emergency treatment of status epilepticus

(*c*)





Farmaci utilizzati nel trattamento dello stato di male

Status iniziale e definito

- **Diazepam**
- Clonazepam*
- **Lorazepam**
- **Fenitoina**
- Fosfenitoina*
- *Acido valproico°*
- *Levetiracetam°*
- *Lacosamide°*

Somm. Nasale, Oromucosale, i.m.

Status refrattario e super-refrattario

- Fenobarbital
- **Midazolam**
- **Tiopentale**
- Pentobarbital
- **Propofol**
- **Ketamina**

Topiramato carico via sondino
Perampanel carico via sondino
……

* Non disponibili in Italia

° Non indicazione registrata per SM

Farmacocinetica dei farmaci usati nel trattamento dello stato di male

	LZP	DZP	MDZ	PHT	VPA	LEV	LCM
Time to peak brain	30 m	**6 m**	**3 m**	15-30 m	< 1 hr	5-30 m	6-15 m
Time to stop status	6-10 m	1-3 m	1-3 m	10-30 m	10-60 m	10-60 m	15-120 m
Duration of effect	> 24 h	**15-30** m	**6-15 m**	> 24 h	> 24 h	6-8 h	> 24 h
Elimination half life	8-24 h	20-40 h	**1,5-3 h**	20-70 h	12-15 h	6-8 h	12-16 h
% protein binding	88-92	90-99	98	87-93	85-95	< 10	< 15

Eventi avversi dei farmaci usati nel trattamento dello stato di male

	LZP	DZP	MDZ	PHT	VPA	LEV	LCM
Depressione coscienza	+	+	+	no	no	no	no
Depressione respiratoria	rara	+ (inaspettata dopo vari boli)	+	rara	no	no	no
Ipotensione	rara	rara	+	frequente	no	no	no
Aritmie cardiache	no	no	no	in cardiopatie	no	no	no
Altri eventi avversi	sintomi CNS	flebite, eff. paradosso	no	flebite coreoatetosi	no	sintomi CNS	sintomi CNS

Fase pre-ospedaliera trattamento prima dell'arrivo in PS

- **Obiettivo**: Interrompere il prima possibile crisi seriali/prolungate/stati di male
- ***Familiari*** (se epilessia già nota) → diazepam rettale, lorazepam sublinguale, clobazam orale, midazolam buccale o nasale (5-10 mg 0,3 mg/kg)
- ***Personale sanitario*** (ambulanza) → lorazepam 4 mg e.v. (0.1 mg/kg) o diazepam 10 mg e.v. (0.3 mg/kg). Midazolam nasale, e.v. o i.m. 5-10 mg (0,1-0,3 mg/kg).
- Aspetti organizzativi specifici

Ruolo cruciale delle BZD

Adv Neurol. 1983;34:465-75.

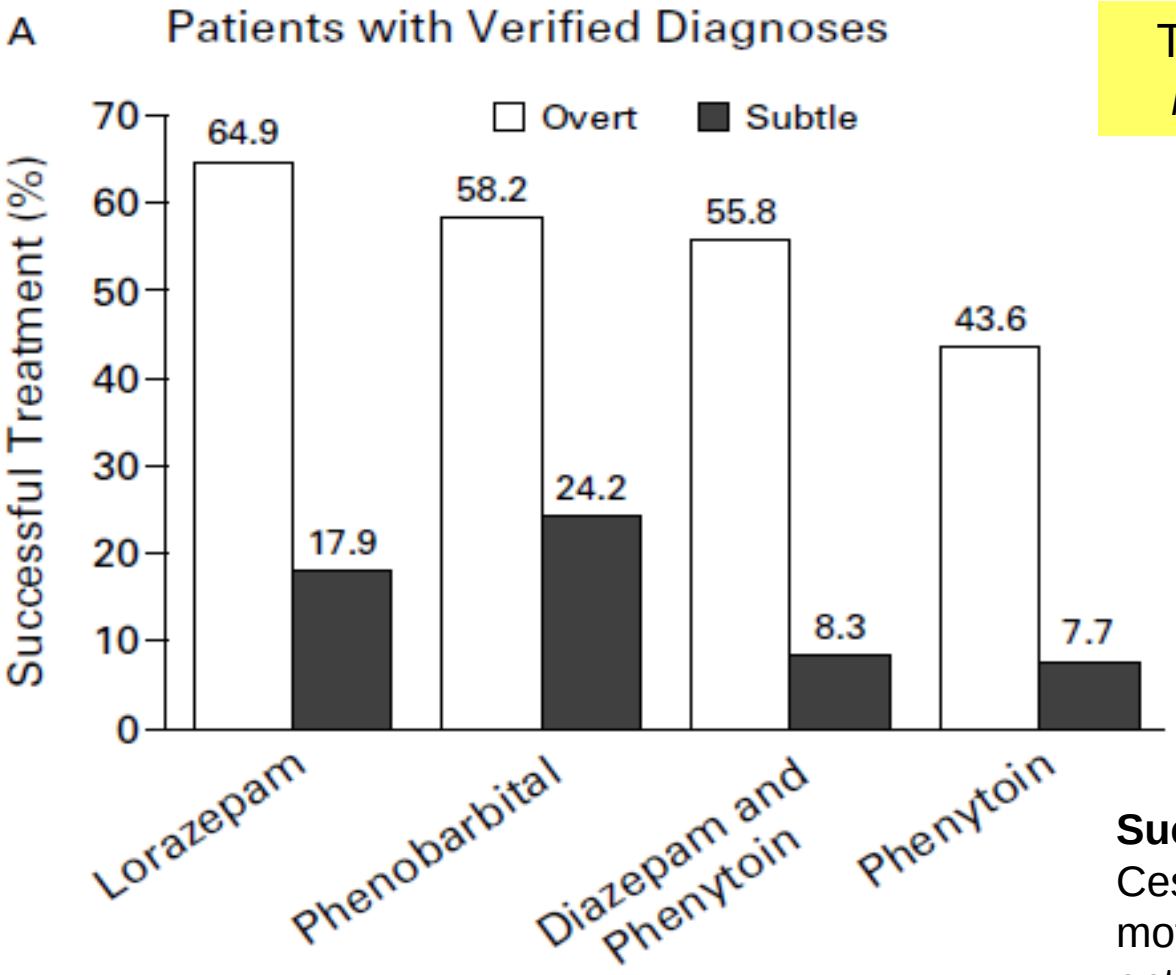
Benzodiazepines: efficacy in status epilepticus.

Tassinari CA, Daniele O, Michelucci R, Bureau M, Dravet C , Roger J.

Abstract

Both our personal experience and the findings of others indicate that the benzodiazepines **(a)** are the drugs of first choice for control of status epilepticus occurring in patients with primary generalized epilepsy (90%-100% effective) or control of hemiclonic convulsions in children without brain lesions, (**b**) are effective in approximately 60% of cases of status epilepticus occurring in partial epilepsy, (**c**) are effective in only 15% to 59% of cases of tonic status or various types of absence status occurring in secondary generalized epilepsy (but no other drug is more effective), (**d**) are helpful in status epilepticus occurring in nonepileptic patients if there is no overt brain lesion (but give only temporary relief when status is the result of a severe organic brain lesion), and (**e**) are generally safe drugs

Treiman et al
N Engl J Med 1998



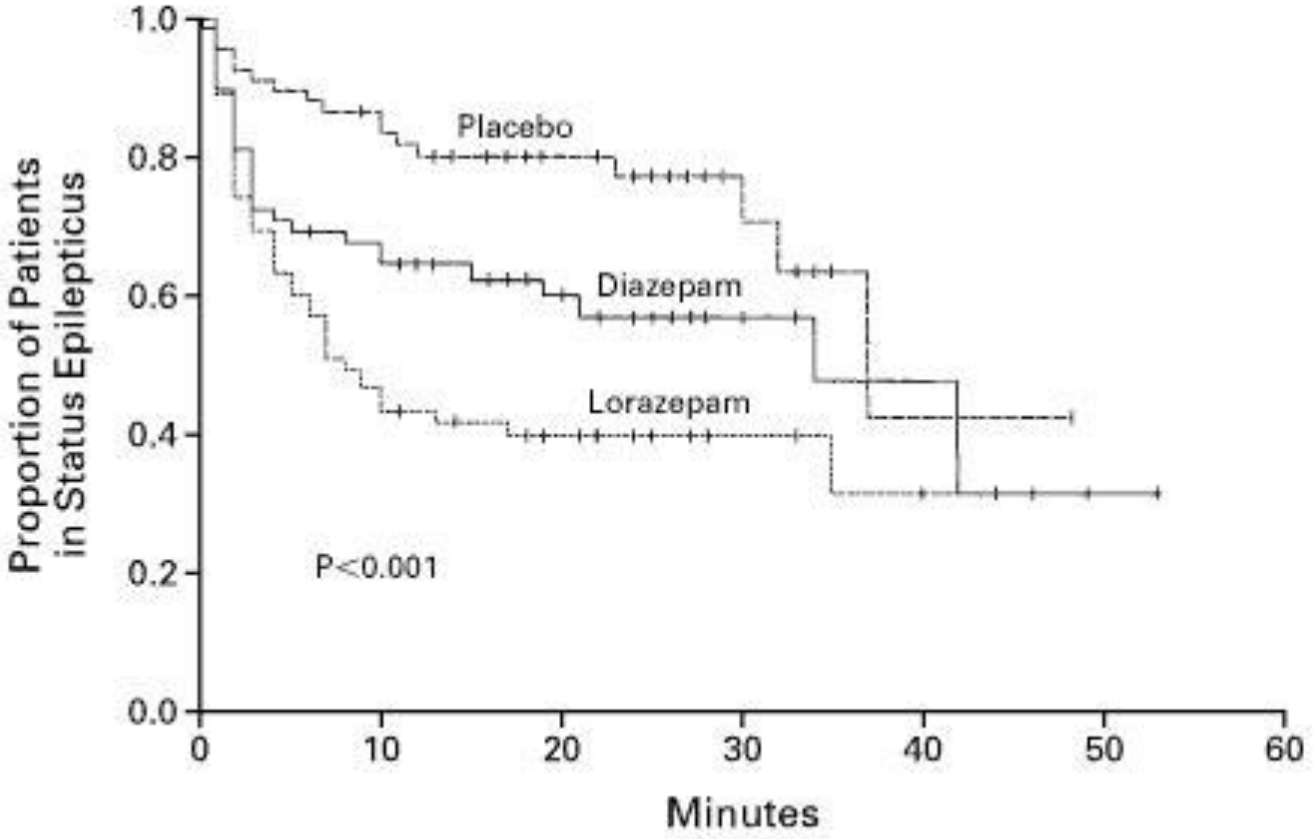
No. of Patients				
Overt	97	91	95	101
Subtle	39	33	36	26

LZP	PB	DZP +PHT	PHT
0.10±0.01 mg/kg	14.96±2.53 mg/kg	0.15±0.02 15.08±4.84 mg/kg	16.2 ±3.21 mg/kg

Successful treatment =
Cessazione manifestazioni motorie e EEGragiche entro 20 m dalla infusione senza ricorrenza durante i 40 m successivi

A comparison of lorazepam, diazepam, and placebo for the treatment of out of hospital status epilepticus

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 FEBRUARY 16, 2012 VOL. 366 NO. 7



No. at Risk

Diazepam	68	41	21	8	2	1
Lorazepam	65	29	15	6	2	0
Placebo	67	53	26	10	1	0

Kaplan–Meier Curves Comparing the Durations of Out-of-Hospital Status Epilepticus after Treatment with Lorazepam, Diazepam, or Placebo.

Alldredge et al N Engl J Med 2001

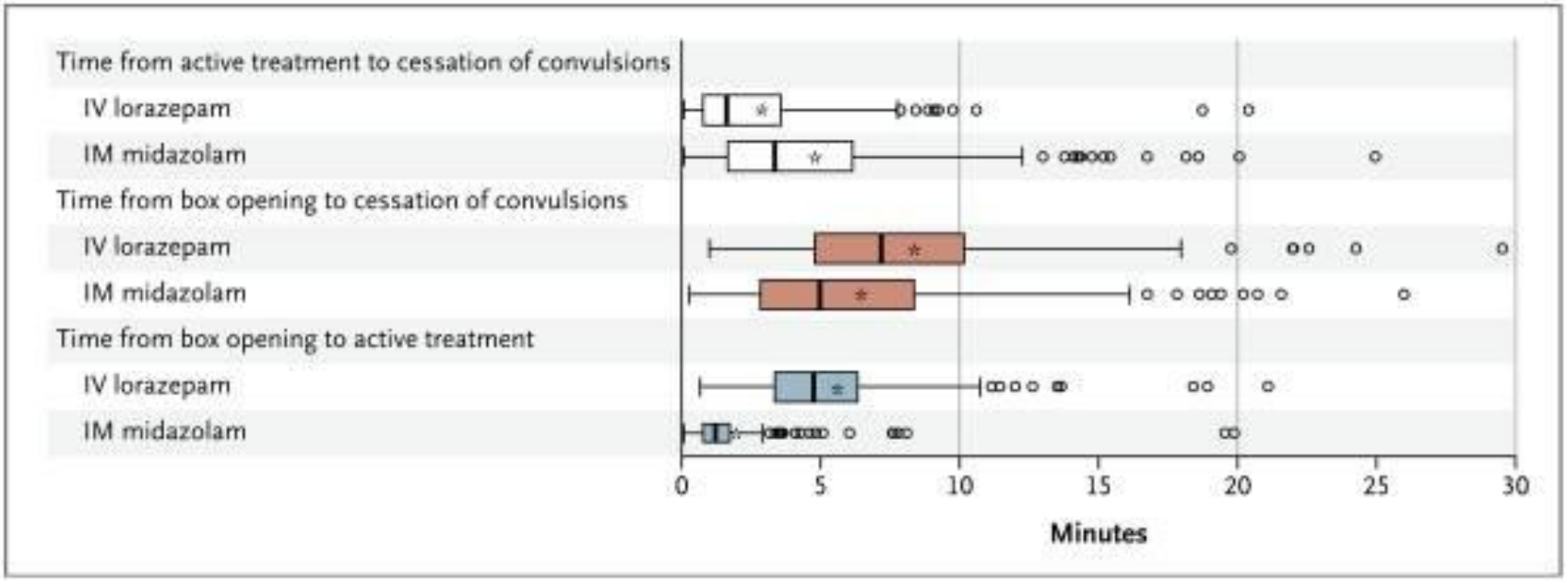
Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

Robert Silbergleit, M.D., Valerie Durkalski, Ph.D., Daniel Lowenstein, M.D., Robin Conwit, M.D., Arthur Pancioli, M.D., Yuko Palesch, Ph.D., and William Barsan, M.D., for the NETT Investigators*

N Engl J Med. 2012 Feb 16; 366(7): 591–600.

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 FEBRUARY 16, 2012 VOL. 366 NO. 7

893 pz assegnati a un trattamento
Successo: 73,4 % MDZ im *vs* 63,4 % LRZ e.v. (non inferiority)
Inizio trattamento: 1,2 min MDZ *vs* 4,8 min LRZ
Delay fra inizio trattamento e stop crisi: 3,3 min MDZ *vs* 1,6 min LRZ



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Anticonvulsant therapy for status epilepticus

Prasad M et al 2014

- Intravenous lorazepam is better than intravenous diazepam or intravenous phenytoin alone for cessation of seizures.
- Intravenous lorazepam also carries a lower risk of continuation of status epilepticus requiring a different drug or general anaesthesia compared with intravenous diazepam.
- For pre hospital management, midazolam IM seemed equal or more effective than lorazepam IV for cessation of seizures.
- Results for other comparisons of anticonvulsant therapies were uncertain due to single studies with few participants.

Trattamento in Ospedale

- **Obiettivo**: Interrompere il prima possibile crisi seriali/prolungate/stati di male
- ***Medico di PS e/o neurologo:*** valutare le BDZ (tipo e dosi) già somministrate in Ambulanza.
- 50 ml di soluzione di Glucosio al 50% (in presenza di ipoglicemia) + 250 mg di tiamina i.m. (stati di denutrizione, alcoolismo)
- Ripetizione o somministrazione iniziale di lorazepam 4 mg e.v. (0.1 mg/kg) o diazepam 10 mg e.v. (0.3 mg/kg) o midazolam nasale, e.v. o i.m. 5-10 mg (0,1-0,3 mg/kg)
- **Video-EEG (soprattutto se NCSE)** per la diagnosi e il monitoraggio dell'efficacia della terapia

Stadio dello SE definito
(benzodiazepine inefficaci)

- **Fenitoina** e.v.15-18 mg/kg in bolo (vel. max. 50 mg/min) (somm. per via e.v. diretta o diluita in soluzioni di salina alla conc. di 5-10 mg/ml)
- **Valproato** e.v. in bolo 15-30 mg/kg in 5-10 min, seguito da infusione continua di 1-2 mg/kg/ora
- **Levetiracetam** e.v. in bolo 30-50 mg/kg in 5-15 min

=

- **Lacosamide** e.v. in bolo (200-400 mg) (vel. max. 60 mg/min)

2a

Stadio dello SE definito
(opzioni non in uso in Italia)

- **Fenobarbital** e.v. in bolo 10-20 mg/kg alla velocità di infusione di 100 mg/min*
- **Fosfenitoina** e.v in bolo 20 mg/kg a 150 mg/m

* la somministrazione richiede la presenza di rianimatore per la frequente depressione di coscienza e respiratoria

The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: a meta-analysis of published studies.

Yasiry Z, Shorvon SD Seizure 2014, 23:167-174

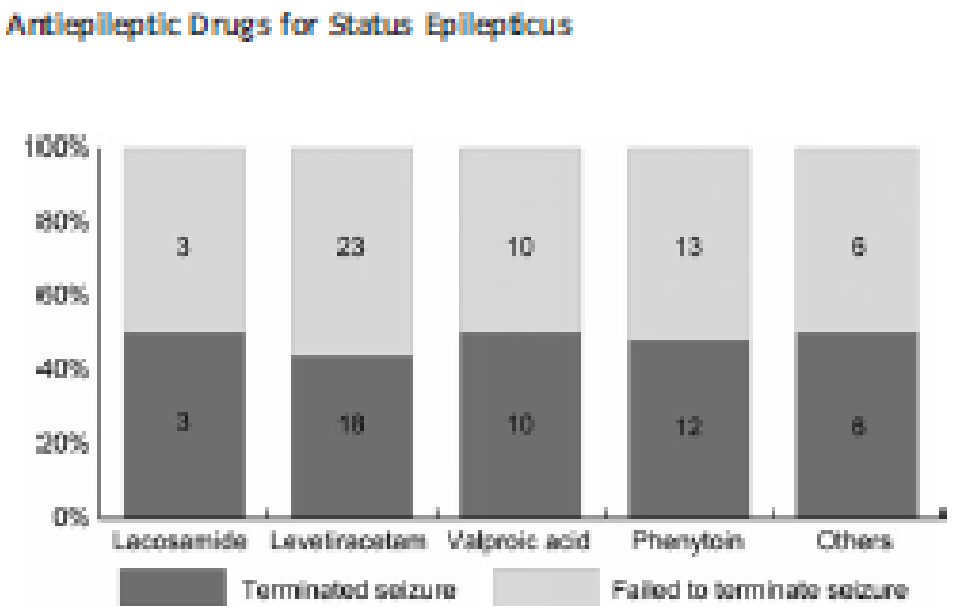
Prospective and retrospective human studies with BDZ-resistant convulsive status
Interventions were intravenous lacosamide, levetiracetam, phenobarbital, phenytoin and valproate.
Outcome measured is clinically detectable cessation of seizure activity.
27 studies (798 cases of convulsive status epilepticus) were identified and 22 included in a meta-analysis
Several sources of clinical and methodological heterogeneity were identified.

Efficacy of **levetiracetam was 68.5%** (95% CI: 56.2-78.7%), **phenobarbital 73.6%** (95% CI: 58.3-84.8%), **phenytoin 50.2%** (95% CI: 34.2-66.1%) and **valproate 75.7%** (95% CI: 63.7-84.8%).
Lacosamide studies were excluded from the meta-analysis due to insufficient data

Valproate, levetiracetam and phenobarbital can all be used as first line therapy in benzodiazepine-resistant status epilepticus.

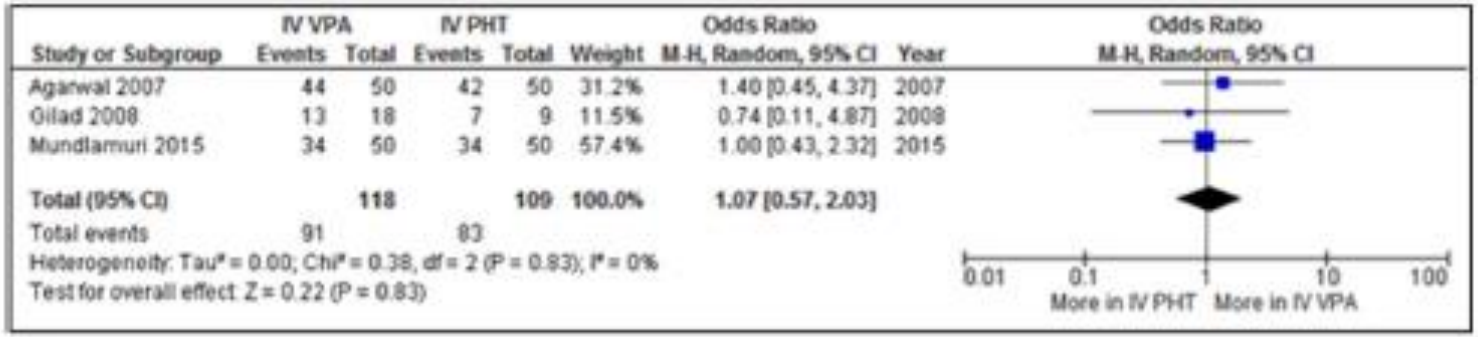
Comparison of Antiepileptic Approaches in Treatment of Benzodiazepine Nonresponsive Status Epilepticus

A. Bachhuber, et al 2015

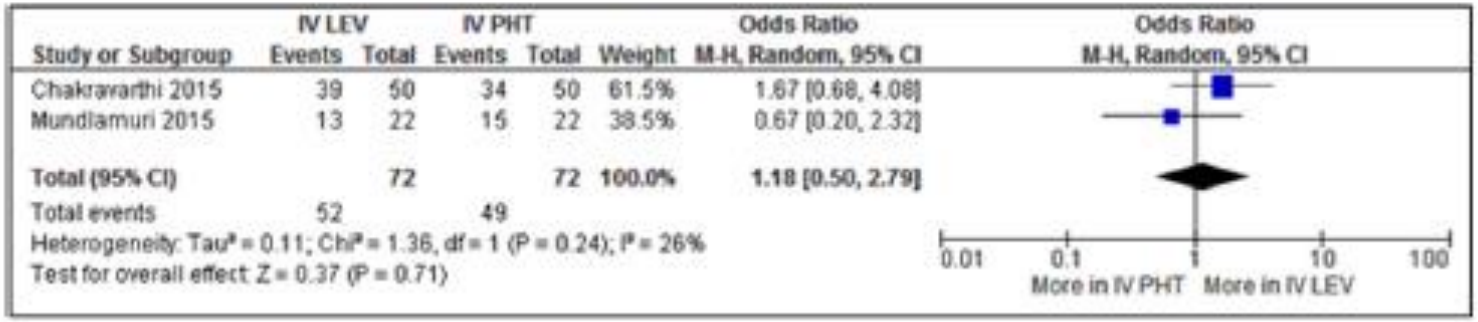


66 patients. Retrospective study

Direct and indirect meta-analysis comparison of levetiracetam vs phenytoin or valproate for convulsive status epilepticus. Brigo et al 2016



A



B

The absence of a statistically significant difference in direct and indirect comparisons is due to the lack of a sufficient statistical power to detect a difference

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Anticonvulsant therapy for status epilepticus

Prasad M et al 2014

- Intravenous lorazepam is better than intravenous diazepam or intravenous phenytoin alone for cessation of seizures.
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- For pre hospital management, midazolam IM seemed equal or more effective than lorazepam IV for cessation of seizures.
- Results for other comparisons of anticonvulsant therapies were uncertain due to single studies with few participants.

Scelta del trattamento nello status definito, resistente a BZD

- Non vi sono evidenze robuste di superiorità di un AED rispetto a un altro
- Ciò dipende in larga misura dal numero insufficiente delle popolazioni studiate
- Qualche dato a favore di una maggiore tollerabilità di VPA e LEV rispetto a PHT
- ***Le uniche differenze riguardano il profilo di tollerabilità che insieme a copatologie e coterapie devono orientare nella scelta***

The Established Status Epilepticus Treatment Trial (ESETT) is a Phase 3 comparative effectiveness trial in patients with established status epilepticus who have failed benzodiazepines.

Lyttle *et al. Trials* (2017) 18:283
DOI 10.1186/s13063-017-2010-8

Trials

STUDY PROTOCOL Open Access

Emergency treatment with levetiracetam or phenytoin in status epilepticus in children—the EcLiPSE study: study protocol for a randomised controlled trial

Mark D. Lyttle[1,2], Carrol Gamble[3], Shrouk Messahel[4], Helen Hickey[5], Anand Iyer[4], Kerry Woolfall[6], Amy Humphreys[5], Naomi E. A. Bacon[3], Louise Roper[6], Franz E. Babl[7,8,9], Stuart R. Dalziel[10,11], Mary Ryan[4], Richard E. Appleton[4*] and supported by Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI)

Dalziel *et al. BMC Pediatrics* (2017) 17:152
DOI 10.1186/s12887-017-0887-8

BMC Pediatrics

STUDY PROTOCOL Open Access

A multicentre randomised controlled trial of levetiracetam versus phenytoin for convulsive status epilepticus in children (protocol): Convulsive Status Epilepticus Paediatric Trial (ConSEPT) - a PREDICT study

Stuart R. Dalziel[1,2*], Jeremy Furyk[3,4], Megan Bonisch[1], Ed Oakley[5,6,7], Meredith Borland[8], Jocelyn Neutze[9], Susan Donath[6], Cynthia Sharpe[1], Simon Harvey[5], Andrew Davidson[5], Simon Craig[10], Natalie Phillips[11], Shane George[12,13,14], Arjun Rao[15], Nicholas Cheng[16], Michael Zhang[17], Kam Sinn[18], Amit Kochar[19], Christine Bratyn[20], Franz E. Babl[5,6,7] and On Behalf of the PREDICT research network[21]

Trattamento pre-ospedaliero e ospedaliero dello SE inziale e definito

Qual’ è il mondo reale?

Treatment with antiepileptic drugs by emergency medical services (EMS) in 199 children with febrile status epilepticus.

Site	Number treated by EMS/Number recruited (%)	
Virginia Commonwealth University	14/37 (38%)	73 (41%)
Montefiore and Jacobi	10/55 (18%)	
Duke University Medical Center	9/25 (36%)	
Lurie Children's Hospital	23/45 (51%)	
Eastern Virginia Medical School	17/37 (46%)	

	1st AED
Family	2 (1%)
EMS	73 (41%)
ED	104 (58%)

Seinfeld et al. Emergency Management of Febrile Status Epilepticus: Results of the FEBSTAT study. Epilepsia 2014

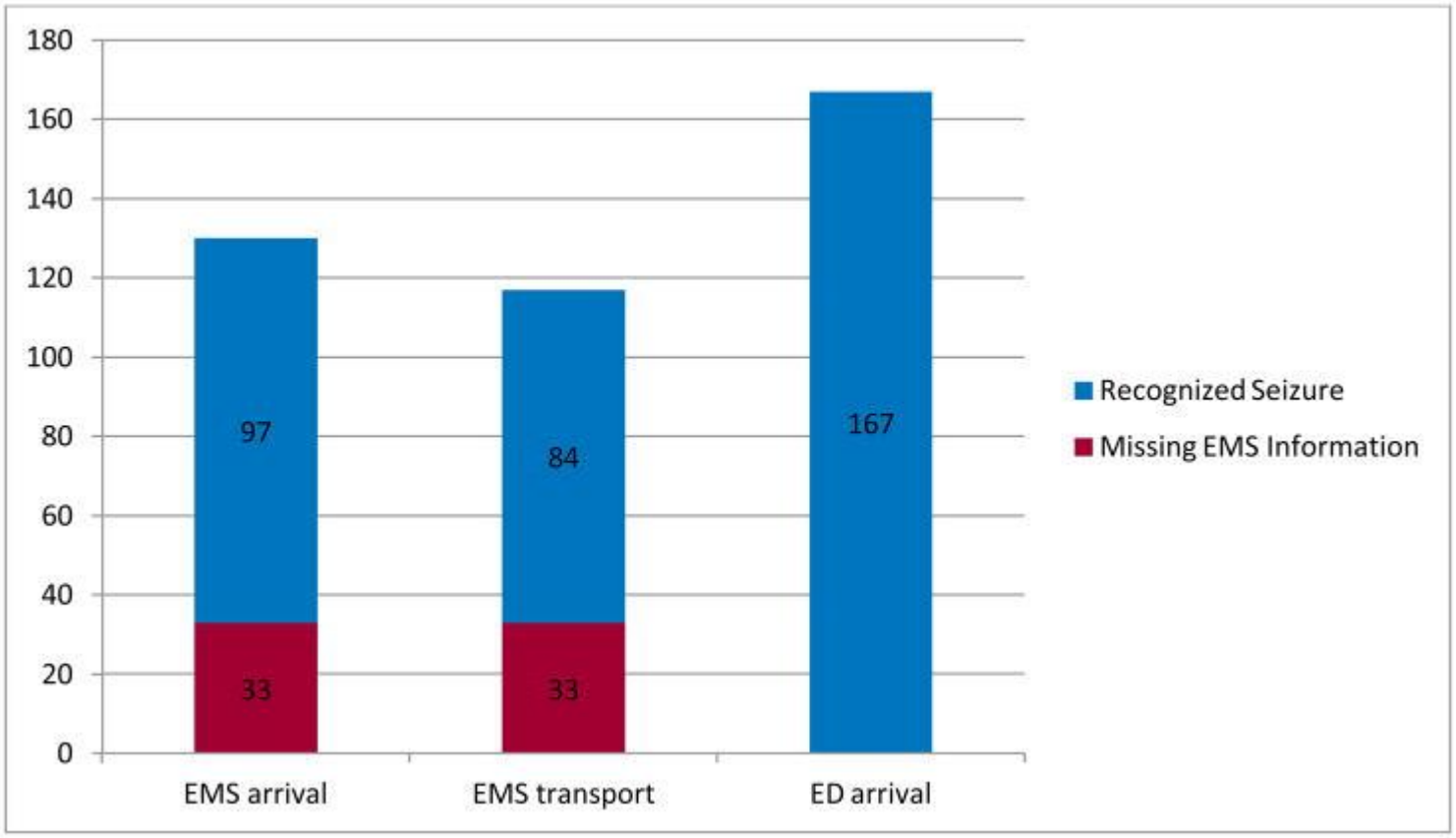
Timeline of seizure onset to AED administration.

	Median time
Seizure onset to EMS arrival	12,5 min
EMS arrival to 1st AED*	9,8 min
Seizure onset to ED arrival	33 min
ED arrival to 1st AED**	10 min

* Only includes children given AED by EMS.

**Only includes children given 1st AED by ED

Seinfeld et al. Emergency Management of Febrile Status Epilepticus: Results of the FEBSTAT study. Epilepsia 2014



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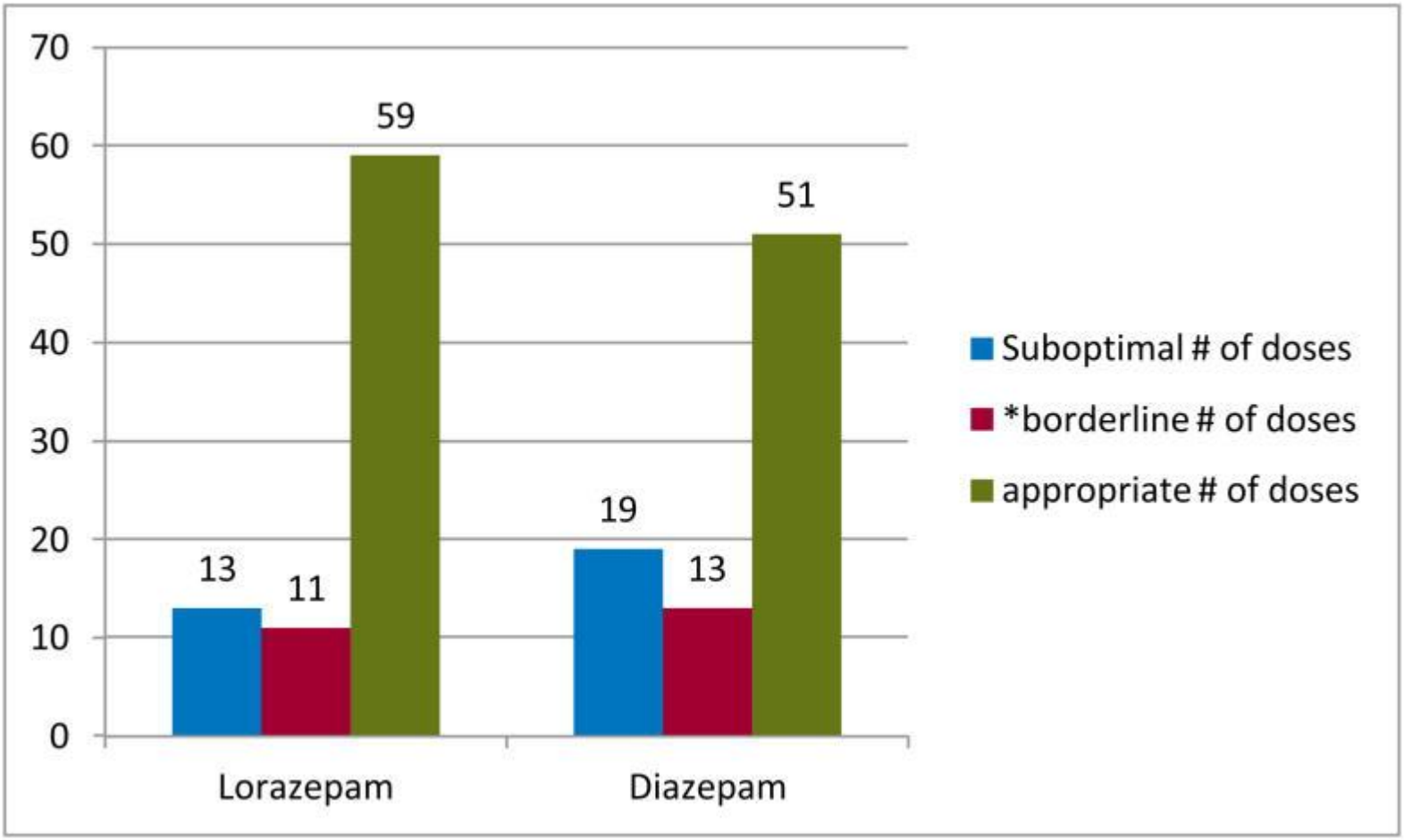


Seinfeld et al. Emergency Management of Febrile Status Epilepticus: Results of the FEBSTAT study. Epilepsia 2014

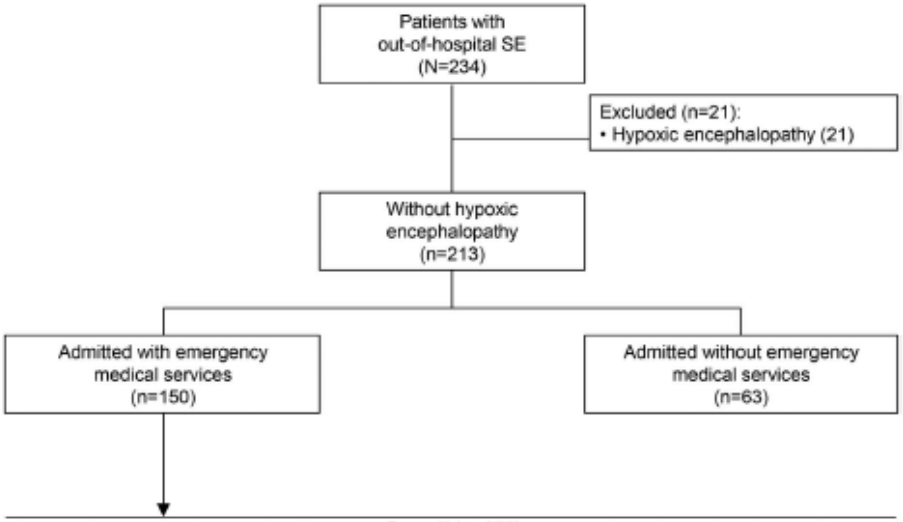
Saskia Semmlack, MD
Désirée Yeginsoy
Rainer Spiegel, MD, PhD
Kai Tisljar, MD
Stephan Rüegg, MD
Stephan Marsch, MD
Raoul Sutter, MD

Emergency response to out-of-hospital status epilepticus

A 10-year observational cohort study

Neurology® 2017;89:376-384

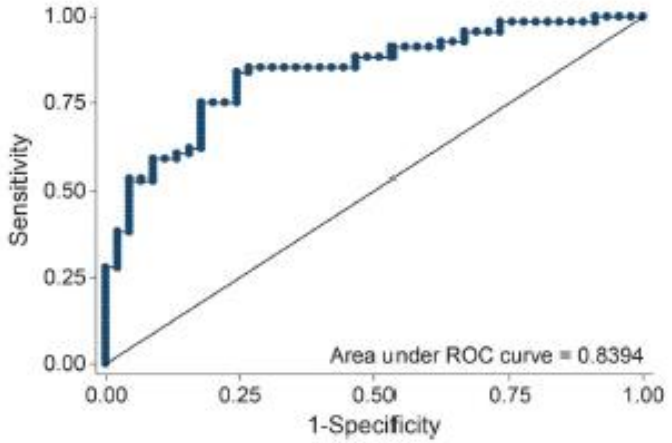
Figure 1 Flow chart



Prehospital principal diagnosis	Overall (n=150) Suspected by emergency medical service		Confirmed after medical workup	
	n	%	n	%
Suspected epileptic event	67	44.7	67	100
• Status epilepticus	32	21.3		
• Seizures	35	23.3		
Missed epileptic event (=Alternative suspected diagnosis without suspected SE)	83	55.3		
• Unknown neurologic event	37	24.7	0	0
• Acute ischemic stroke	35	23.3	5	14.3
• Intracranial hemorrhage	4	2.7	0	0
• Cardiac emergency	4	2.7	4	100
• Traumatic brain injury	3	2.0	3	100

SE = status epilepticus.

Figure 2 Prediction of missed out-of-hospital nonconvulsive status epilepticus



ROC = receiver operating characteristic.

Among patients admitted with out-of-hospital SE, CSE is mostly recognized while NCSE is frequently missed especially in patients with increasing age and no seizure history. This calls for heightened awareness for out-of-hospital NCSE in such patients, as missed NCSE is associated with lack of treatment and less recovery to functional baseline in survivors independent of established outcome predictors

EDITORIAL

Missed diagnosis of prehospital status epilepticus

Is it serious, doctor?

Andrea O. Rossetti, MD
Elizabeth Waterhouse, MD

Neurology® 2017;89:314–315

Conseguenze sull'outcome?

Seizure 55 (2018) 9–16

Contents lists available at ScienceDirect

Seizure

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

The essence of the first 2.5 h in the treatment of generalized convulsive status epilepticus

Leena Kämppi[a,*], Harri Mustonen[b], Kaisa Kotisaari[a], Seppo Soinila[c]

70 pz adulti consecutivi con SM convulsivo
Fattori di rischio per un basso GOS sono i lunghi ritardi fra:
- Esordio → diagnosi
- Esordio → farmaco di seconda linea
- Esordio → ripresa di coscienza

lungo ricovero in Rianimazione

Cut-off per aumentato rischio:
- Esordio → diagnosi 2,4 h
- Esordio → seconda linea 2,5 h
- Esordio → coscienza 41,5 h

SE condizione dinamica in cui i vari ritardi devono essere ottimizzati

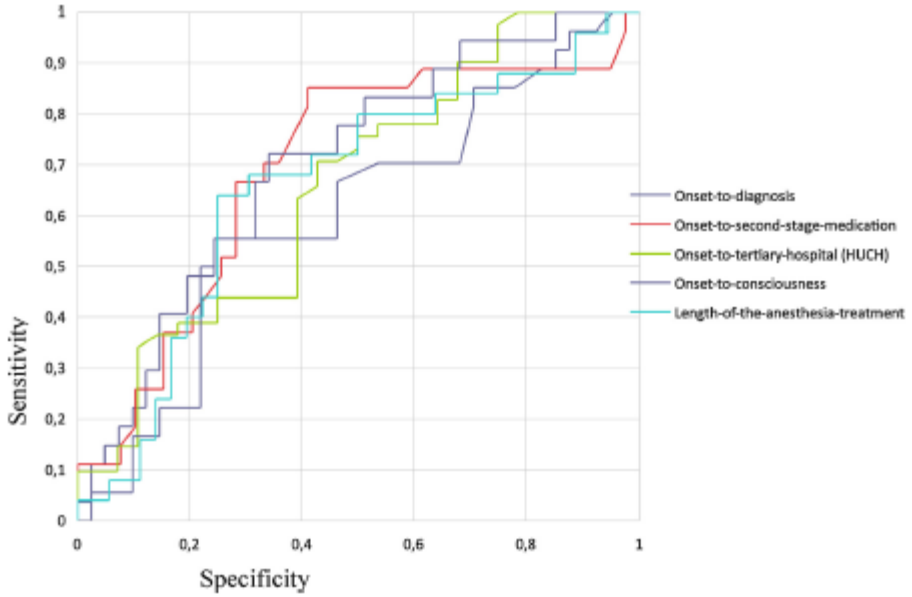


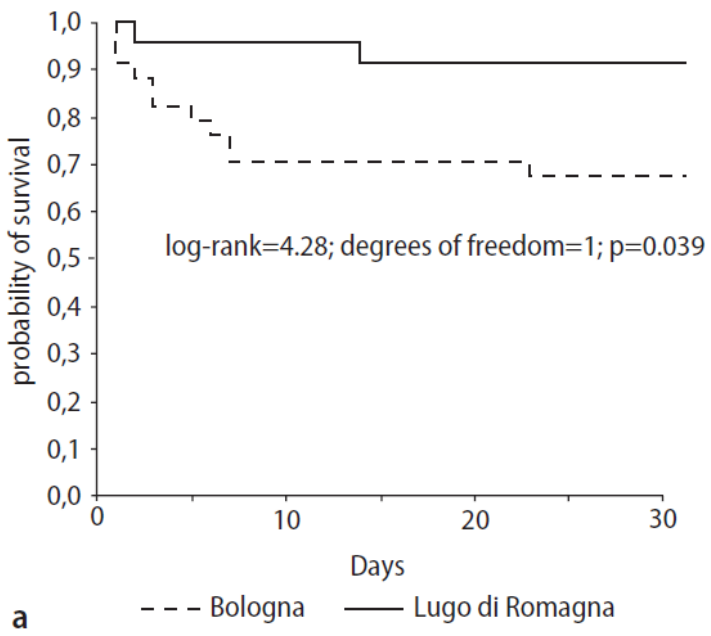
Fig. 1. Receiver operating characteristics curves (ROC-Curves) for the delays. Outcome variable for onset-to-diagnosis, onset-to-second-stage-medication, consciousness and total-anesthesia-time is low GOS score (1–3) at hospital discharge and for onset-to-tertiary-hospital (HUCH) is worse-than-baseline-condi

J Neurol (2008) 255:197–204
DOI 10.1007/s00415-008-0635-y

ORIGINAL COMMUNICATION

Luca Vignatelli
Rita Rinaldi
Elisa Baldin
Paolo Tinuper
Roberto Michelucci
Massimo Galeotti
Piero de Carolis
Roberto D'Alessandro

Impact of treatment on the short-term prognosis of status epilepticus in two population-based cohorts



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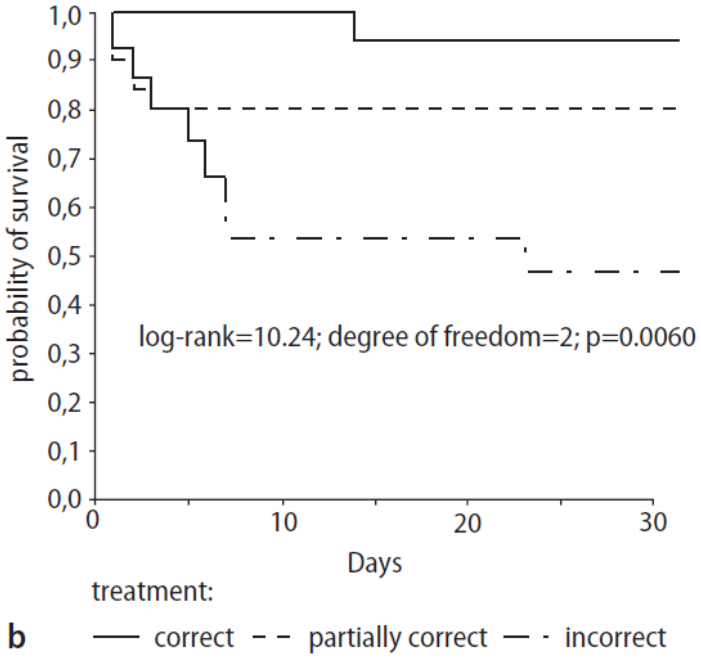


b

Timing Is Everything: Where Status Epilepticus Treatment Fails

Chloe E. Hill, MD,[1,2] Alomi O. Parikh, BA,[1] Colin Ellis, MD,[1]
Jennifer S. Myers, MD,[2,3] and Brian Litt, MD[1,4]

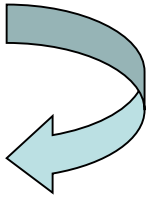
ANN NEUROL 2017;82:155–165

TABLE 5. Proposed Future Directions

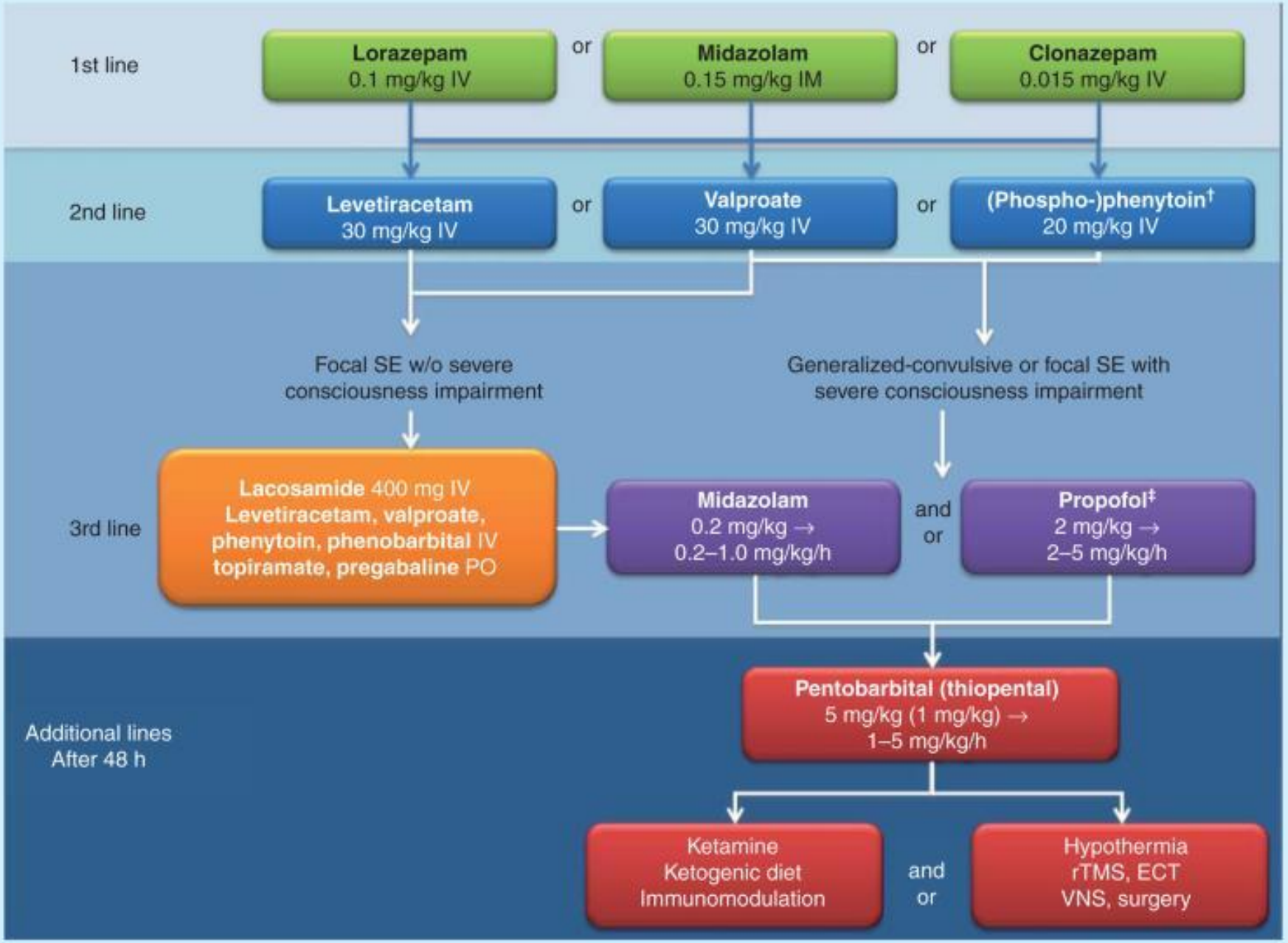
Problem	Solutions
Minority of patients receive treatment before arrival in the hospital	Develop more effective, user-friendly methods for family and caregivers to administer rescue medication
Journey to hospital is often prolonged	Outfit paramedics with the capability to deliver second-line therapy or early polytherapy
Unreliable administration and dosage of benzodiazepines as the first-line agent	Simplify and clarify recommended first-line dosing Create an explicit single, continuous protocol bridging prehospital to in-hospital treatment
Delays in diagnosis of status epilepticus	Improve the education of emergency personnel and family members Advance technologies for EEG diagnosis in the field and/or immediately upon arrival to the ED
Unclear relationship between treatment nonadherence and patient outcome	Establish and employ standard quality indicators of treatment adherence (timing, dose, sequence) Adopt consistent clinical outcomes, covariate considerations, and definitions of status epilepticus
Difficult to retrospectively assess seizure duration and clinical decision making	Collect patient data in real-time through technology innovation
Limited and laborious data collection	Innovate data abstraction and visualization tools Encourage reporting as performance measures
Health system and institution-specific factors impact protocol adherence	Apply quality improvement methodology to explore the local context and then implement responsive, targeted countermeasures

Stadio dello SE refrattario (lorazepam e fenitoina inefficaci)

- Lo SE diventa di competenza del **rianimatore**



- Intubazione e induzione di anestesia generale (propofol, tiopentone, midazolam)
- **Ruolo del neurologo**: stretto ***dialogo*** con il rianimatore nel monitoraggio clinico-EEG dello SE (induzione della anestesia fino alla burst suppression, SE non convulsivo, SE “subtle”)


1st line
Lorazepam
0.1 mg/kg IV
or
Midazolam
0.15 mg/kg IM
or
Clonazepam
0.015 mg/kg IV
2nd line
Levetiracetam
30 mg/kg IV
or
Valproate
30 mg/kg IV
or
(Phospho-)phenytoin†
20 mg/kg IV
Focal SE w/o severe consciousness impairment
Generalized-convulsive or focal SE with severe consciousness impairment
3rd line
Lacosamide 400 mg IV
Levetiracetam, valproate, phenytoin, phenobarbital IV
topiramate, pregabaline PO
Midazolam
0.2 mg/kg →
0.2–1.0 mg/kg/h
and
or
Propofol‡
2 mg/kg →
2–5 mg/kg/h
Additional lines
After 48 h
Pentobarbital (thiopental)
5 mg/kg (1 mg/kg) →
1–5 mg/kg/h
Ketamine
Ketogenic diet
Immunomodulation
and
or
Hypothermia
rTMS, ECT
VNS, surgery

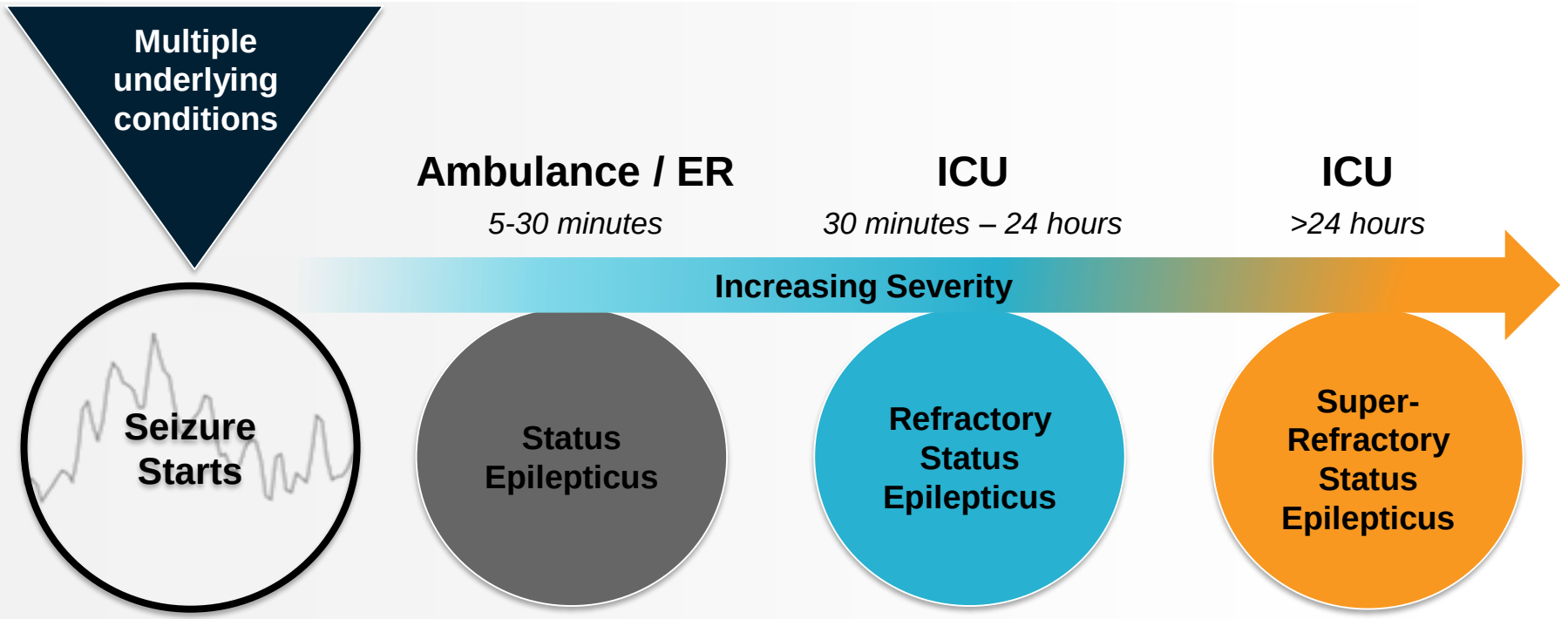
Pharmacological characteristics of anesthetics used in refractory SE

	Barbiturates	Propofol	Midazolam
Used since	Before 1960	End of 1980	Early1990
Mechanism of action			
GABA$_A$ agonistic	+++	+++	+++
NMDA antagonistic	+	(+)	
Ca channel modulation	(+)	(+)	
Na channel modulation		(+)	
Elimination half-life after prolonged administration			
	THP: 14–36 h PTB: 15–22 h	1–2 h	6–50 h
Accumulation	+++	(+)	++
Tachyphylaxis		(+)	+++
Hypotension	+++	+++	++
Other adverse effects	Immunological suppression	Infusion syndrome	
Administration			
Loading dose	THP: 2–7 mg/kg PTB: 5–15 mg/kg	2 mg/kg	0.1–0.3 mg/kg
Maintenance dose	THP: 3–5 mg/kg/h PTB: 1–5 mg/kg/h	2–10 mg/kg/h	0.05–0.6 mg/kg/h
Remarks	Long wash-out time	Limit to 48 h Combine with BDZ	Increasing doses needed with time

THP, thiopental; PTB, pentobarbital; BDZ, benzodiazepines

Rossetti 2007

Current Standard of Care of SE



1st / 2nd Line Treatment
(benzodiazepines, antiepileptics)

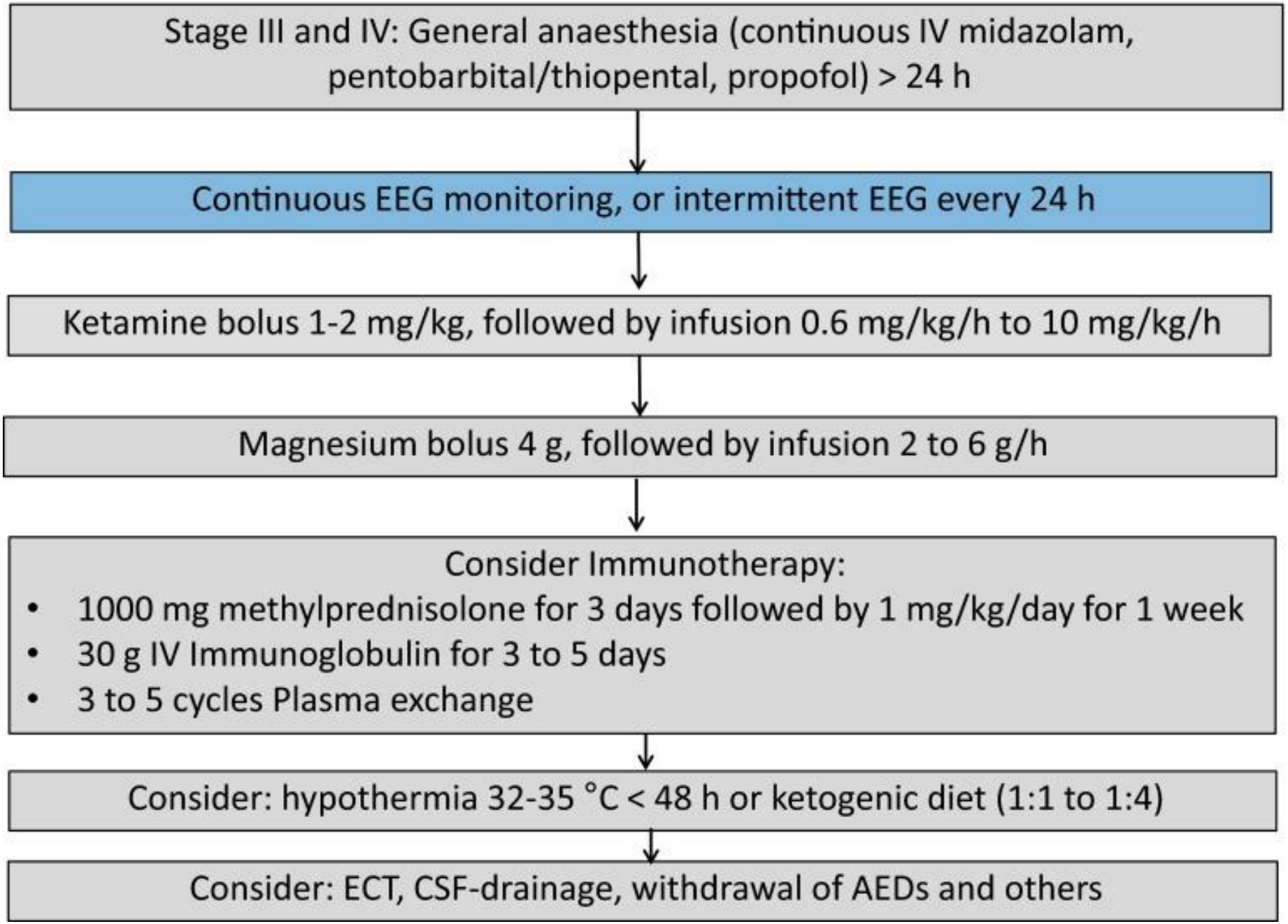
Seizure continues despite treatment

3rd Line Treatment
(burst suppression with anesthetics/antiepileptics)

Seizure continues; Initiate medically-induced coma

3rd Line Adjunct Treatment
(repeated rounds of burst suppression)

Failure to control seizures while weaning 3rd line


Stage III and IV: General anaesthesia (continuous IV midazolam, pentobarbital/thiopental, propofol) > 24 h
Continuous EEG monitoring, or intermittent EEG every 24 h
Ketamine bolus 1-2 mg/kg, followed by infusion 0.6 mg/kg/h to 10 mg/kg/h
Magnesium bolus 4 g, followed by infusion 2 to 6 g/h
Consider Immunotherapy:
• 1000 mg methylprednisolone for 3 days followed by 1 mg/kg/day for 1 week
• 30 g IV Immunoglobulin for 3 to 5 days
• 3 to 5 cycles Plasma exchange
Consider: hypothermia 32-35 °C < 48 h or ketogenic diet (1:1 to 1:4)
Consider: ECT, CSF-drainage, withdrawal of AEDs and others

Efficacy and safety of ketamine in refractory status epilepticus in children

Anna Rosati, MD, PhD
Manuela L'Erario, MD
Lucrezia Ilvento, MD
Costanza Cecchi, MD
Tiziana Pisano, MD
Lorenzo Mirabile, MD
Renzo Guerrini, MD

Neurology® 2012;79:2355-2358

Table 2 Treatment regimen in 9 children with refractory convulsive status epilepticus

Patient no.	Baseline AED treatment	Treatment of SE prior to KE	Duration of SE prior to KE, d	KE dosage, gamma/kg/min	Drugs associated with KE	KE response[a]	Duration of KE treatment
1[b]	CZP, PB, RUF	MDZ, PB, TP	4	27	MDZ, RUF, CZP	Yes	6 d
1[c]	CZP, PB	MDZ, PB, PR, TP	3	55	MDZ, PB, STP, CLB	Yes	17 d
2[b]	PB, TPM	MDZ, PB, TP	16	20	MDZ, PB, TPM	Yes	4 d
2[c]	LTG, PB, TPM	MDZ, PB	2	30	MDZ, PB	Yes	3 d
3	CBZ, ETM, PB	MDZ, PB, VPA, LEV	7	50	MDZ, PB	Yes	3 d
4	LZP, PB, VPA	MDZ, VPA, PB	5 h	10	MDZ, LZP	No	6 h
5	FBM, NZP, PB	MDZ, PB	6	40	MDZ, NZP, PB, FBM	Yes	9 d
6	CBZ	MDZ, PHT, VPA, PB	6	10	MDZ	No	8 h
7	LEV, PHT, VPA	MDZ, PR	26	60	MDZ, VPA, PB	No	1 d
8	None	MDZ, PHT, VPA, LEV, PB, PR, TP	12	40	MDZ, PHT, PB	Yes	6 d
9	None	MDZ, PHT, PR, TP	3	60	MDZ, PB, PR, TPM	Yes	6 d

Epilepsia, 54(8):1498–1503, 2013
doi: 10.1111/epi.12247

FULL-LENGTH ORIGINAL RESEARCH

Intravenous ketamine for the treatment of refractory status epilepticus: A retrospective multicenter study

*Nicolas Gaspard, †Brandon Foreman, ‡Lilith M. Judd, §James N. Brenton, §Barnett R. Nathan, ¶Blathnaid M. McCoy, ¶Ali Al-Otaibi, #Ronan Kilbride, **Ivan Sánchez Fernández, ††Lucy Mendoza, ‡‡Sophie Samuel, ‡‡Asma Zakaria, ‡‡Giridhar P. Kalamangalam, §§Benjamin Legros, ††¶¶Jerzy P. Szaflarski, **Tobias Loddenkemper, ¶Cecil D. Hahn, §Howard P. Goodkin, †Jan Claassen, *Lawrence J. Hirsch, ‡Suzette M. LaRoche, and From the Critical Care EEG Monitoring Research Consortium

Table 2. Determinants of ketamine efficacy (N = 60 episodes)

	Likely response (N = 7)	Possible response (N = 12)	Likely or possible response (N = 19)	No response (N = 41)	p-Value (univ.)[a]	p-Value (multiv.)
Latency to ketamine; median (range)	12 h (6 h–7 d)	5 d (18 h–30 d)	4.5 d (6 h–30 d)	10 d (12 h–122 d)	0.0053	NS
Number of previously failed drugs; median (range)	4 (3–7)	6 (3–11)	6 (3–11)	8 (3–16)	0.0012	<0.01
Etiology						
Unknown (N = 34)	1	7	8	26	<0.001	NS
Anoxic (N = 7)	4	0	4	3		
Acute nonanoxic (N = 13)	2	2	4	9		
Remote (N = 6)	0	3	3	3		
SE classification						
Generalized convulsive (N = 14)	2	4	6	8	NS	–
Generalized nonconvulsive (N = 3)	0	1	1	2		
Focal convulsive (N = 4)	0	2	2	2		
Focal nonconvulsive (N = 38)	5	5	10	28		
Infantile spasms (N = 1)	0	0	0	1		
Maximum infusion rate (mg/kg/h); median (range)[a]	7 (0.9–10)	1.8 (0.6–7)	2 (0.6–10)	3 (0.05–10)	NS	–
Loading dose administered[b]	6/6 (100%)	5/8 (63%)	11/14 (79%)	23/32 (72%)	NS	–
Duration of administration	1 (0–2)	3 (0–10)	2 (0–10)	5 (0–27)	<0.001	NS
Number of concurrent drugs	3 (1–5)	5 (1–11)	4 (1–11)	6 (1–10)	<0.001	NS
Number of concurrent anesthetic drugs[c]	1 (0–1)	1 (1–3)	1 (0–3)	2 (1–3)	<0.001	NS

ANNALS of Clinical and Translational Neurology
Open Access

BRIEF COMMUNICATION

First-in-man allopregnanolone use in super-refractory status epilepticus

Henrikas Vaitkevicius[1,2], Aatif M. Husain[3], Eric S. Rosenthal[2,4], Jonathan Rosand[2,4], Wendell Bobb[3], Kiran Reddy[5], Michael A. Rogawski[6] & Andrew J. Cole[2,4]

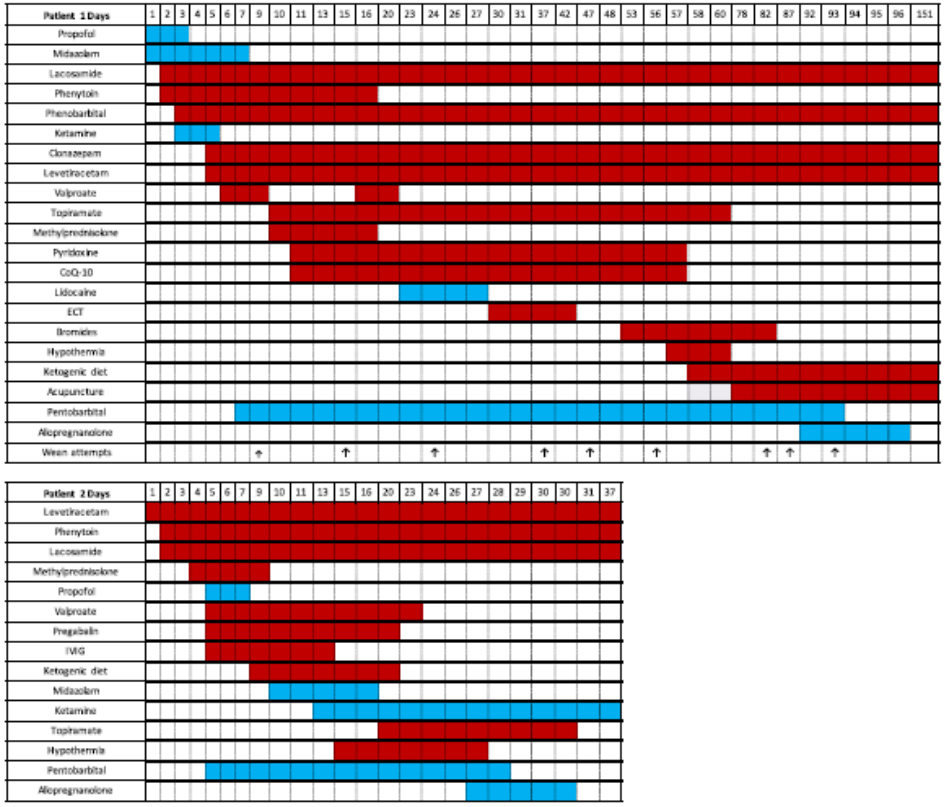


Figure 1. Graphical representation of most significant interventions during hospitalization. The color shadings correspond to the days of exposure. The blue shading represents continuous infusion and the red shading represents interval dosing. Arrows signify formal wean initiations.

ANNALS of Clinical and Translational Neurology
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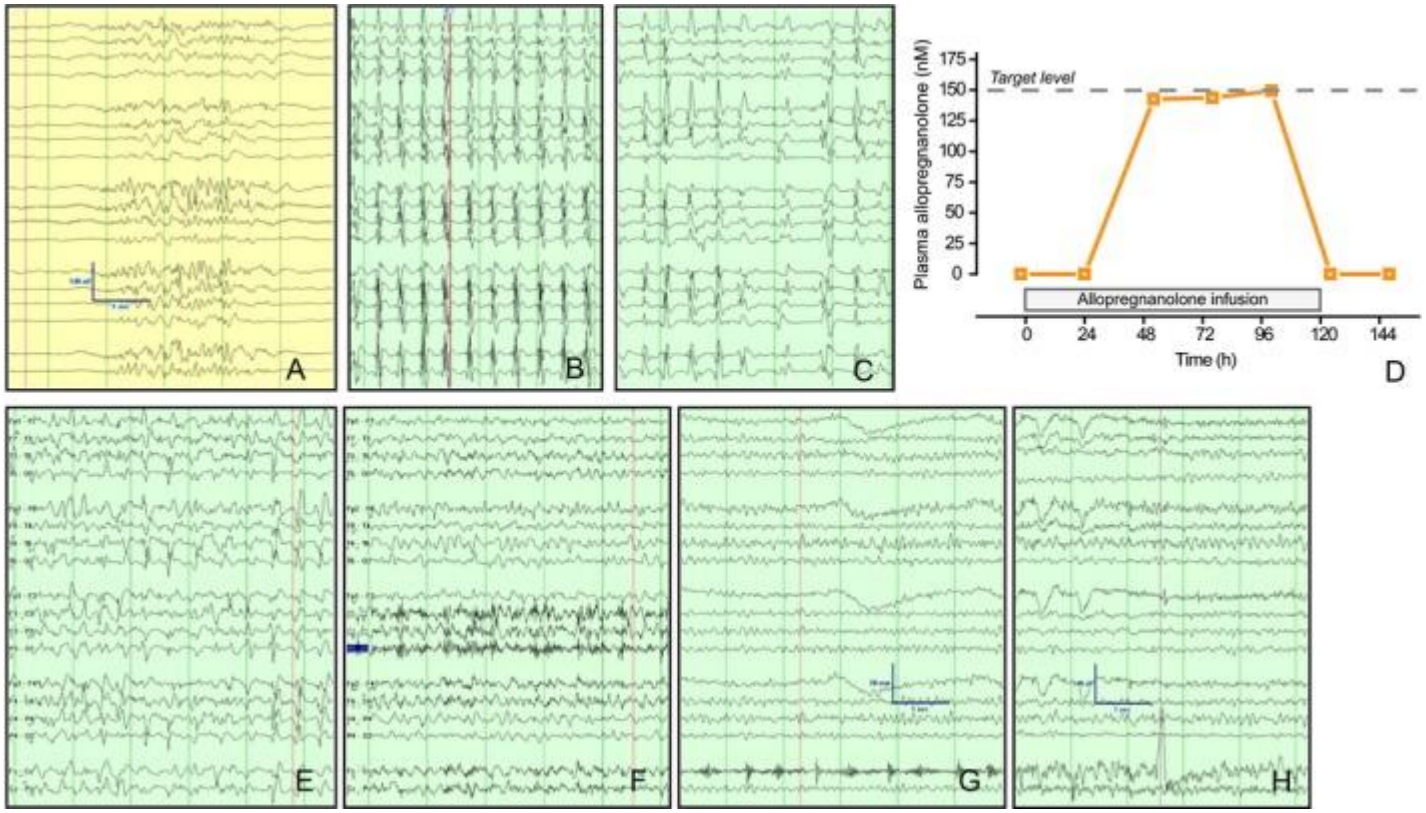
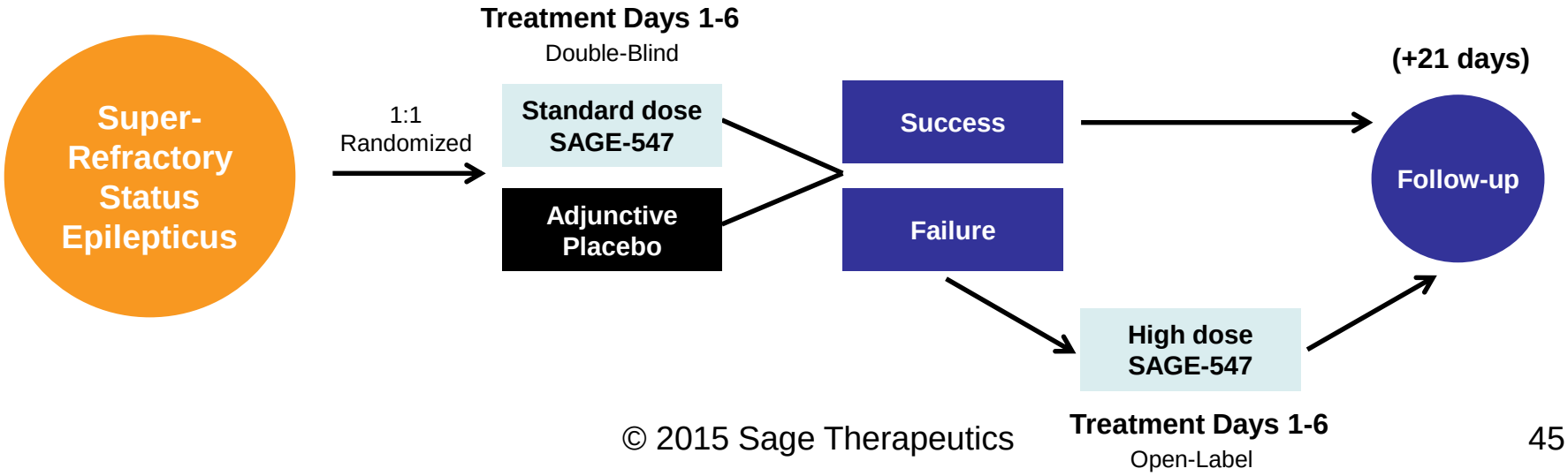


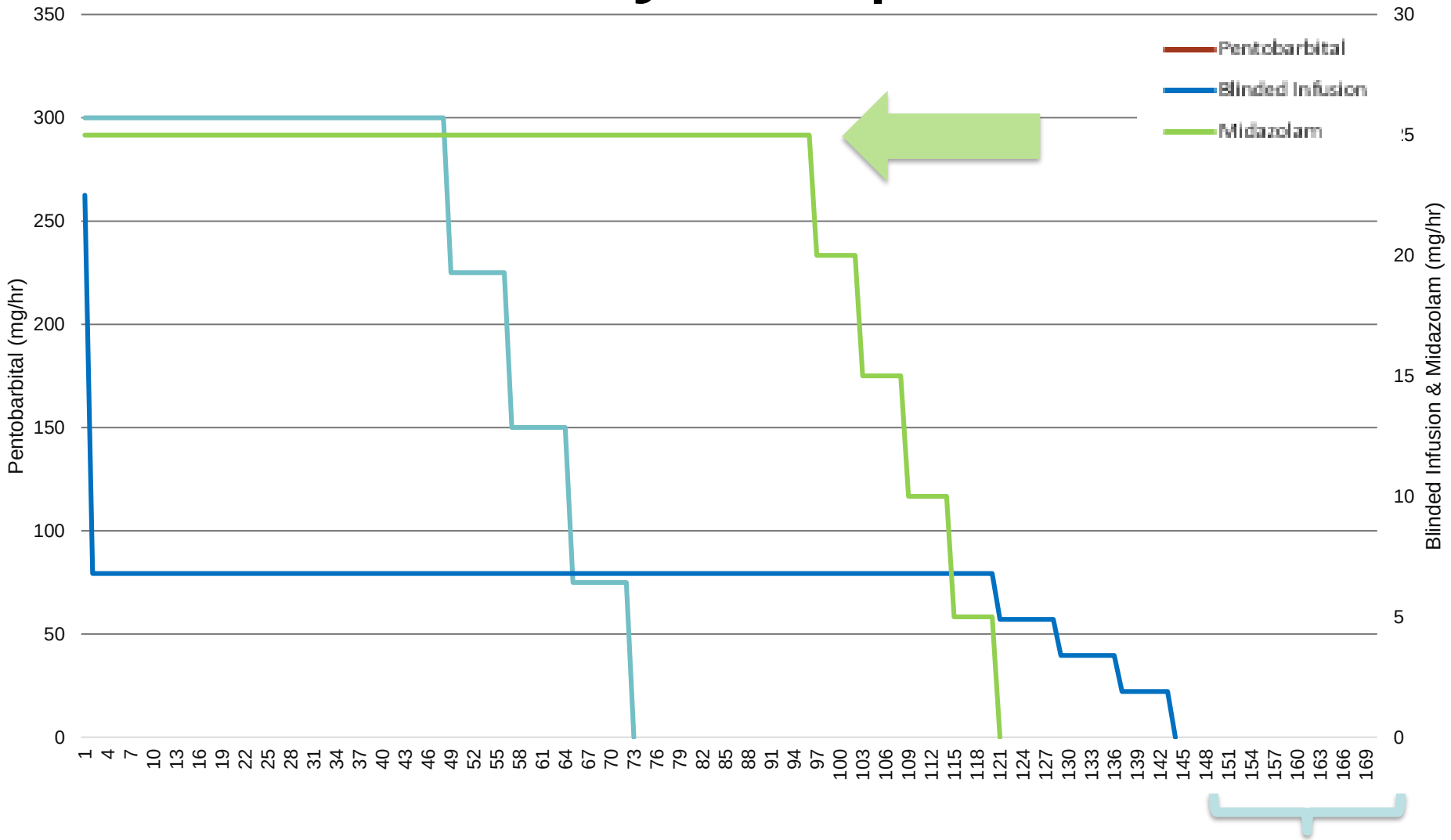
Study Design Overview

STATUS TRIAL

- Randomized, double-blind, placebo-controlled
- Expect up to 140 patients enrolled to get 126 evaluable patients
- Anticipate ~150 sites in U.S., Canada and Europe
- Non-responders eligible for open-label, SAGE-547 retreatment
- SPA agreement with FDA
- Primary Efficacy Endpoint: Continued resolution of SE for 24 hours following wean of all 3rd-line agents and SAGE-547/placebo



Primary Response



Hour 145-168

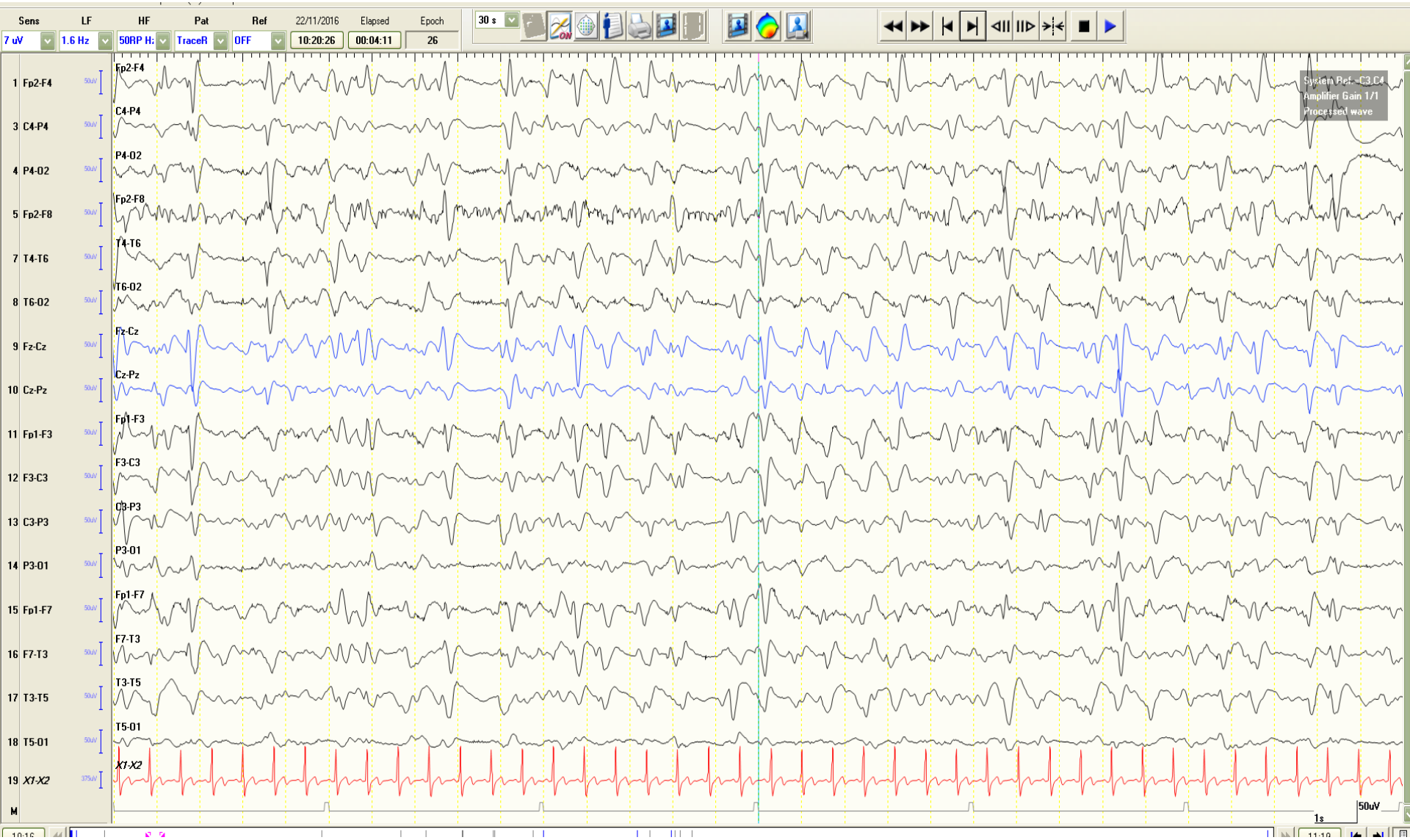
Bad news!

- September 12, 2017
- **Sage Therapeutics Reports Top-Line Results from Phase 3 STATUS Trial of Brexanolone in Super-Refractory Status Epilepticus**
- *-- Study did not achieve its primary endpoint in first-of-its kind trial for patients suffering from life-threatening seizure condition --*

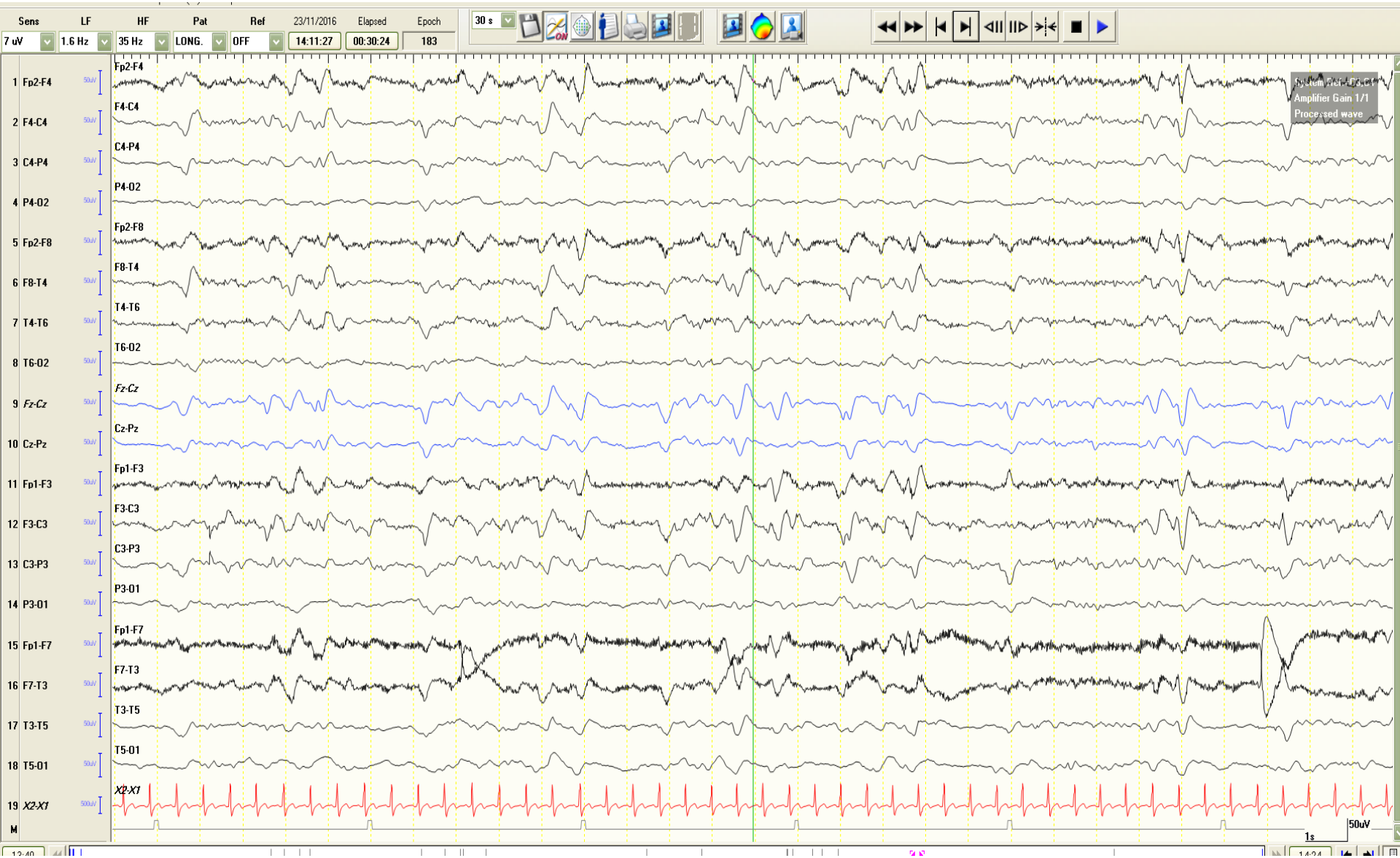
Stato di male non convulsivo in pazienti in coma

- Fino all'8% dei pazienti in coma senza evidenza clinica di crisi
- Come evoluzione di SE convulsivo, con o senza minime manifestazioni motorie (SE "subtle"), o come forma primitiva (SE vero o espressione di sofferenza cerebrale diffusa?)
- Ruolo del monitoraggio video-EEG (difficoltà di riconoscimento)
- Prognosi spesso sfavorevole (mortalità o conseguenze permanenti)
- **terapia aggressiva giustificata**

FF, 74 aa, coma persistente dopo emorragia intraparenchimale TO sn



Dopo lorazepam



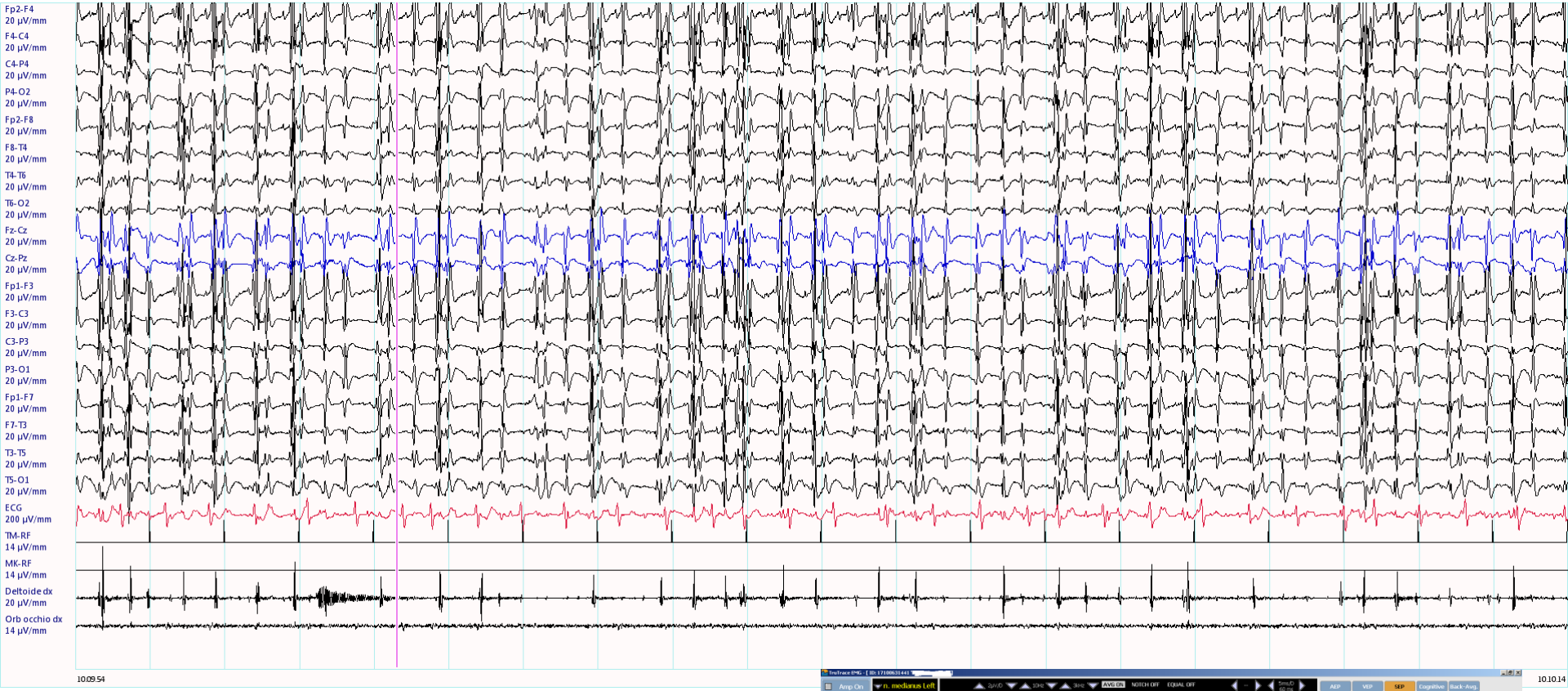
Osp. Bellaria (3.1 – 31.10.2015) stati di male in RIA

Pz	Classificazione dello stato epilettico					età	STESS	outcome
	semeiologia delle crisi	eziologia	EEG					
			sede	pattern	effetti della terapia			
1	focale motorio	non nota	F3-C3	punte subcontinue	scomparsa delle anomalie all'EEG di superficie	42	1	restitutio ad integrum
2	focale motorio e afasico	ematoma sottodurale acuto	C3	PLD+F alternate a crisi focali emisferiche sinistre	induzione della burst suppression ma ripresa di PLD alla sospensione	68	3	grave cerebroleso con minima coscienza
3	focale motorio e afasico	esiti di asportazione meningioma	C3-P3	PLD+F alternate a crisi secondariamente generalizzate	induzione burst suppression	80	2	restitutio ad integrum
4	non convulsivo con coma	esiti di asportazione meningioma	emisferico sn	PLD o PLD+F	persistenza di PLD con aspetto di punta lenta	75	5	deceduto
5	focale motoria	ematoma sottodurale acuto	emisferico dx (max T4)	PLD+F alternate a crisi focali emisferiche destre	persistenza di PLD senza ripresa di coscienza	78	4	deceduto
6	focale sensitivo-motoria	iperglicemia non chetosica	C3-P3	crisi focali subentranti	scomparsa delle anomalie all'EEG di superficie	53	1	restitutio ad integrum
7	convulsivo	non nota	Frontali dx>sn	scariche di polipunta alternate a diffuso rallentamento dell'elettrogenesi	scomparsa delle anomalie dopo induzione di burst suppression	56	4	risoluzione dello status e ripresa ADL
8	focale con arresto del contatto	ematoma sottodurale acuto	C3-P3	PLD+F alternate a crisi focali emisferiche sinistre	persistenza di PLD	76	3	interruzione stato di male/esito clinico non noto
9	focale con arresto del contatto	ematoma sottodurale acuto	F8-P4	sharp-waves FP destre	PLD+F	87	5	deceduto
10	focale distonico	encefalite da anticorpi anti-LGI1	P3	PLD sn alternato a crisi	scomparsa anomalie EEGgrafiche	68	3	restitutio ad integrum

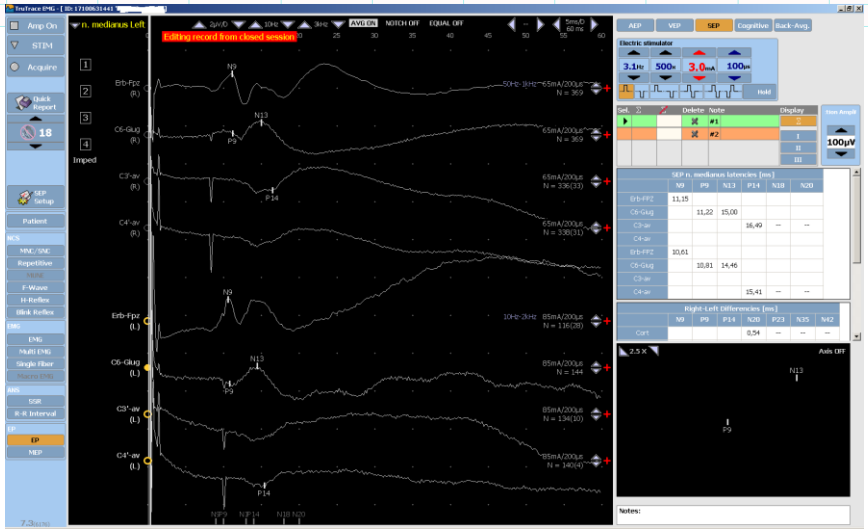
Pasini E, Zanello M, Michelucci R 2016

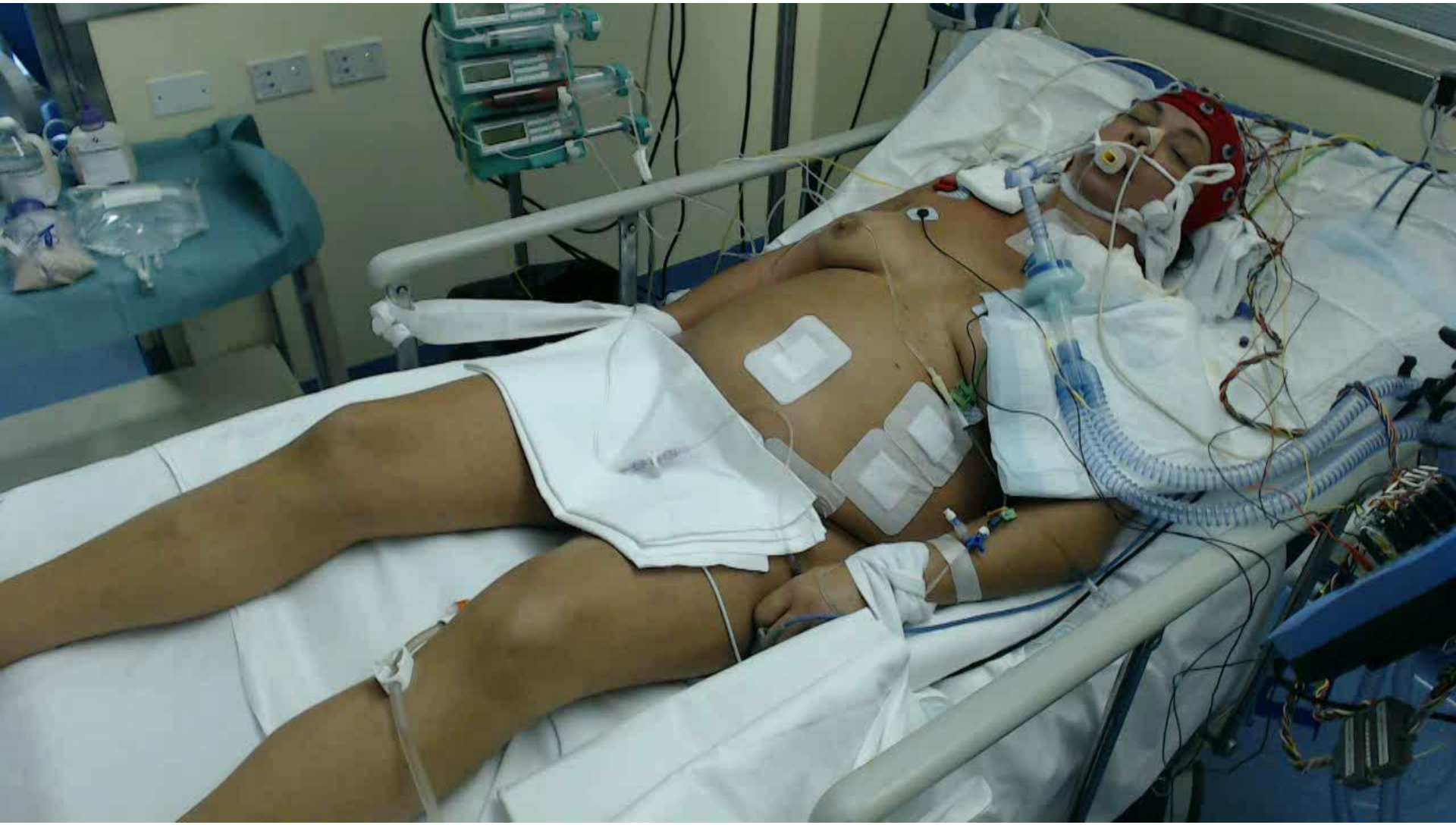
Stato di male mioclonico nei pazienti in coma

- Complicanza di arresto cardio-circolatorio
- Mioclono stimolo-sensitivo o spontaneo
- EEG con burst-suppression
- Prognosi sfavorevole, correlata alla gravità del danno ipossico e non al mioclono
- Non è indicata una terapia aggressiva



- Donna di 67 aa
- Arresto cardiocircolatorio
- Valutazione a 48 ore
- Coma profondo e stato mioclonico





Conclusioni: unmet needs

- Migliorare riconoscimento SE (soprattutto non convulsivo) e trattamento in tempi rapidi
- Chiarire il ruolo dei farmaci alternativi alla fenitoina: LEV, LCM, VPA e.v. (studi controllati e con numerosità sufficiente)
- Quanti trials con AEDs da effettuare prima di ricorrere alla ICU?
- Come monitorare le conseguenze prodotte dalla persistenza di crisi nei diversi tipi di SE
- Migliore integrazione dei vari attori (Neurologo, spec di PS, Rianimatore) → monitoraggio video-EEG continuo **Percorso diagnostico-terapeutico**

Quanto aspettare prima dell'ICU ?

Kellinghaus et al. BMC Neurology (2015) 15:230
DOI 10.1186/s12883-015-0486-y

BMC Neurology

STUDY PROTOCOL Open Access

Making SENSE - Sustained Effort Network for treatment of Status Epilepticus as a multicenter prospective registry

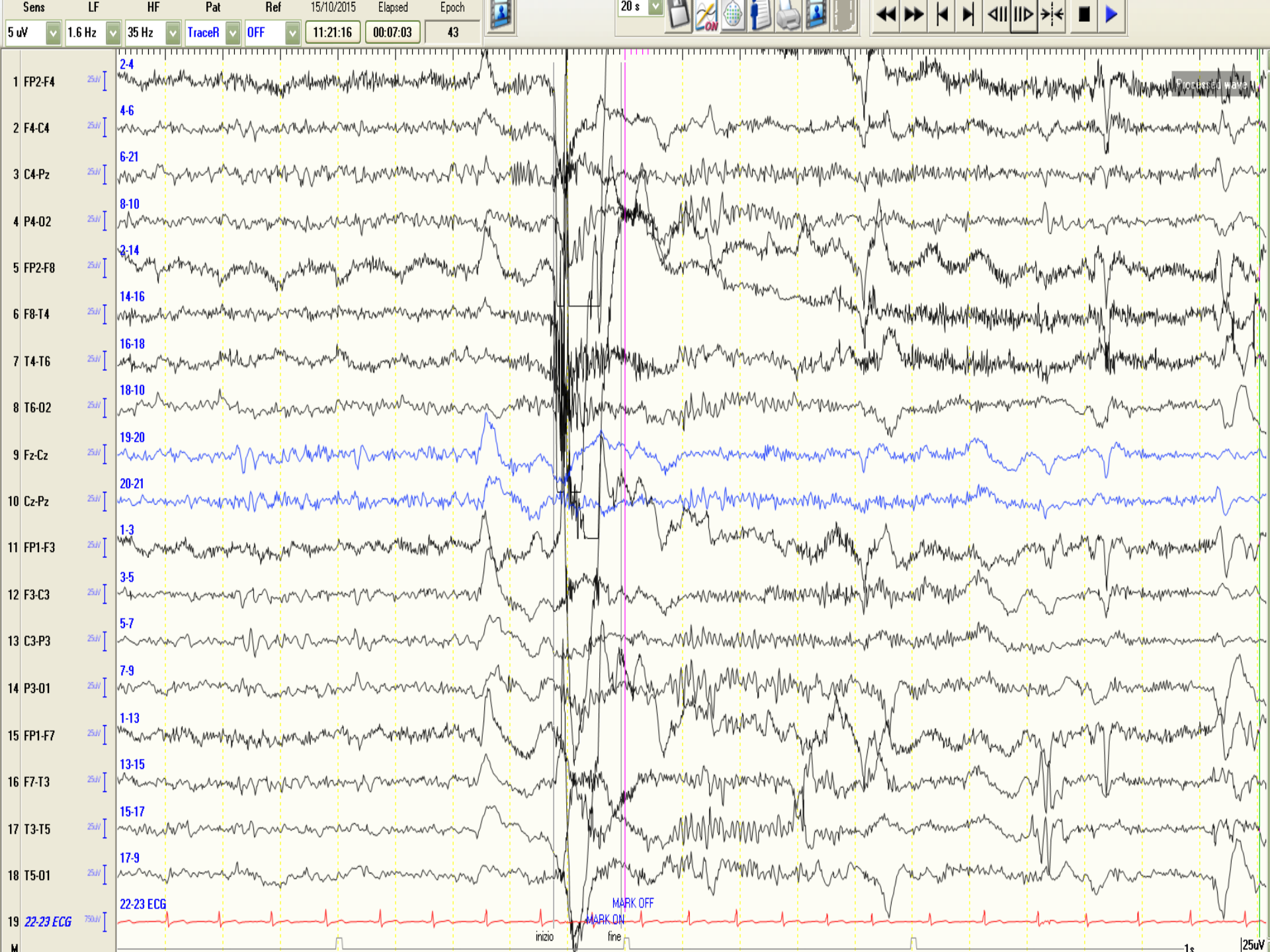
Christoph Kellinghaus[1*], Nicolas Lang[2], Andrea O. Rossetti[3], Stephan Rüegg[4], Christian Tilz[5], Eugen Trinka[6,10], Iris Unterberger[7], Zeljko Uzelac[8] and Felix Rosenow[9]

Preliminary results of the global audit of treatment of refractory status epilepticus.

Ferlisi M[1], Hocker S[2], Grade M[3], Trinka E[4], Shorvon S[5]; International Steering Committee of the StEp Audit.

Epilepsy Behav. 2015 Aug;49:318-24

riconoscimento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Elapsed
Epoch
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1.6 Hz
35 Hz
TraceR
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00:07:03
43
20 s
1 FP2-F4
2 F4-C4
3 C4-Pz
4 P4-O2
5 FP2-F8
6 F8-T4
7 T4-T6
8 T6-O2
9 Fz-Cz
10 Cz-Pz
11 FP1-F3
12 F3-C3
13 C3-P3
14 P3-O1
15 FP1-F7
16 F7-T3
17 T3-T5
18 T5-O1
19 22-23 ECG
2-4
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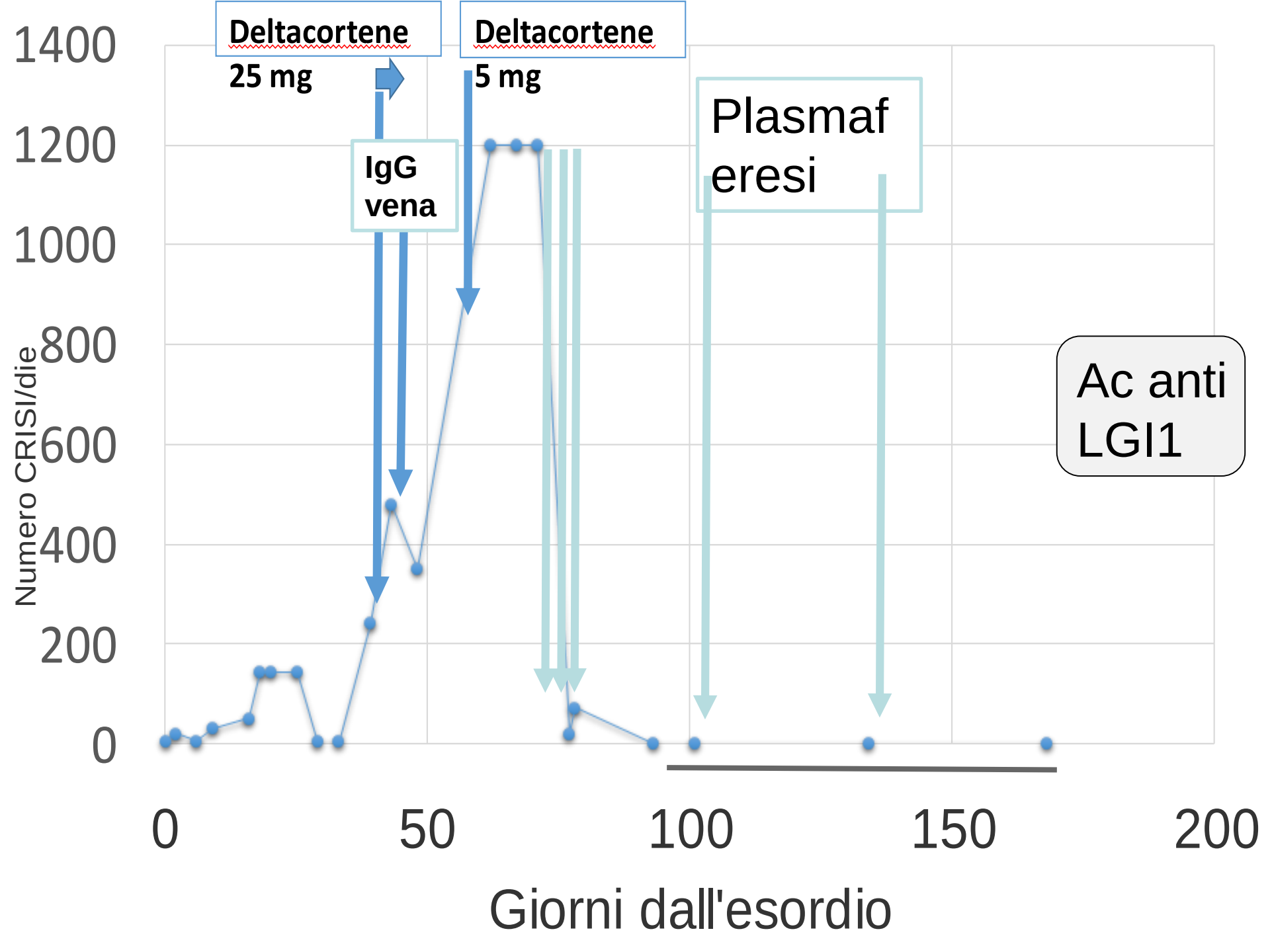
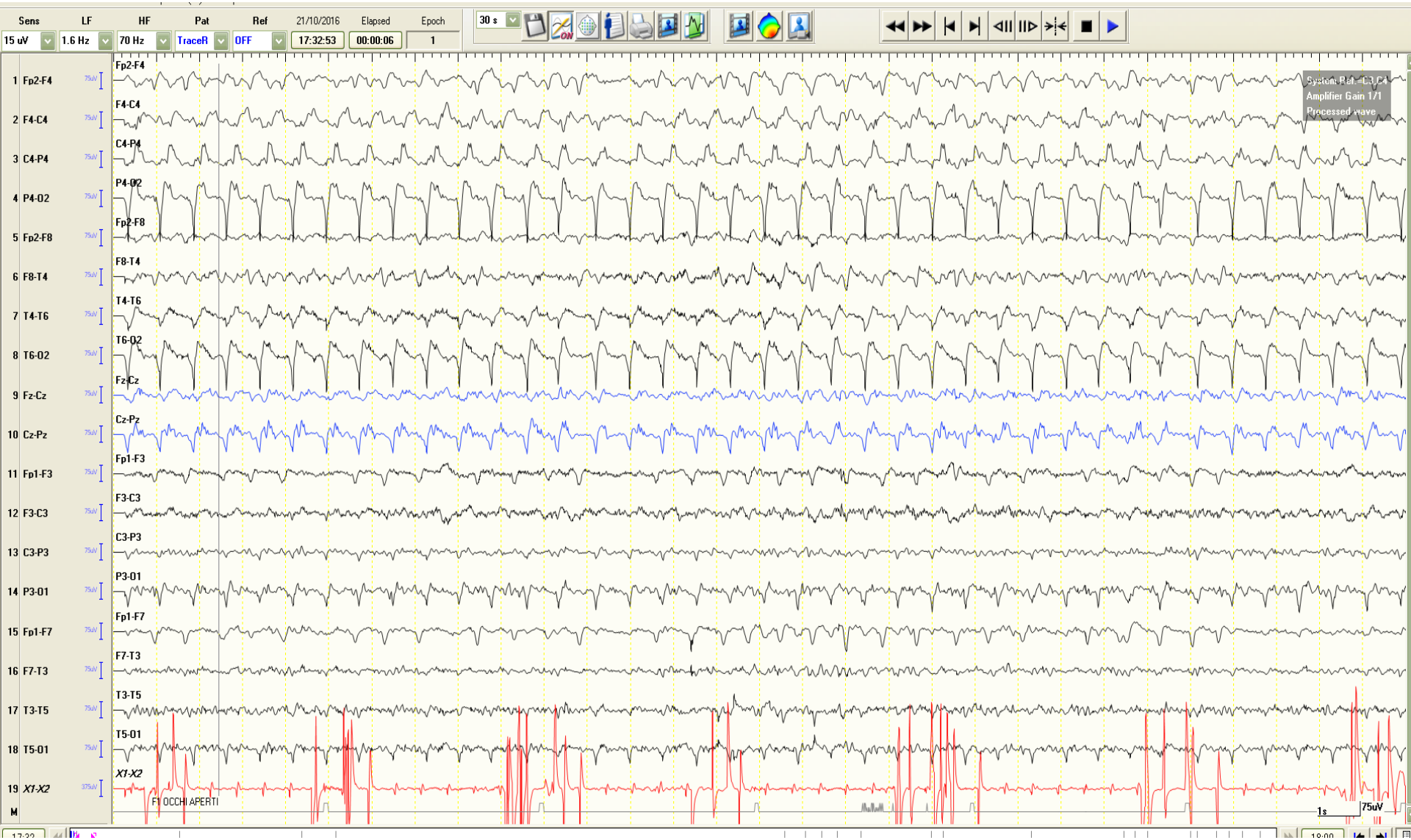
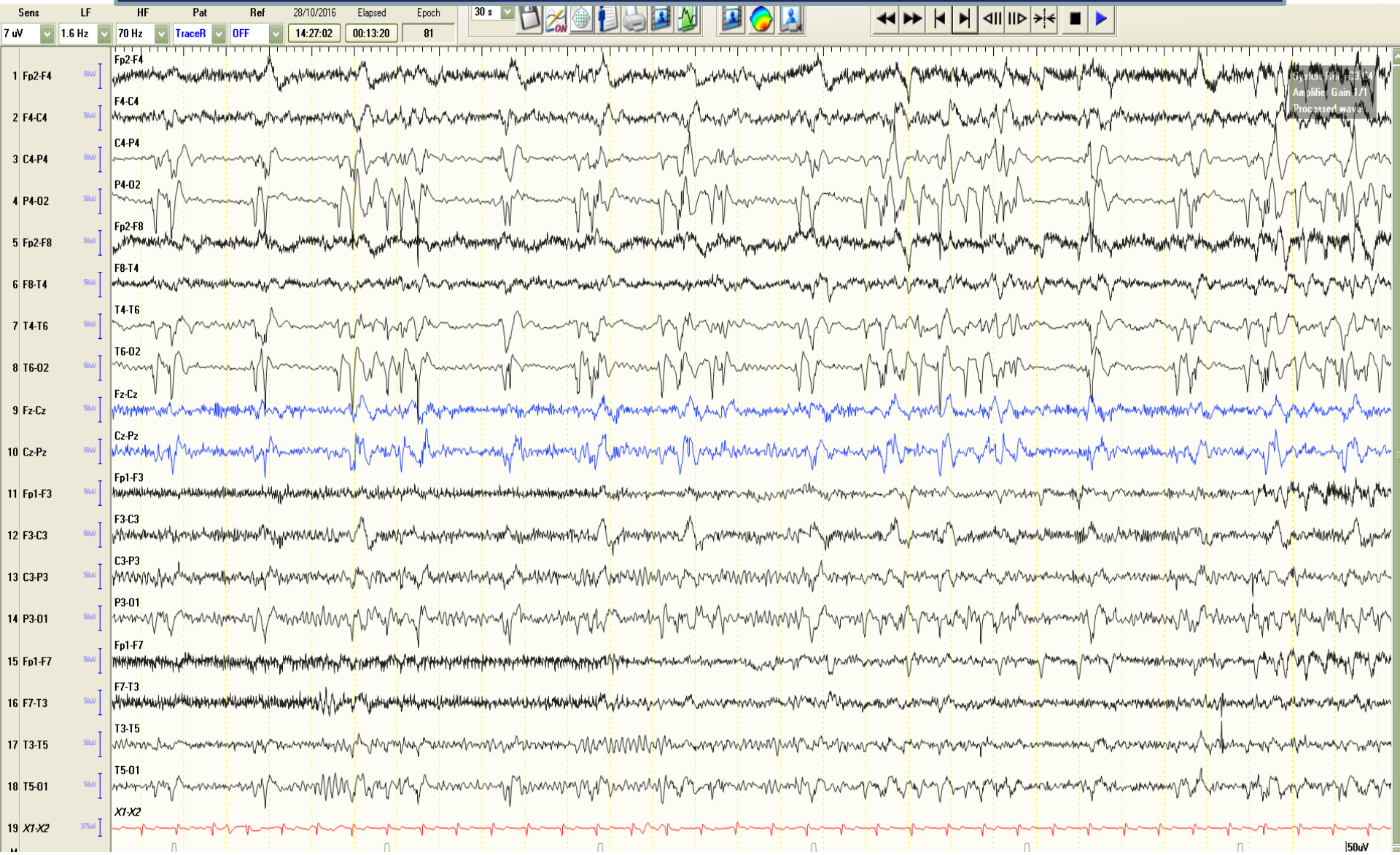
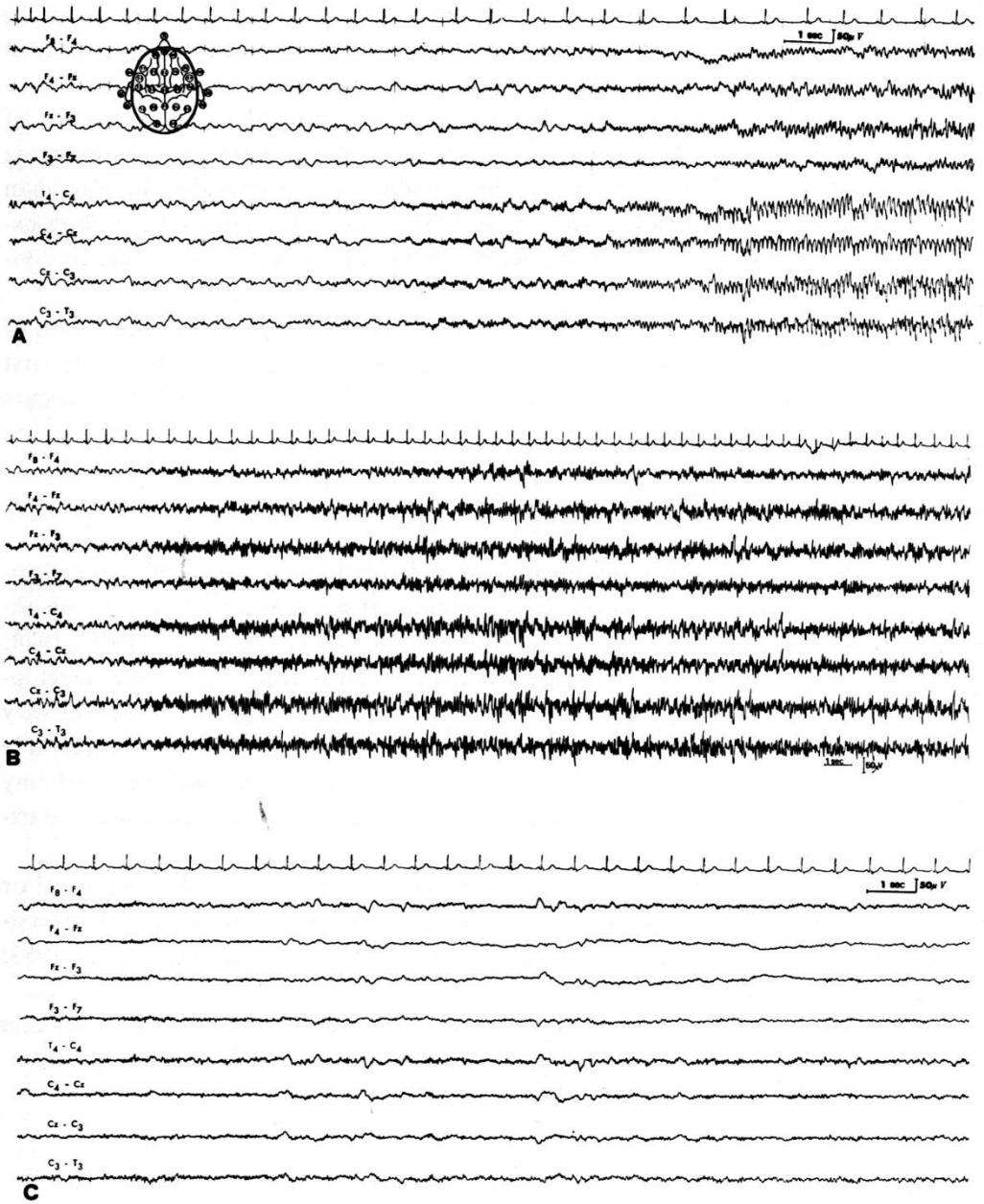

Deltacortene
25 mg
Deltacortene
5 mg
IgG
vena
Plasmaf
eresi
Ac anti
LGI1
Numero CRISI/die
1400
1200
1000
800
600
400
200
0
0
50
100
150
200
Giorni dall'esordio

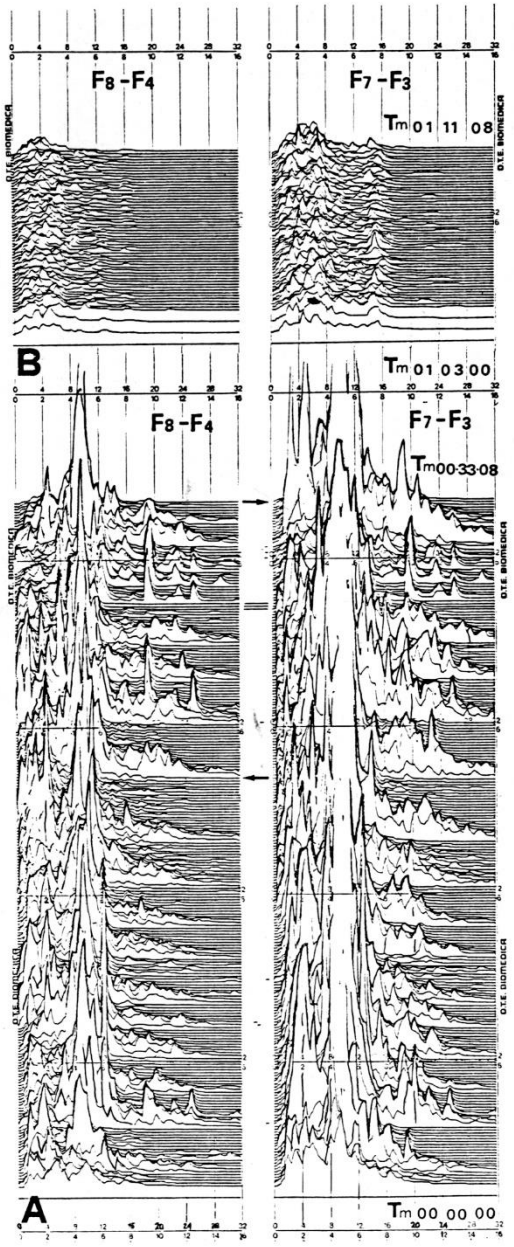
FV, 82 aa neglect sn, encefalite autoimmune



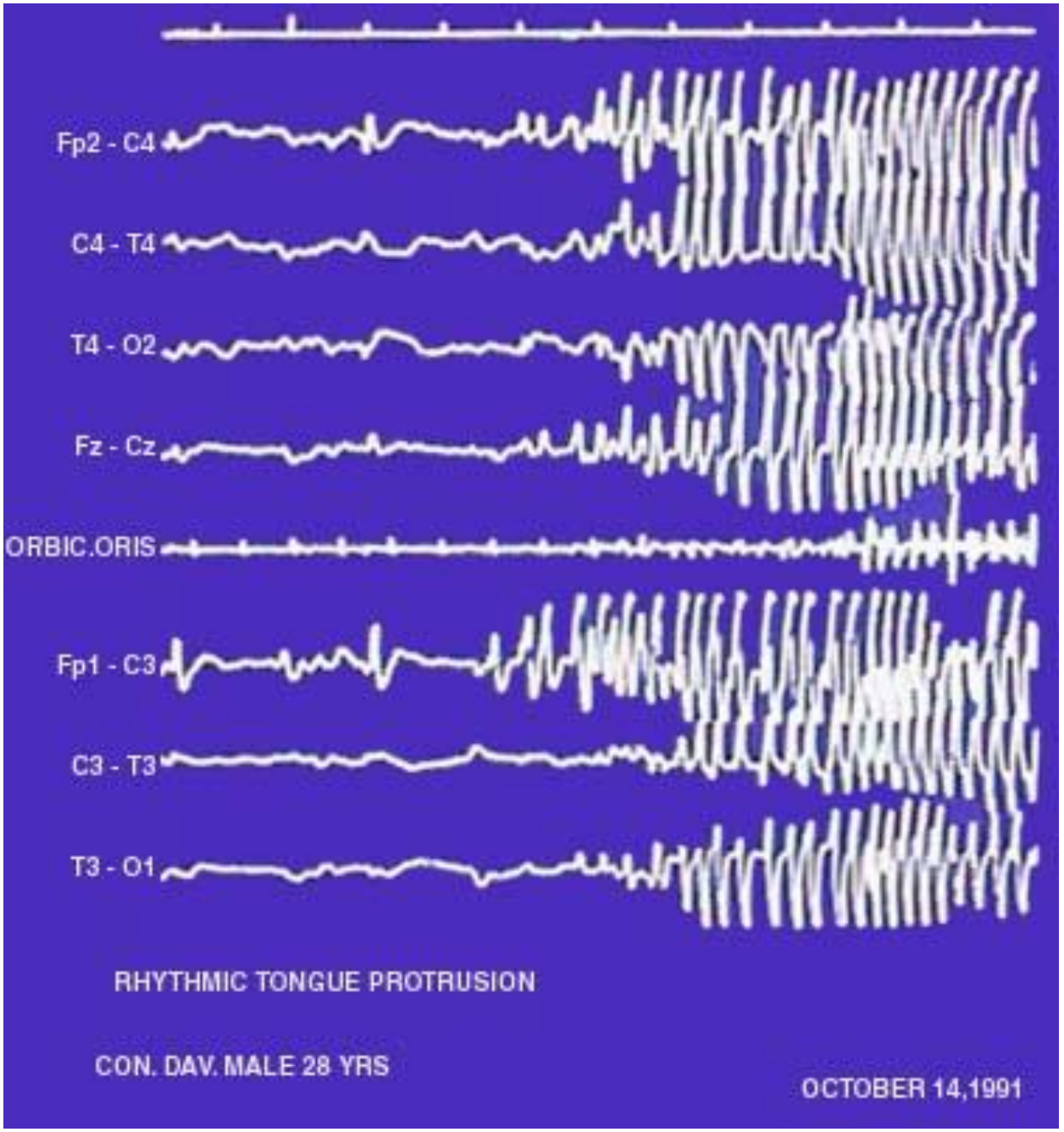
FV, 82 aa neglect sn, encefalite autoimmune







Michelucci et al 1985


Fp2 - C4
C4 - T4
T4 - O2
Fz - Cz
ORBIC.ORIS
Fp1 - C3
C3 - T3
T3 - O1
RHYTHMIC TONGUE PROTRUSION
CON. DAV. MALE 28 YRS
OCTOBER 14,1991

FASE 6: GESTIONE DELLE EMERGENZE

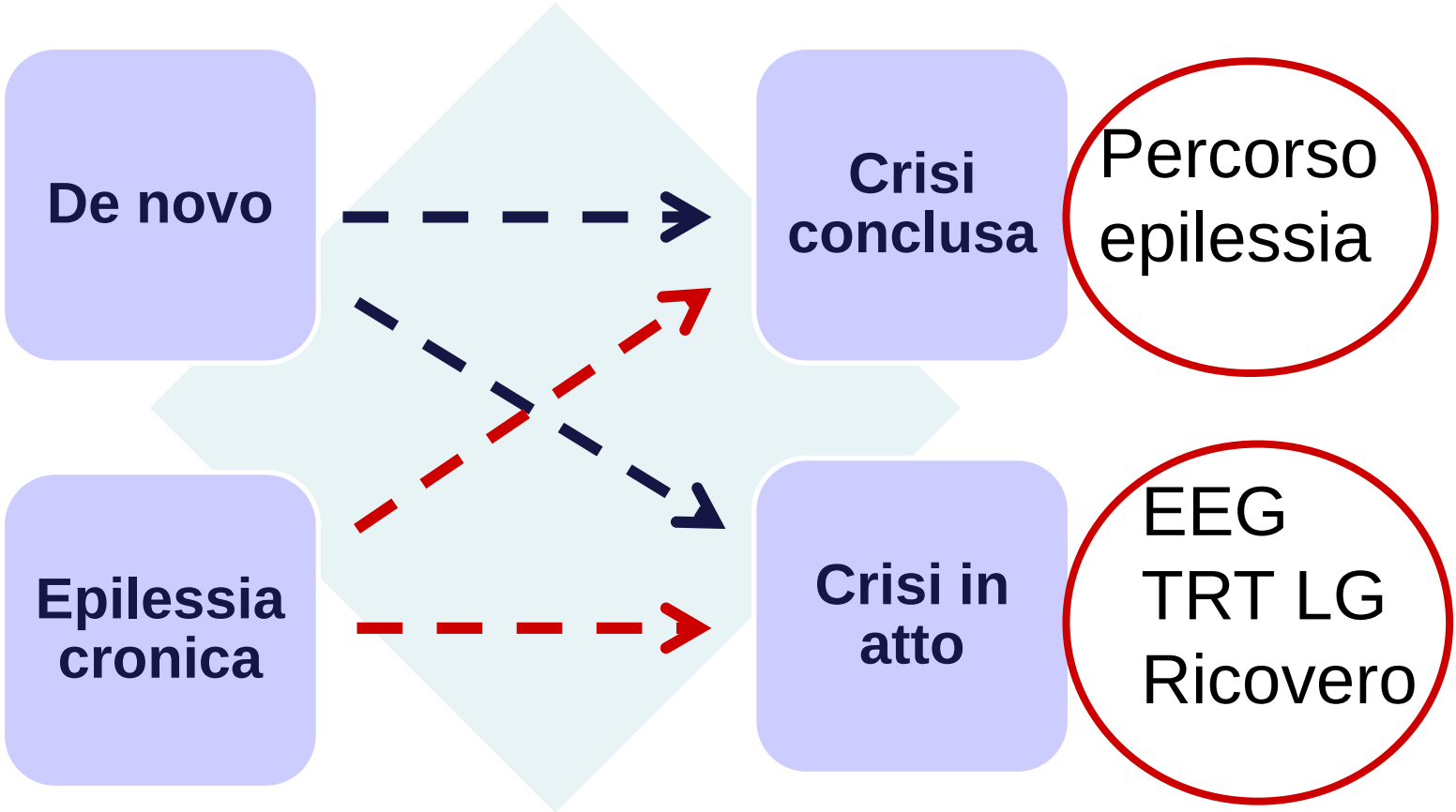
Criteri di ingresso:

↑Paziente epilettico noto con crisi epilettiche che accede al PS

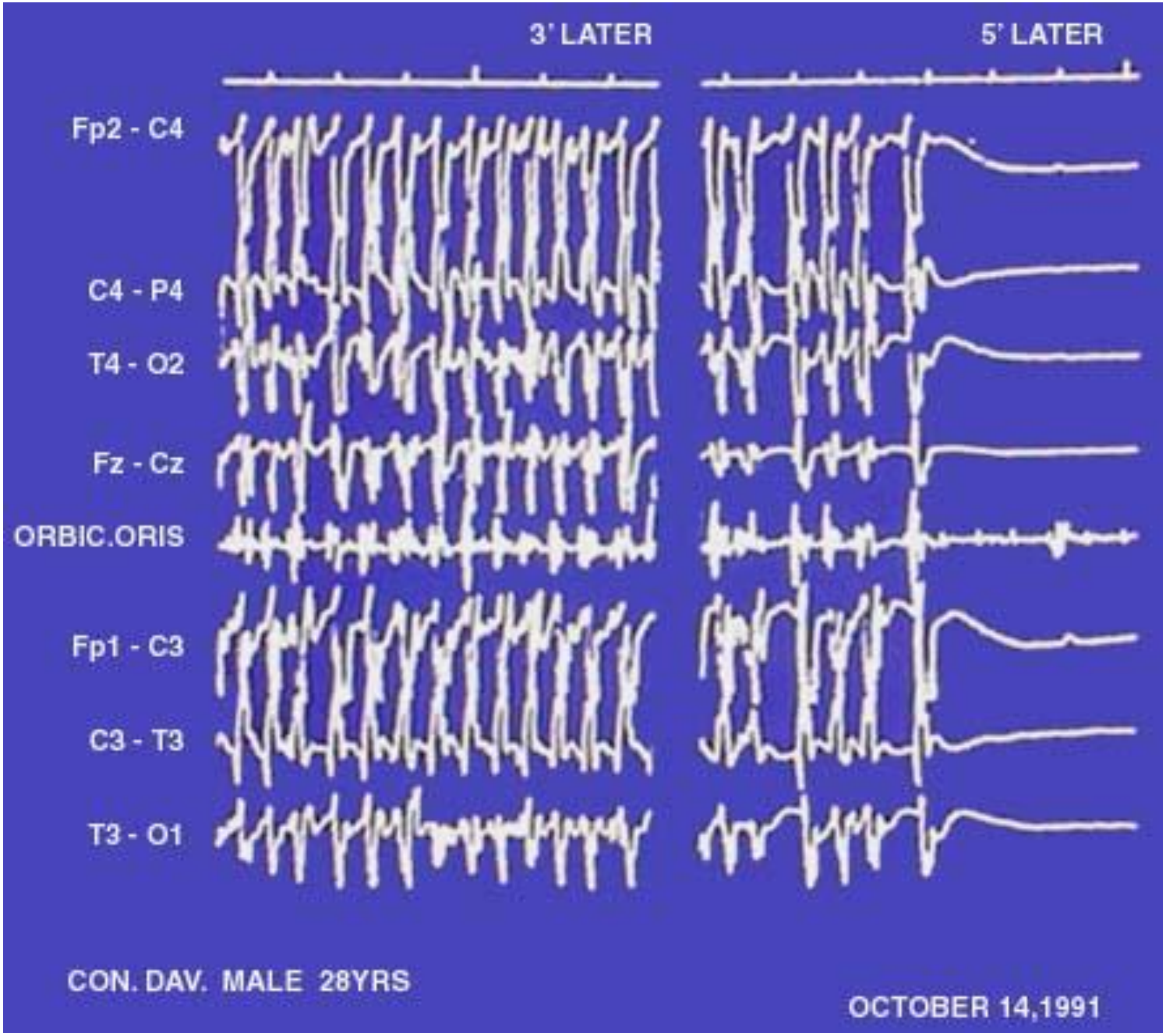
↑Paziente con stato di male che accede al PS

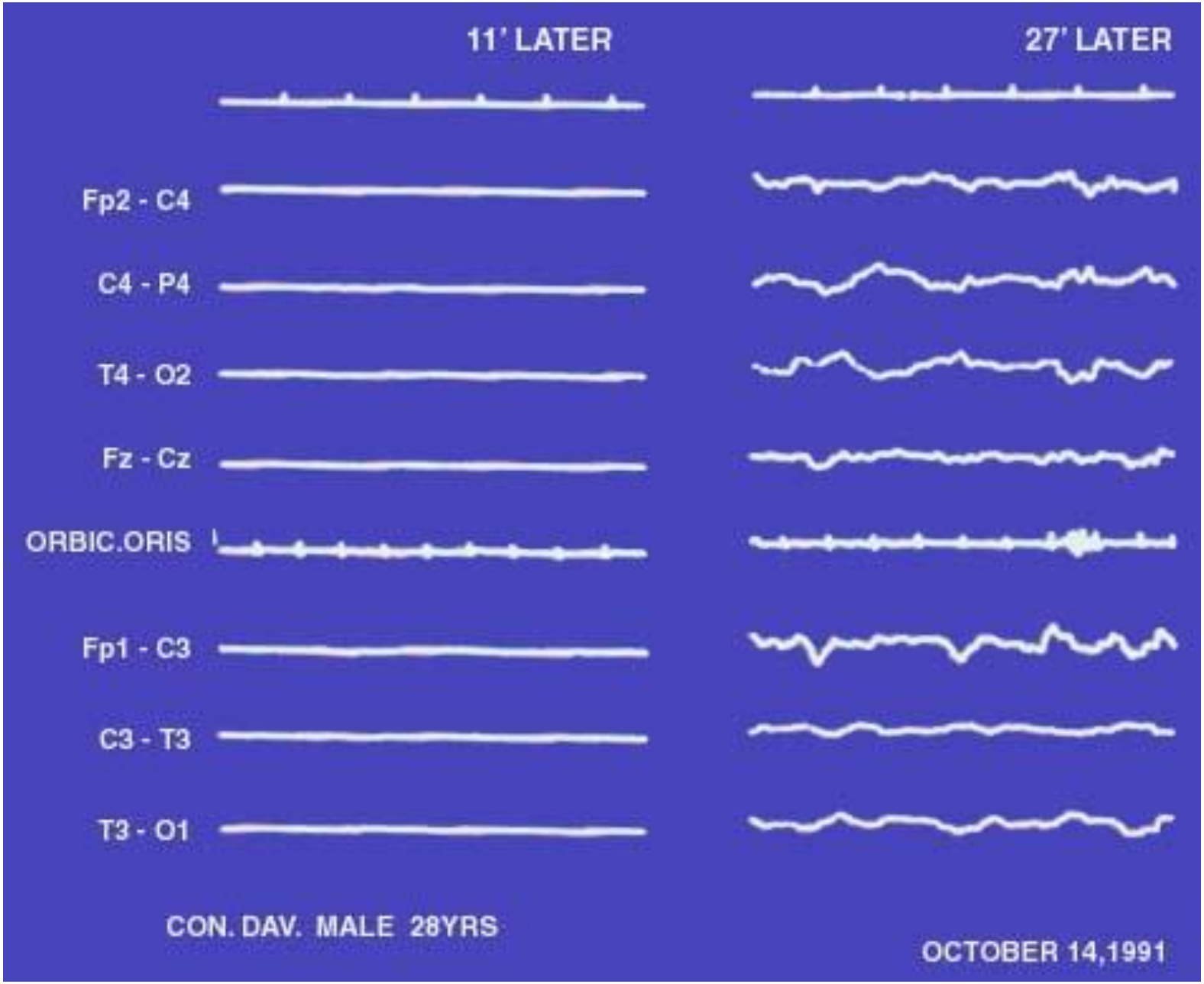
Criteri di uscita:

↑Termine dell'evento acuto



310 EEG urgenti per PS OM 2016


3' LATER
5' LATER
Fp2 - C4
C4 - P4
T4 - O2
Fz - Cz
ORBIC.ORIS
Fp1 - C3
C3 - T3
T3 - O1
CON. DAV. MALE 28YRS
OCTOBER 14,1991


11' LATER
27' LATER
Fp2 - C4
C4 - P4
T4 - O2
Fz - Cz
ORBIC.ORIS
Fp1 - C3
C3 - T3
T3 - O1
CON. DAV. MALE 28YRS
OCTOBER 14,1991

Criteri EEG

A comparison of lorazepam, diazepam, and placebo for the treatment of out of hospital status epilepticus

TABLE 2. STATUS EPILEPTICUS AT THE TIME OF ARRIVAL AT THE EMERGENCY DEPARTMENT.*

VARIABLE	LORAZEPAM GROUP (N=66)	DIAZEPAM GROUP (N=68)	PLACEBO GROUP (N=71)
		no. of patients (%)	
Status epilepticus terminated	39 (59.1)	29 (42.6)	15 (21.1)
Ongoing status epilepticus	27 (40.9)	39 (57.4)	56 (78.9)
	LORAZEPAM VS. PLACEBO	LORAZEPAM VS. DIAZEPAM	DIAZEPAM VS. PLACEBO
Odds ratio (simultaneous 95 percent CI) for termination of status epilepticus			
Unadjusted	5.4 (2.3–13.2)	1.9 (0.9–4.3)	2.8 (1.2–6.7)
Adjusted†	4.8 (1.9–13.0)	1.9 (0.8–4.4)	2.3 (1.0–5.9)

*CI denotes confidence interval.

†Each odds ratio was adjusted for race or ethnic group, the intervals from the onset of status epilepticus to study treatment and from study treatment to arrival at the emergency department, and cause of status epilepticus within each prognostic group.

Alldredge et al N Engl J Med 2001

Epilepsia, 51(2):177–190, 2010
doi: 10.1111/j.1528-1167.2009.02297.x

CRITICAL REVIEW AND INVITED COMMENTARY

Nonconvulsive status epilepticus and coma

Gerhard Bauer and Eugen Trinka

Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria

Table 1
Old and new terms of EEG patterns in the patients with critical illness, modified according to the 2012 version of the American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology [2].

Commonly used terminology	New terminology
Triphasic waves (TWs)	Continuous 2/s GPDs with triphasic morphology
Periodic lateralized epileptiform discharges (PLEDs)	Lateralized periodic discharges (LPDs)
Bilateral periodic epileptiform discharges (BiPLEDs)	Bilateral periodic discharges (BPDs)
Generalized periodic epileptiform discharges (GPEDs)	Generalized periodic discharges (PDs)
Frontal intermittent rhythmic delta activity (FIRDA)	Occasional frontally predominant brief 2/s generalized rhythmic delta activity
Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) with focal evolving rhythmic delta activity	Stimulus-induced-evolving lateralized rhythmic delta activity (SI-evolving LRDA)
Lateralized seizure, delta frequency range	Evolving lateralized rhythmic delta activity (LRDA)
Semirhythmic delta	Quasi RDA
Coma with lateralized epileptiform discharges (coma-LEDs) [14]	Coma with lateralized periodic discharges (coma-LPDs)
Coma with generalized epileptiform discharges (coma-GEDs)	Coma with generalized periodic discharges (coma-GPDs)

Patients without known epileptic encephalopathy
EDs > 2.5 Hz, or
EDs ≤ 2.5 Hz or rhythmic δ/θ activity (>0.5 Hz) AND one of the following:
EEG and clinical improvement after IV AED[a], or
Subtle clinical ictal phenomena, or
Typical spatiotemporal evolution[b]
Patients with known epileptic encephalopathy
Increase in prominence or frequency when compared with baseline with observable change in clinical state
Improvement of clinical and EEG[a] features with IV AEDs

EDs, epileptiform discharges (spikes, polyspikes, sharp-waves and sharp-and-slow-wave complexes); EEG, electroencephalography; IV AEDs, intravenous antiepileptic drugs. Reproduced with permission from [41].
[a]If EEG improvement without clinical improvement, or if fluctuation without definite evolution, this should be considered possible NCSE.
[b]Incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency >1 Hz or change in location), or decrementing termination (voltage or frequency).

Recent advances in status epilepticus.
Trinka, Eugen; Brigo, Francesco; Shorvon, Simon

Current Opinion in Neurology. 29(2):189-198, April 2016.
DOI: 10.1097/WCO.0000000000000307

Table 2 Salzburg Electroencephalography Consensus Criteria for nonconvulsive status epilepticus

Pattern EEG critico o non critico?

Timing Is Everything: Where Status Epilepticus Treatment Fails

Chloe E. Hill, MD,[1,2] Alomi O. Parikh, BA,[1] Colin Ellis, MD,[1]
Jennifer S. Myers, MD,[2,3] and Brian Litt, MD[1,4]

Status epilepticus is an emergency; however, prompt treatment of patients with status epilepticus is challenging. Clinical trials, such as the ESETT (Established Status Epilepticus Treatment Trial), compare effectiveness of antiepileptic medications, and rigorous examination of effectiveness of care delivery is similarly warranted. We reviewed the medical literature on observed deviations from guidelines, clinical significance, and initiatives to improve timely treatment. We found pervasive, substantial gaps between recommended and "real-world" practice with regard to timing, dosing, and sequence of antiepileptic therapy. Applying quality improvement methodology at the institutional level can increase adherence to guidelines and may improve patient outcomes.

ANN NEUROL 2017;82:155–165

Timing Is Everything: Where Status Epilepticus Treatment Fails

Chloe E. Hill, MD,[1,2] Alomi O. Parikh, BA,[1] Colin Ellis, MD,[1]
Jennifer S. Myers, MD,[2,3] and Brian Litt, MD[1,4]

ANN NEUROL 2017;82:155–165

TABLE 1. Time-Related Deviations From Protocol

Citation	Patient Population	Method	Presentation of Included Patients	Delay to First-Line Therapy	Delay to Second-Line Therapy	Delay to Third-Line Therapy
Pellock et al. (2004)[29]	889 adults and children with SE at multiple hospitals in the US	Prospective database	Sz ≥30 min	>30 min for 58% (520/889) of pts; >60 min for 29% (256/889) of pts		
Eriksson et al. (2005)[31]	157 children with convulsive sz in the ED or pediatric ICU at an academic hospital in Finland	Retrospective review	Convulsive sz ≥5 min	>30 min for 17% (26/157) of pts		
Lewena et al. (2009)[23]	542 episodes in 467 children with convulsive sz in the ED of eight hospitals in Australia and New Zealand	Retrospective review	Motor sz activity >10 min		Median 24 min from hospital presentation (IQR, 15–36 min)	Median 45 min from hospital presentation (IQR, 25–68 min)
Hillman et al. (2013)[21]	109 consecutive visits in 100 adults with SE in the ED at an academic hospital in Finland	Retrospective review	Sz ≥30 min or recurring szs without return to baseline in between	Median 70 min for out-of-hospital treatment		
Kämppi et al. (2013)[33]	82 adults with SE in the ED at an academic hospital in Finland	Retrospective review	Continuous sz ≥30 min, recurrent szs without return of consciousness, or >4 szs within 60 min	Median 35 min (range 0 min–77 h 5 min)	Median 3 h (range 30 min –77 h 5 min)	Median 2 h 55 min (range 0 min –81 h 45 min)
Rantsch et al. (2013)[30]	167 episodes in 118 adults with SE seen by neurology at an academic hospital in Germany	Retrospective review	Continuous sz ≥5 min or ≥2 discrete szs with incomplete return to baseline in between	>30 min for 61% (99/162) of pts		
Rossetti et al. (2013)[36]	263 episodes in 225 adults with SE at an academic center in Switzerland	Prospective data set	Continuous sz >5 min or repeated szs without return to baseline in between	>60 min for 62% (139/225) of pts		
Seinfeld et al. (2014)[22]	179 children with febrile (convulsive) SE at five academic hospitals in the US	Prospective observation	Sz ≥30 min or a series of szs without full recovery in between lasting ≥30 min	Median 30 min (IQR, 35; range 1–175 min)		
Ferlisi et al. (2015)[35]	488 children and adults with refractory SE in an ICU, multinational	Online registry dataset	Refractory SE with initiation of anesthetic agent in the ICU	>60 min for 62% (282/453) of pts		>60 min for 84% (393/466) of pts
Kämppi et al. (2015)[34]	70 adults with generalized convulsive SE in the ED at an academic hospital in Finland	Retrospective review	≥1 convulsive sz within (a) continuous sz ≥30 min, (b) recurrent szs without return of consciousness, or (c) >4 szs within 60 min irrespective of return of consciousness	Median 30 min (range 0 min–8 h 5 min)	Median 2 h 40 min (range 30 min –61 hours 54 min)	Median 2 h 38 min (range 0 min –66 h 20 min)
Sánchez Fernández et al. (2015)[27]	81 children with refractory convulsive SE at nine tertiary pediatric hospitals in the US	Prospective observation	Focal or generalized convulsive szs at onset with (a) failure of ≥2 AEDs, or (b) initiation of continuous AED infusion	Median 30 min (IQR 6–70 min)	Median 69 min (IQR 40–120 min)	Median 180 min (IQR 120–645 min)
Cheng et al. (2016)[32]	151 adults treated for SE at an academic hospital in the US	Retrospective review	≥5 min of (a) continuous clinical and/or electrographical sz activity, or (b) recurrent szs without recovery in between	>30 min for 64% (97/151) of pts		

SE = status epilepticus; US = United States; sz = seizure; min = minute(s); pts = patients; ED = emergency department; ICU = intensive care unit; IQR = interquartile range; h = hour(s); EEG = electroencephalogram; AED = antiepileptic drug.

A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus

*†‡Eugen Trinka, §Hannah Cock, ¶Dale Hesdorffer, #Andrea O. Rossetti, **Ingrid E. Scheffer, ††Shlomo Shinnar, ‡‡Simon Shorvon, and §§Daniel H. Lowenstein

Epilepsia, **(*):1–9, 2015

"None of the ictal EEG patterns of any type of SE is specific. Epileptiform discharges are regarded as the hallmark, but with increasing duration of SE, the EEG changes and rhythmic non-epileptiform patterns may prevail. Similar EEG-patterns, such as triphasic waves, can be recorded in various pathologic conditions, leading to substantial confusion in the literature"

Sodium valproate vs phenytoin in status epilepticus: A pilot study

U. K. Misra, DM,
Jayantee Kalita, DM and
Rajesh Patel, DM

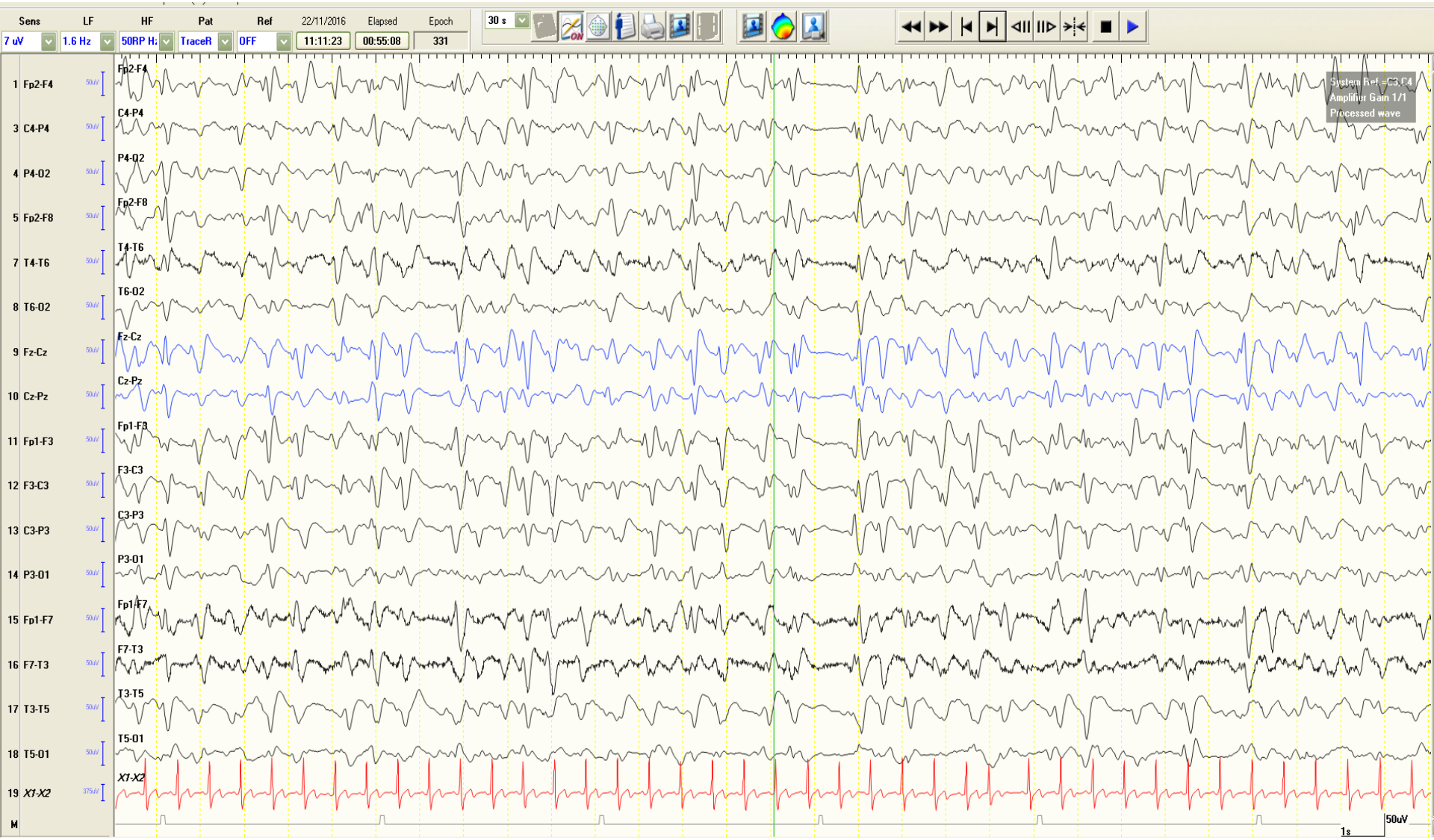
NEUROLOGY 2006;67:340–342

Table 2 *Clinical seizure cessation after infusion and 24-hour seizure freedom in patients with status epilepticus after VPA, PHT, VPA-PHT, and PHT-VPA*

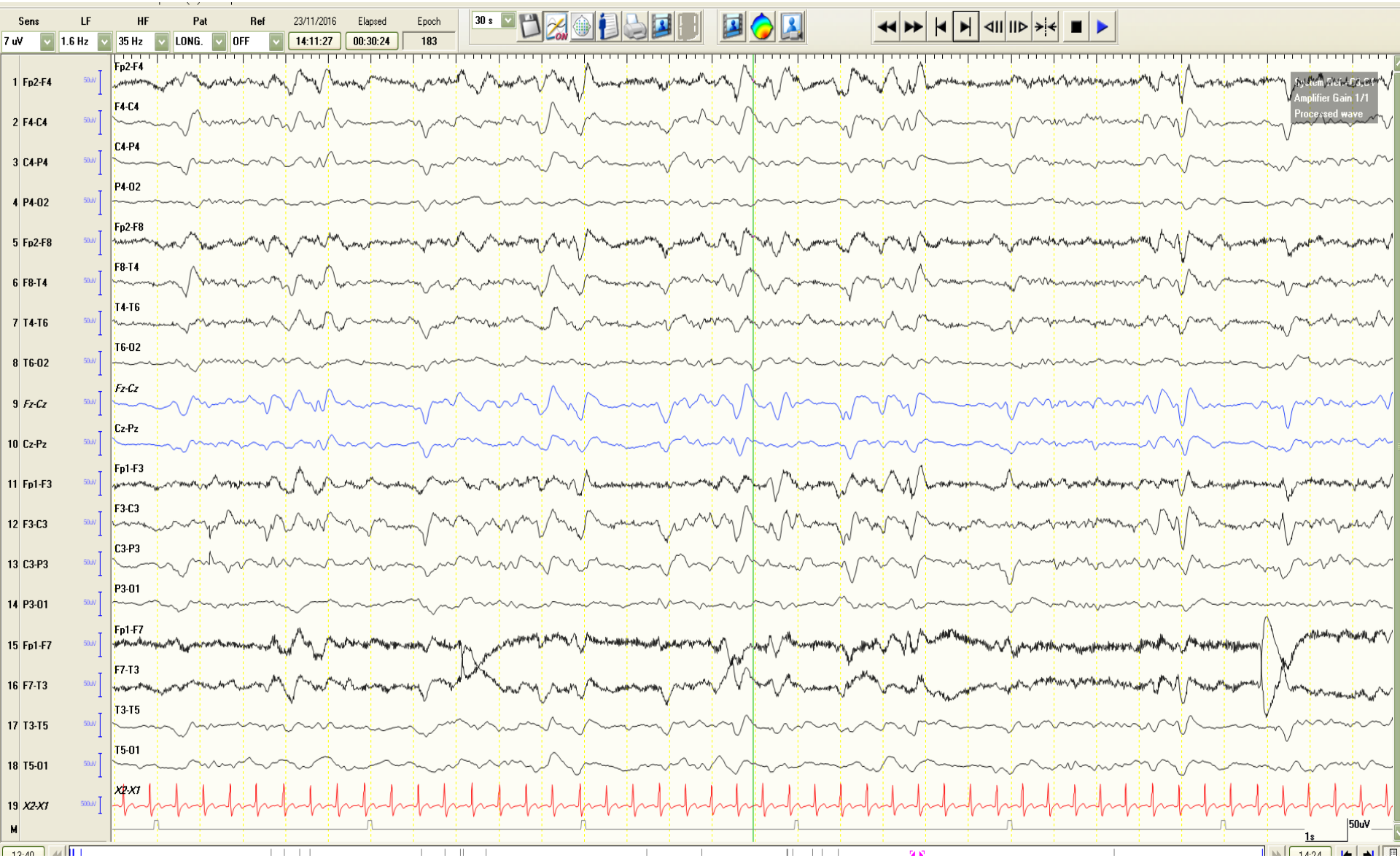
Primary outcome	Status aborted	Status not aborted	SE	One-sided *p* value
VPA	23 (65.7%)	12 (34.3%)	0.08	0.046
PHT	14 (42%)	19 (58%)	0.09	
VPA-PHT	3 (25%)	9 (75%)	0.12	0.004
PHT-VPA	15 (79%)	4 (21%)	0.09	
Secondary outcome	**24-h seizure freedom**	**Recurrence within 24 h**		
VPA	8 (57%)	6 (43%)	0.13	0.32
PHT	10 (43.4%)	13 (56.6%)	0.10	
Combination	11 (61%)	7 (39%)	0.11	

VPA = valproate; PHT = phenytoin; VPA-PHT = valproate followed by phenytoin; PHT-VPA = phenytoin followed by valproate.

FF, 74 aa, coma persistente dopo emorragia intraparenchimale TO sn



Dopo lorazepam



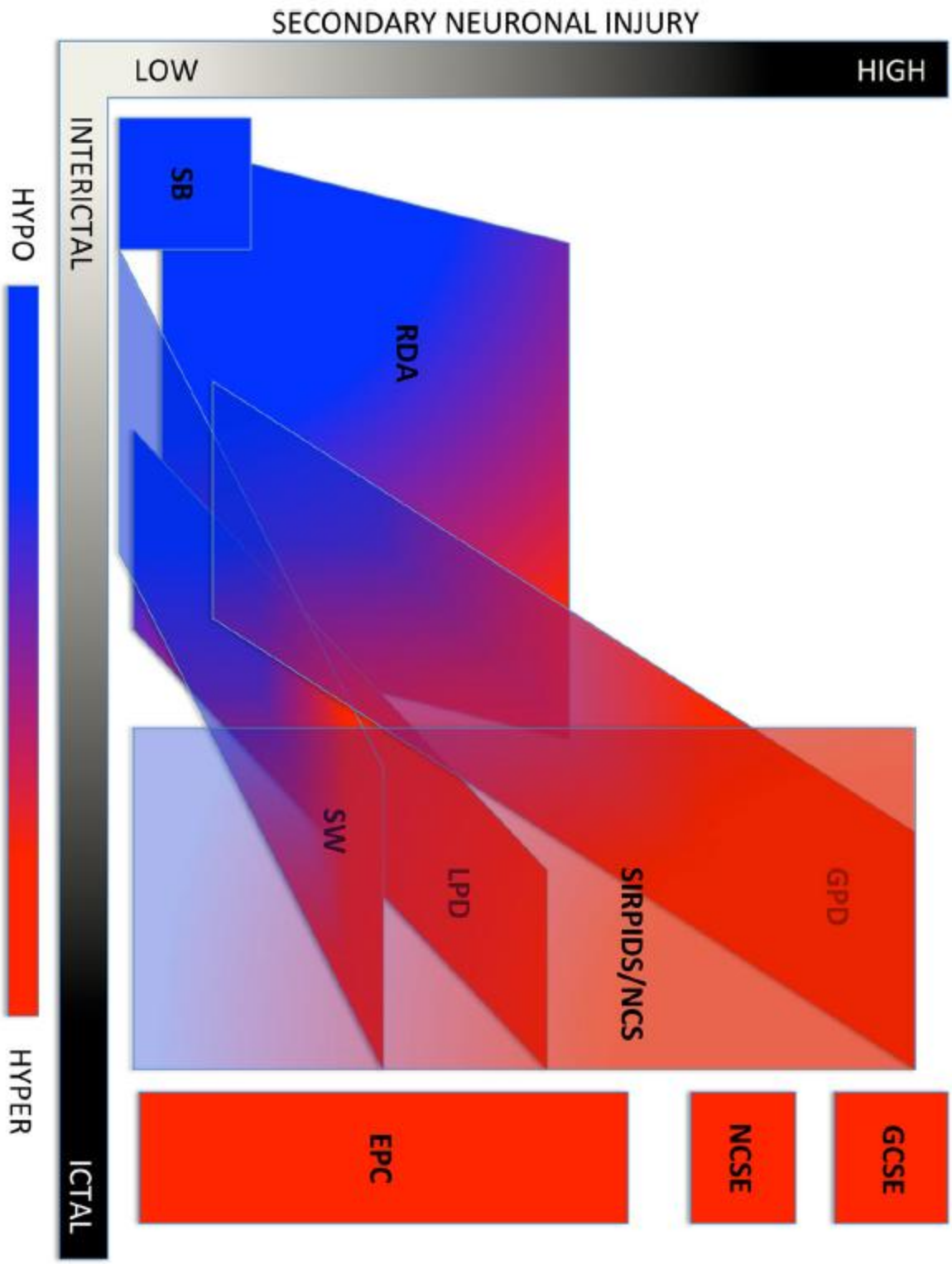
neurocritical care society Neurocrit Care (2016) 24:324–331
DOI 10.1007/s12028-016-0245-y

ORIGINAL ARTICLE

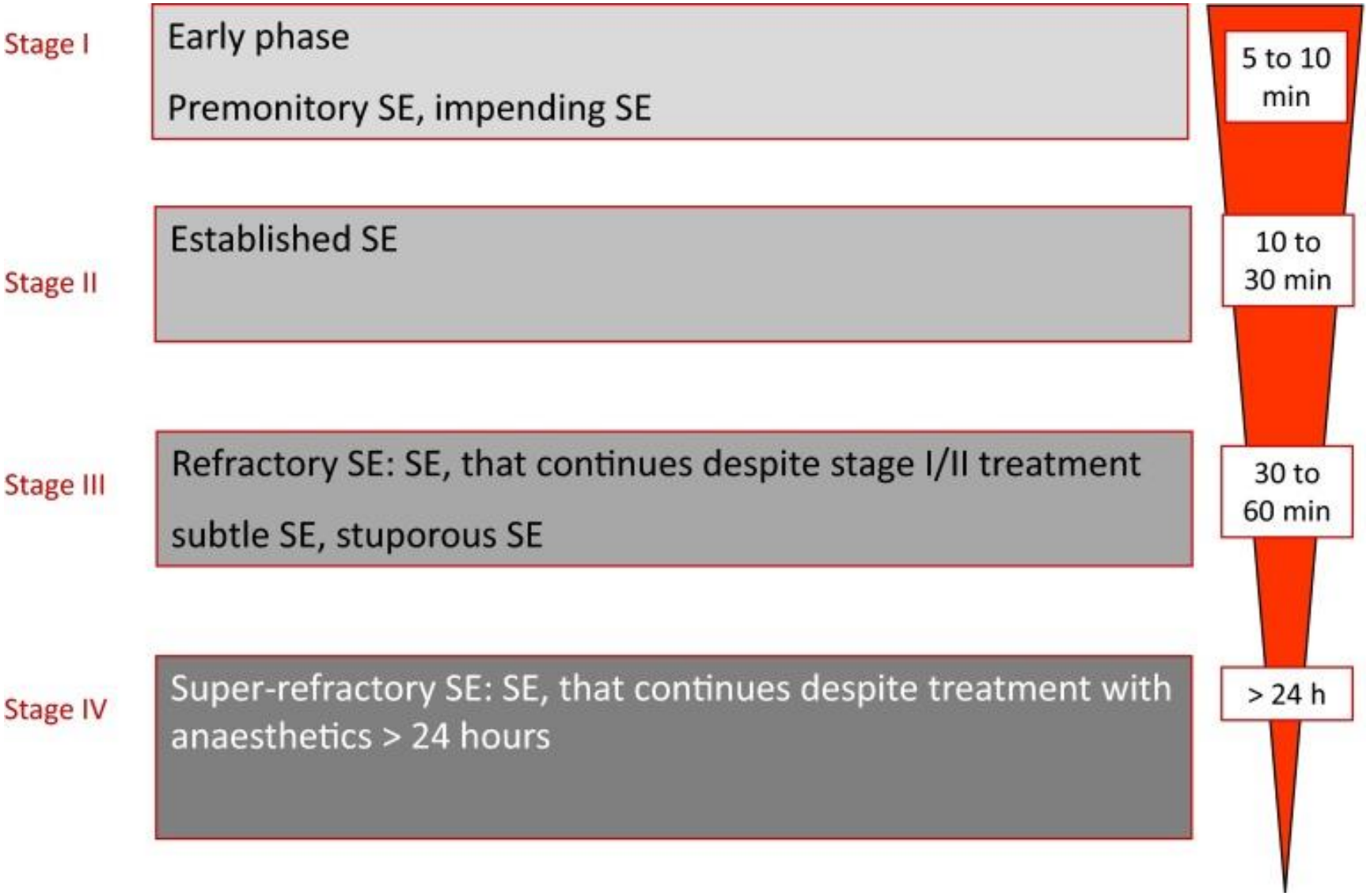
Metabolic Correlates of the Ictal-Interictal Continuum: FDG-PET During Continuous EEG

Aaron F. Struck[1] · M. Brandon Westover[1] · Lance T. Hall[2] · Gina M. Deck[1] · Andrew J. Cole[1] · Eric S. Rosenthal[1]

The ictal-interictal-injury-metabolism continuum



Clinical course of convulsive SE



Prognosi

J Neurol (2008) 255:1561–1566
DOI 10.1007/s00415-008-0989-1

ORIGINAL COMMUNICATION

Andrea O. Rossetti
Giancarlo Logroscino
Tracey A. Milligan
Costas Michaelides
Christiane Ruffieux
Edward B. Bromfield

Status Epilepticus Severity Score (STESS)

A tool to orient early treatment strategy

	Features	STESS
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type	Simple-partial, complex-partial, absence, myoclonic*	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Total		0–6

J Neurol (2008) 255:1561–1566
DOI 10.1007/s00415-008-0989-1

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Status Epilepticus Severity Score (STESS)

A tool to orient early treatment strategy

	Alive	Dead	Total
Score 0–2 (favorable)	72 (97 %)	2 (3 %)	74
Score 3–6 (unfavorable)	49 (61 %)	31 (39 %)	80
Total	121 (79 %)	33 (21 %)	154

⇩

Mortalità alla dimissione

⇩

l’intensità di cure più corretta per la tipologia di paziente

RISULTATI

INCIDENZA

→ 10 pz in 10 mesi = 12 in un anno

→ Attesa: 36 e 45 pazienti in un anno (4.1-5.3/100000 abitanti, area metropolitana di Bologna circa 900.000 abitanti)

TERAPIA

→ Refrattari: 7 casi

→ Super-refrattari: 3 casi (due sospensione delle terapie, uno risolto con reintroduzione della burst suppression)

PROGNOSI

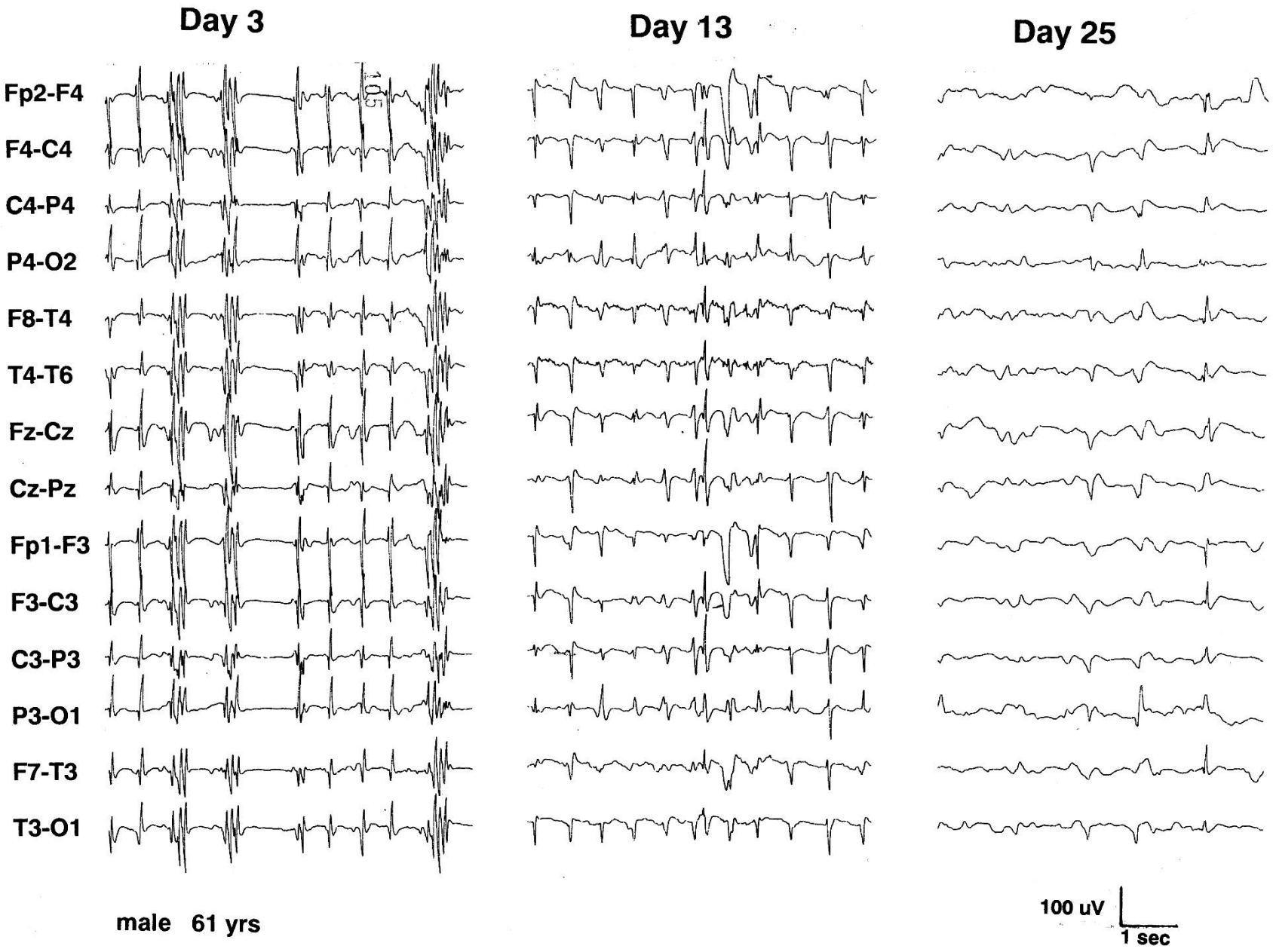
→ 3 pazienti con STESS 1-2 : restitutio ad integrum

→ 7 pazienti con STESS 3-5 : 4 risoluzione dello stato di male (1 con gravi esiti) e 3 deceduti

MORTALITA’

→ 30% ad un mese: 2 pz con STESS 5 e 1 pz con STESS 4.

Post-anoxic status epilepticus



A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus

*†‡Eugen Trinka, §Hannah Cock, ¶Dale Hesdorffer, #Andrea O. Rossetti, **Ingrid E. Scheffer, ††Shlomo Shinnar, ‡‡Simon Shorvon, and §§Daniel H. Lowenstein

Epilepsia, **(*):1–9, 2015
doi: 10.1111/epi.13121

Table 3. Currently indeterminate conditions (or "boundary syndromes")

Epileptic encephalopathies
Coma with non evolving epileptiform EEG pattern[a]
Behavioral disturbance (e.g., psychosis) in patients with epilepsy
Acute confusional states, (e.g., delirium) with epileptiform EEG patterns

[a]Lateralized and generalized periodic discharges with monotonous appearance are not considered as evolving EEG patterns.[26,27]

1. Esordio **tumultuoso** di crisi **facio-brachiali distoniche**

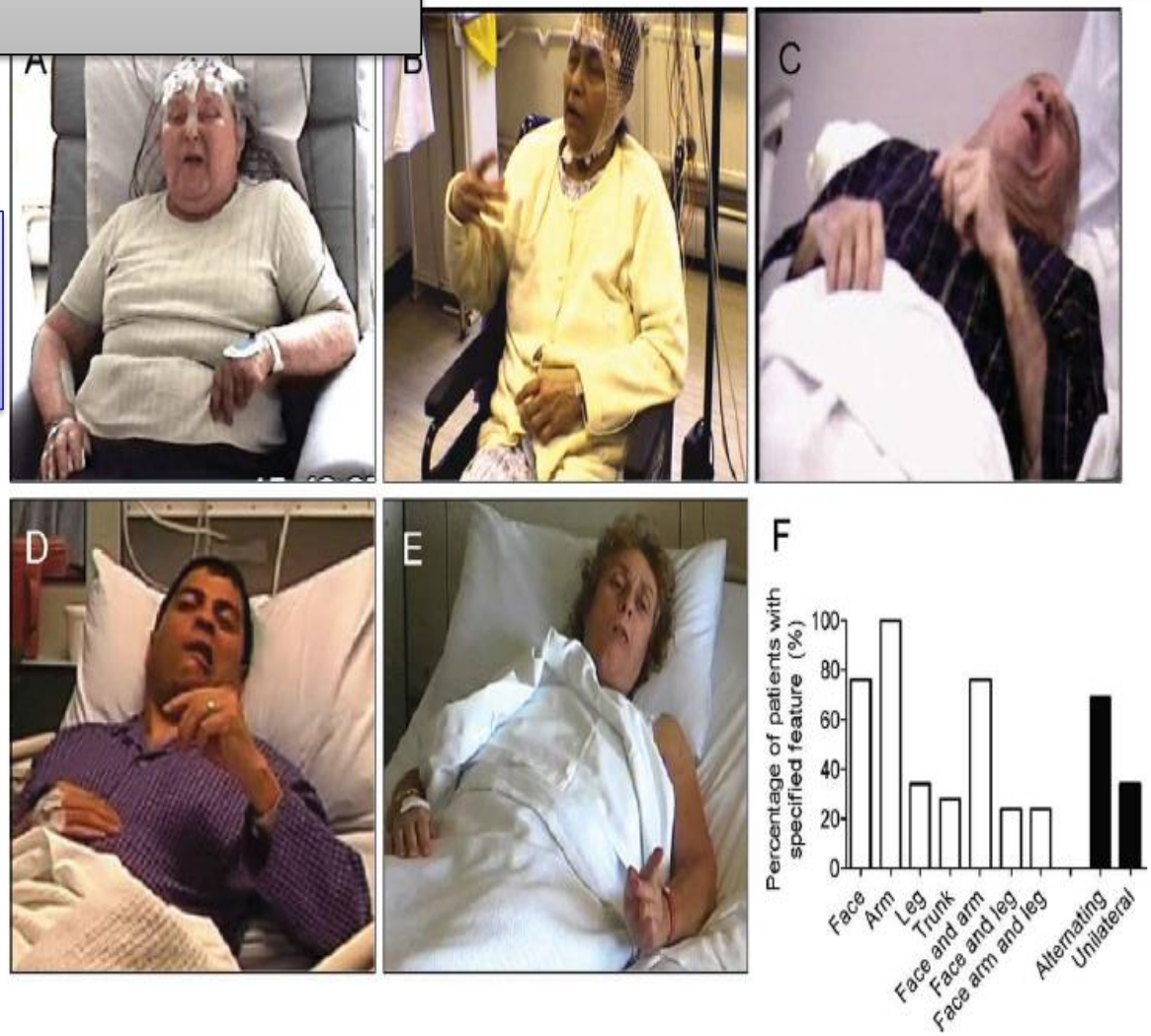
2. Negatività di tutti gli esami strumentali

Encefalite da Ac anti-GI1

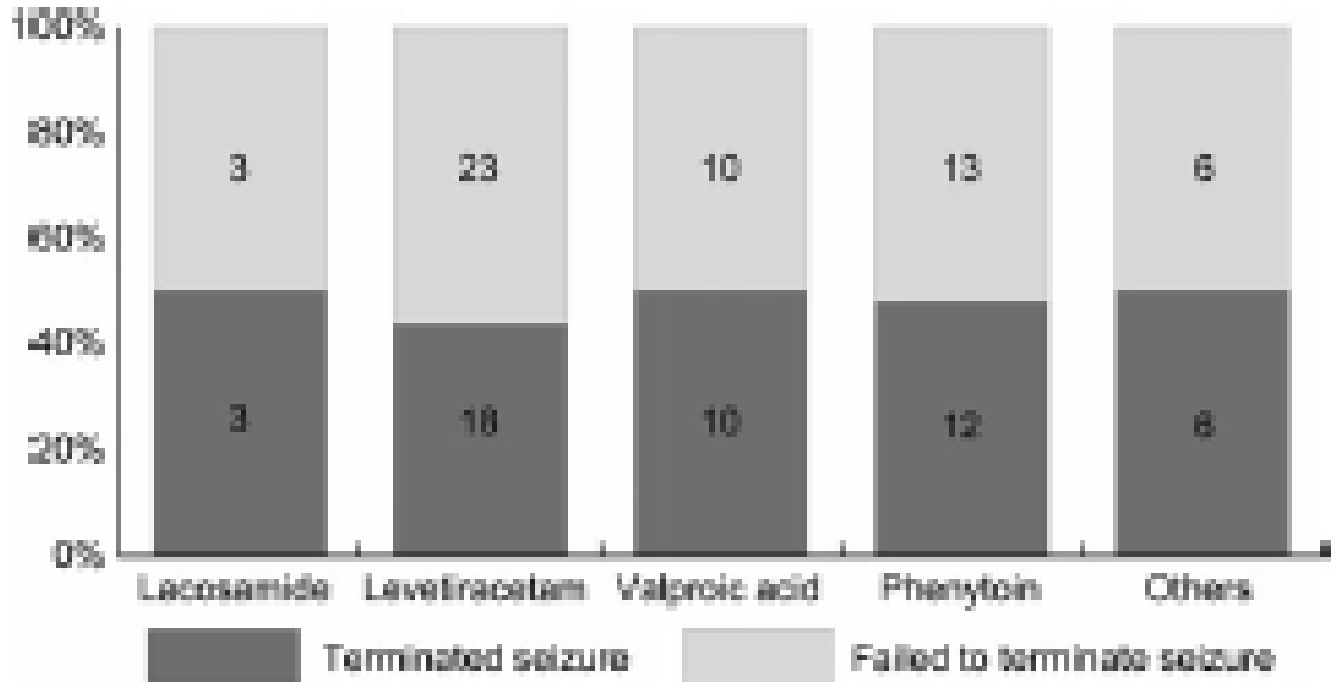
Ciclo di corticosteroide ad alte dosi/Px/Ig

Faciobrachial Dystonic Seizures Precede Lgi1 Antibody Limbic Encephalitis

Sarosh R. Irani, DPhil,[1] Andrew W. Michell, PhD,[2] Bethan Lang, PhD,[1] Philippa Pettingill, BSc,[1] Patrick Waters, PhD,[1] Michael R. Johnson, PhD,[3] Jonathan M. Schott, MD,[4] Richard J. E. Armstrong, PhD,[1,4] Alessandro S. Zagami, MD,[5] Andrew Bleasel, PhD,[6] Ernest R. Somerville, FRCAP,[5,7] Shelagh M. J. Smith, FRCP,[8] and Angela Vincent, FRCPath[1,9]



Antiepileptic Drugs for Status Epilepticus

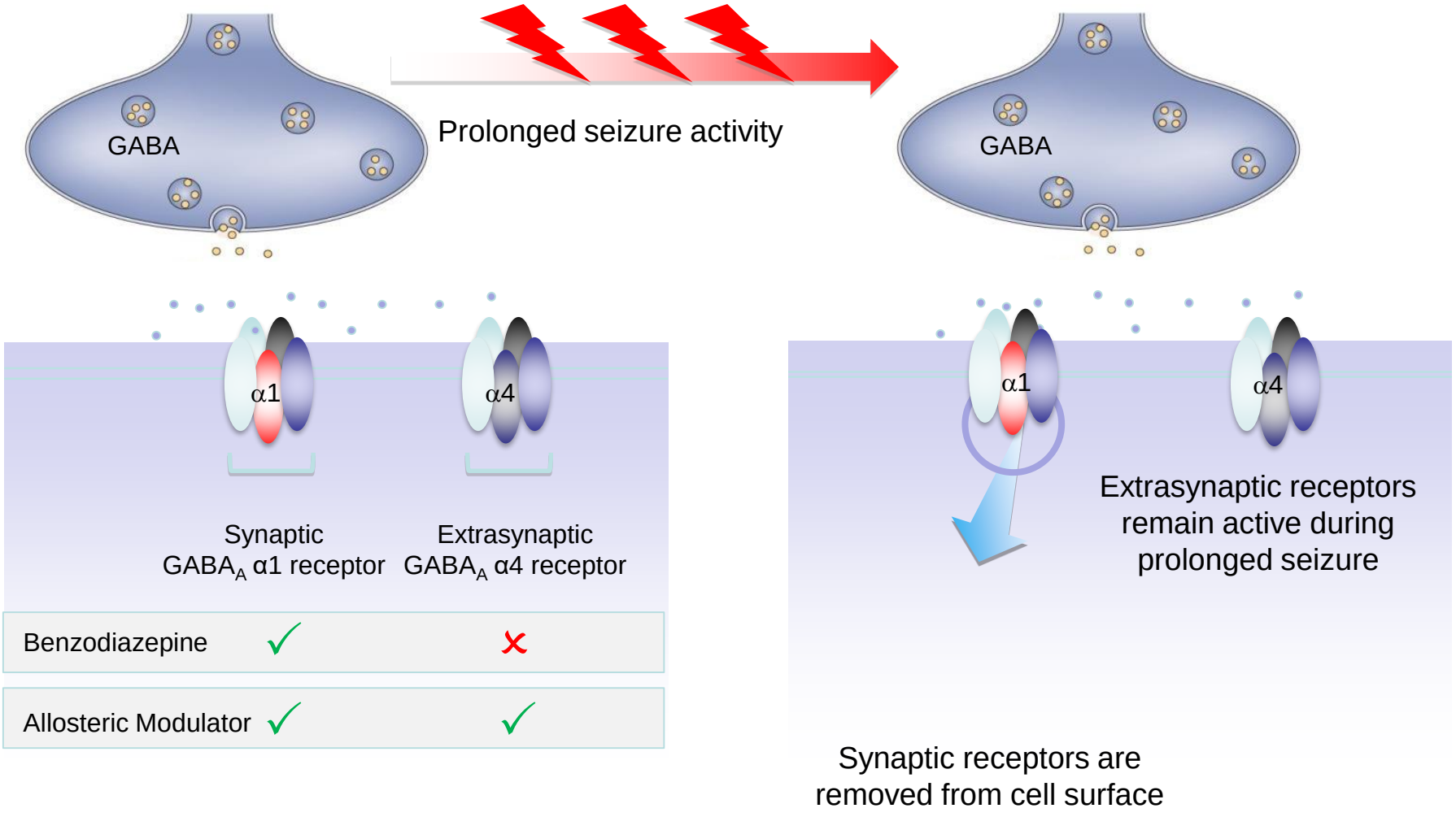


Uso off-label: è un problema?

- Vuoto normativo per l'uso off-label in urgenza/emergenza
- Usare in prima battuta i farmaci con indicazione registrata a parte condizioni specifiche in cui si possa ritenere più valido il farmaco off label
- Il consenso informato può essere procrastinato dopo la risoluzione del quadro
- La Commissione farmaco può essere «saltata» in emergenza ma deve comunque ricevere la richiesta
- Comportamento medico supportato da evidenze scientifiche adeguate

Activity of Neurosteroids

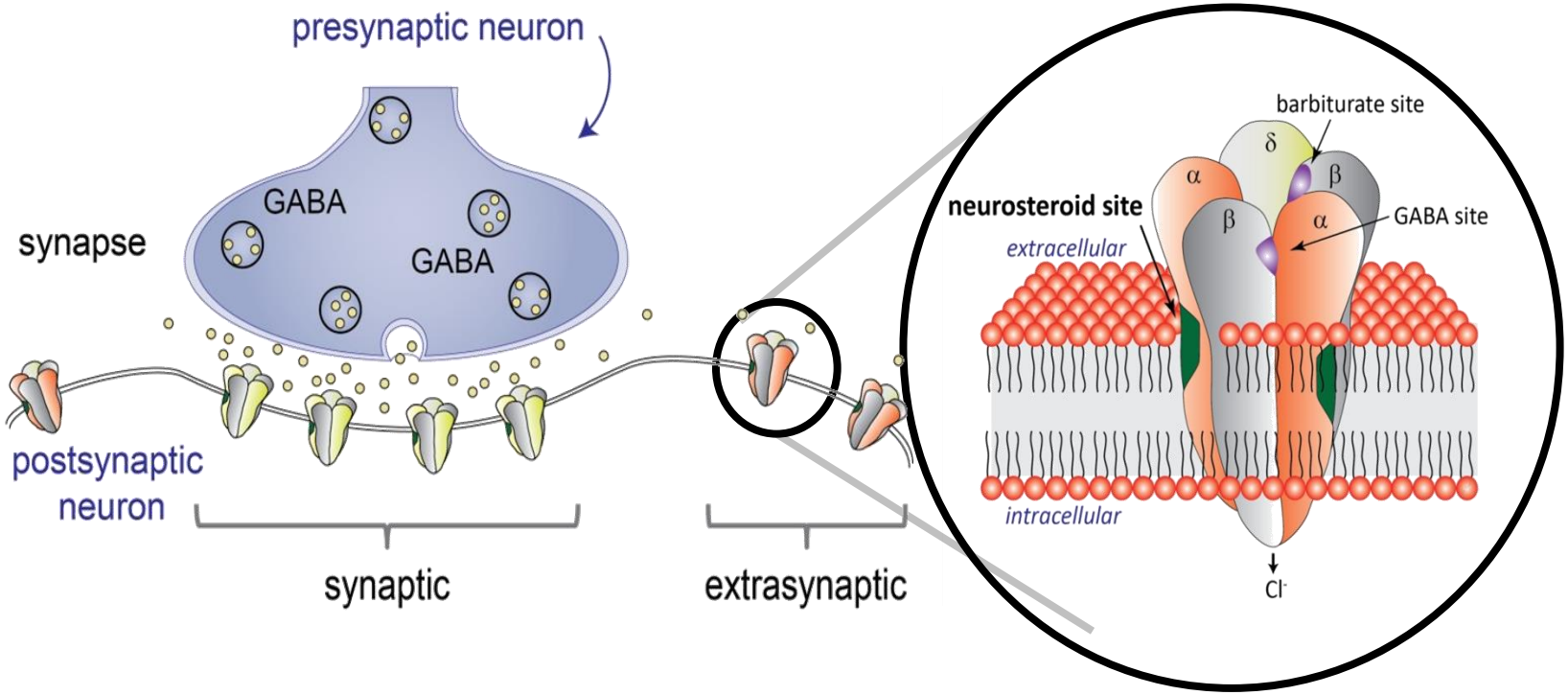
Targeting receptors to treat seizures when other therapeutic sites disappear



About SAGE-547

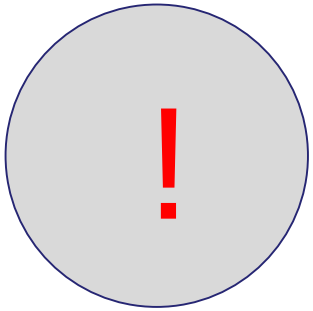
SAGE-547 is an allosteric modulator of both synaptic and extra-synaptic $GABA_A$ receptors.

SAGE-547 is an intravenous agent being studied as an adjunctive therapy for the treatment of super-refractory status epilepticus (SRSE).



STATUS Trial Overview

A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY STATUS EPILEPTICUS

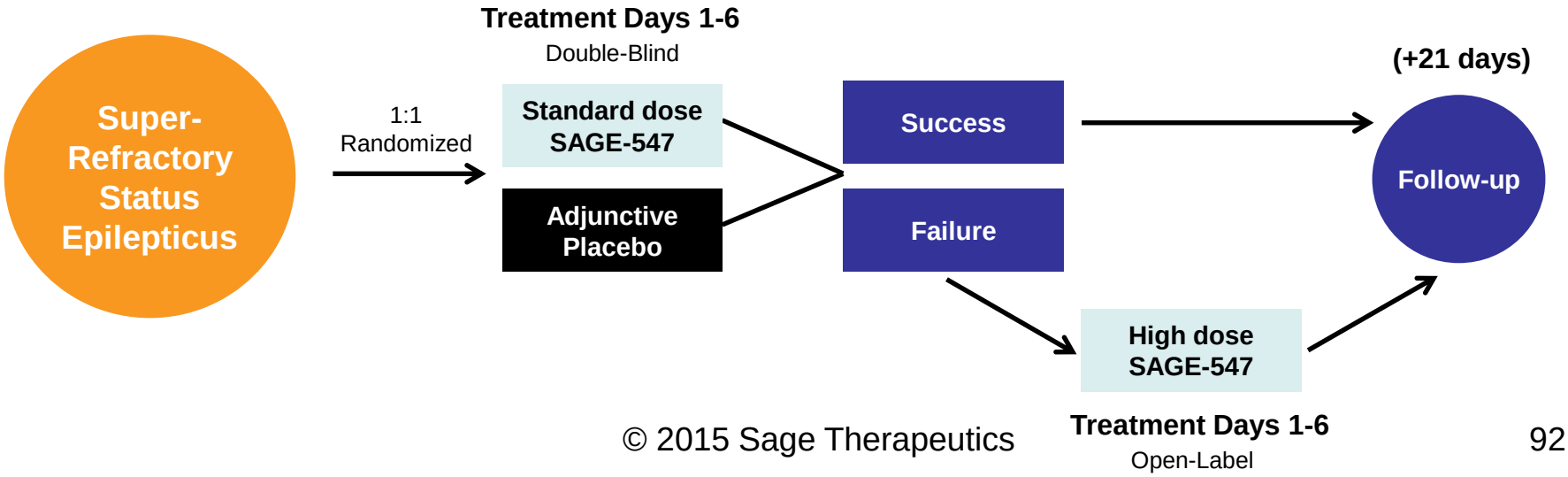


- Protocol: 547-SSE-301
- Randomized 1:1
- Double-Blind
- Placebo Controlled
- Primary Outcome Measure: Number of patients that are able to be weaned off all third-line agents prior to end of the SAGE-547 or placebo infusion, and remain off all third-line agents for > 24 hrs following the end of the SAGE-547 or placebo infusion

Study Design Overview

STATUS TRIAL

- Randomized, double-blind, placebo-controlled
- Expect up to 140 patients enrolled to get 126 evaluable patients
- Anticipate ~150 sites in U.S., Canada and Europe
- Non-responders eligible for open-label, SAGE-547 retreatment
- SPA agreement with FDA
- Primary Efficacy Endpoint: Continued resolution of SE for 24 hours following wean of all 3rd-line agents and SAGE-547/placebo



Kellinghaus et al. BMC Neurology (2015) 15:230
DOI 10.1186/s12883-015-0486-y

BMC Neurology

STUDY PROTOCOL Open Access

Making SENSE - Sustained Effort Network for treatment of Status Epilepticus as a multicenter prospective registry

Christoph Kellinghaus[1*], Nicolas Lang[2], Andrea O. Rossetti[3], Stephan Rüegg[4], Christian Tilz[5], Eugen Trinka[6,10], Iris Unterberger[7], Zeljko Uzelac[8] and Felix Rosenow[9]

Preliminary results of the global audit of treatment of refractory status epilepticus.

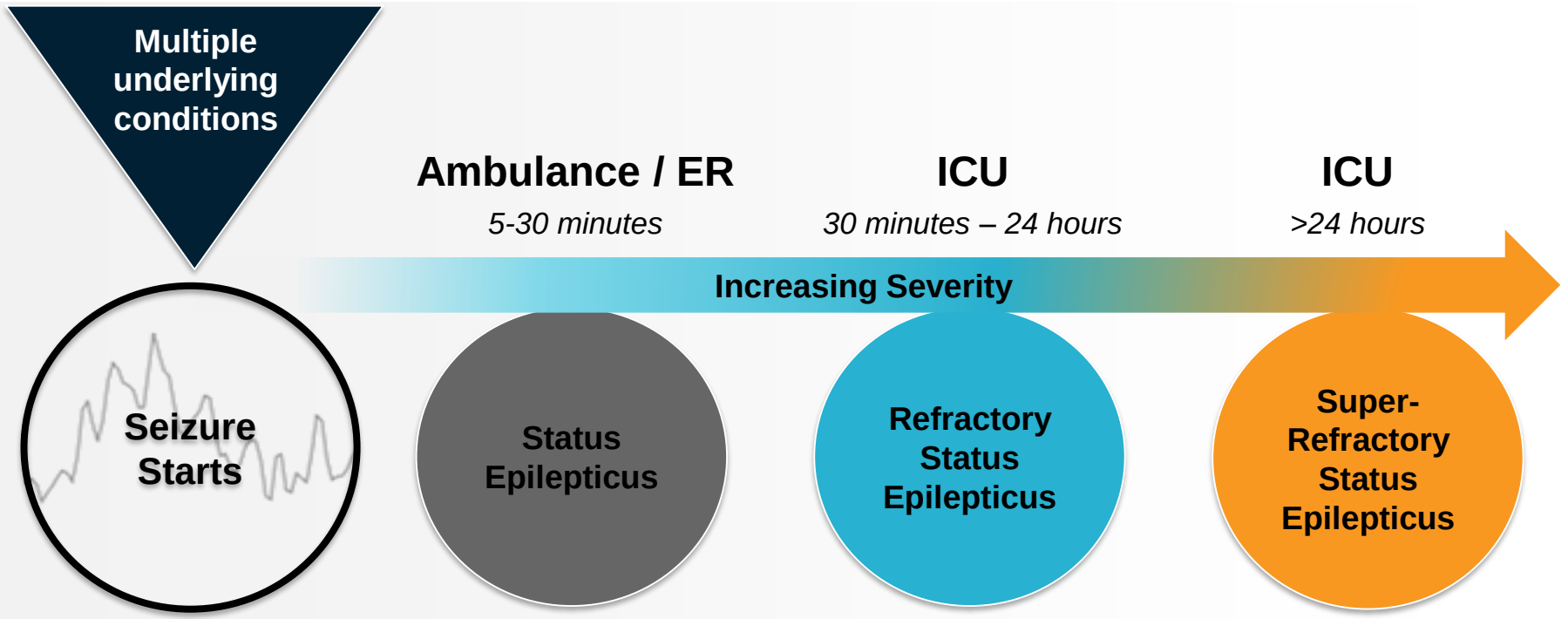
Ferlisi M[1], Hocker S[2], Grade M[3], Trinka E[4], Shorvon S[5]; International Steering Committee of the StEp Audit.

Epilepsy Behav. 2015 Aug;49:318-24

SAGE Therapeutics

- SAGE Therapeutics is a clinical-stage biopharmaceutical company.
- SAGE is committed to developing novel medicines to treat life-threatening, rare CNS disorders.
- Lead program, SAGE-547, is currently in Phase 3 clinical development for SRSE.
- SAGE-547 is the first of several compounds in SAGE's portfolio of potential anti-seizure medicines.
- Proprietary chemistry platform has generated multiple new compounds that target $GABA_A$ and NMDA receptors, which are broadly accepted as impacting many psychiatric and neurological disorders.

Current Standard of Care of SE



1st / 2nd Line Treatment
(benzodiazepines, antiepileptics)

Seizure continues despite treatment

3rd Line Treatment
(burst suppression with anesthetics/antiepileptics)

Seizure continues; Initiate medically-induced coma

3rd Line Adjunct Treatment
(repeated rounds of burst suppression)

Failure to control seizures while weaning 3rd line

About SAGE-547

- SAGE-547 is an allosteric modulator of both synaptic and extra-synaptic $GABA_A$ receptors.

- SAGE-547 is an intravenous agent being studied as an adjunctive therapy for the treatment of super-refractory status epilepticus (SRSE).

Off-label in urgenza

- E’ sempre buona norma, per quanto non sia necessario il consenso per procedere alla procedura terapeutica ritenuta più idonea, ottenere sempre il consenso informato dopo la risoluzione del quadro clinico (?) o comunque deve risultare dalla documentazione la motivazione per cui si è ricorsi all’off-label

Conclusioni

- Vuoto normativo per l'uso off-label in urgenza/emergenza
- Usare in prima battuta i farmaci con indicazione registrata a parte condizioni specifiche in cui si possa ritenere più valido il farmaco off label
- Il consenso informato può essere procrastinato dopo la risoluzione del quadro
- La Commissione farmaco può essere «saltata» in emergenza ma deve comunque ricevere la richiesta
- Comportamento medico supportato da evidenze scientifiche adeguate

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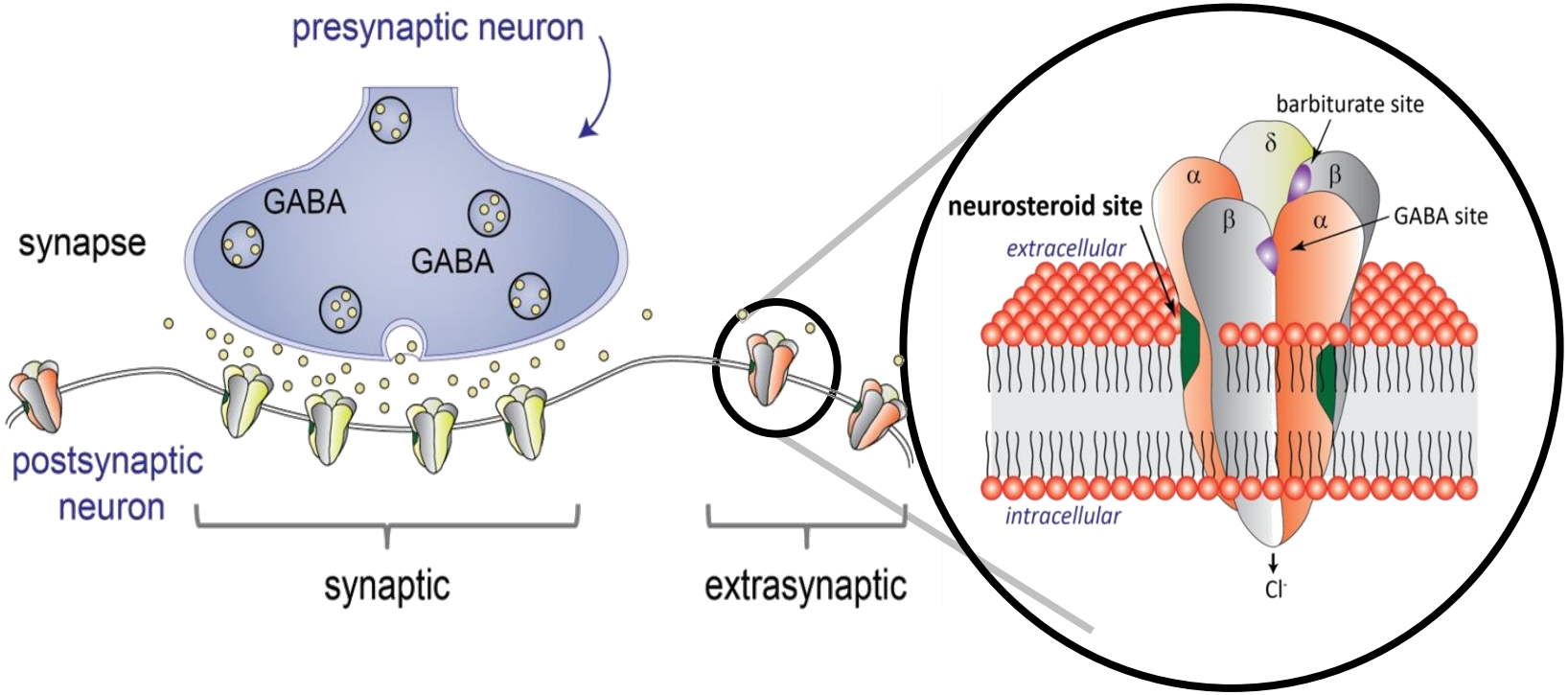
SAGE-547 is an intravenous agent being studied as an adjunctive therapy for the treatment of super-refractory status epilepticus (SRSE).



SAGE-547 SRSE Research – *Past, Present, and Future*

- Concluded Open-Label SAGE-547 SRSE Phase I/II Trial in 2015:
  - 77% wean success rate – successful weaning of third-line agents during SAGE-547 administration over 5 day (120hr) treatment period without recurrence of SRSE in the 24hr period following treatment
  - 64% of subjects experienced SAEs, none considered to be related to SAGE-547 by the Safety Review Committee
  - Six deaths, related to underlying medical conditions
  - cEEG evaluated as an exploratory endpoint for subset of subjects, SAGE-547 associated with an increase in EEG suppression with increasing plasma concentrations of SAGE-547
- STATUS Trial FPI July 2015
- STATUS Trial to Activate > 150 US/CAN/EU Sites
- Ongoing Open-Label SAGE-547 Expanded Access Protocol in US
- STATUS Trial Data expected 2H 2016

STATUS Trial – *Time is Critical*

- Outcome of SRSE worsens with time
- Neurotoxicity (and other toxicities) from continuing seizures
- Neurotoxicity (and other toxicities) from treating drugs
- ICU morbidities
- Delay in definitive treatment of underlying causes & comorbidities

Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial:

1. Subjects two (2) years of age and older;
2. Subjects who have:
    - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to the institution's standard of care, and;
    - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AEDs), according to the institution's standard of care, and;
    - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agents and in an EEG burst suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on at least one continuous infusion of a third-line agent or are on one or more continuous infusions of third-line agents but not in an EEG burst suppression pattern.

Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible:

1. Subjects who are pregnant
2. Subjects with a known allergy to progesterone or allopregnanolone;
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy;
4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder;
5. Subjects who have any of the following:
    a. a GFR low enough to warrant dialysis for whatever reason, dialysis is not planned or non-continuous dialysis planned (that would not adequately remove Captisol®);
    b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
    c. fulminant hepatic failure;
    d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, for less than 30 days;
    e. a do not resuscitate (DNR) order;

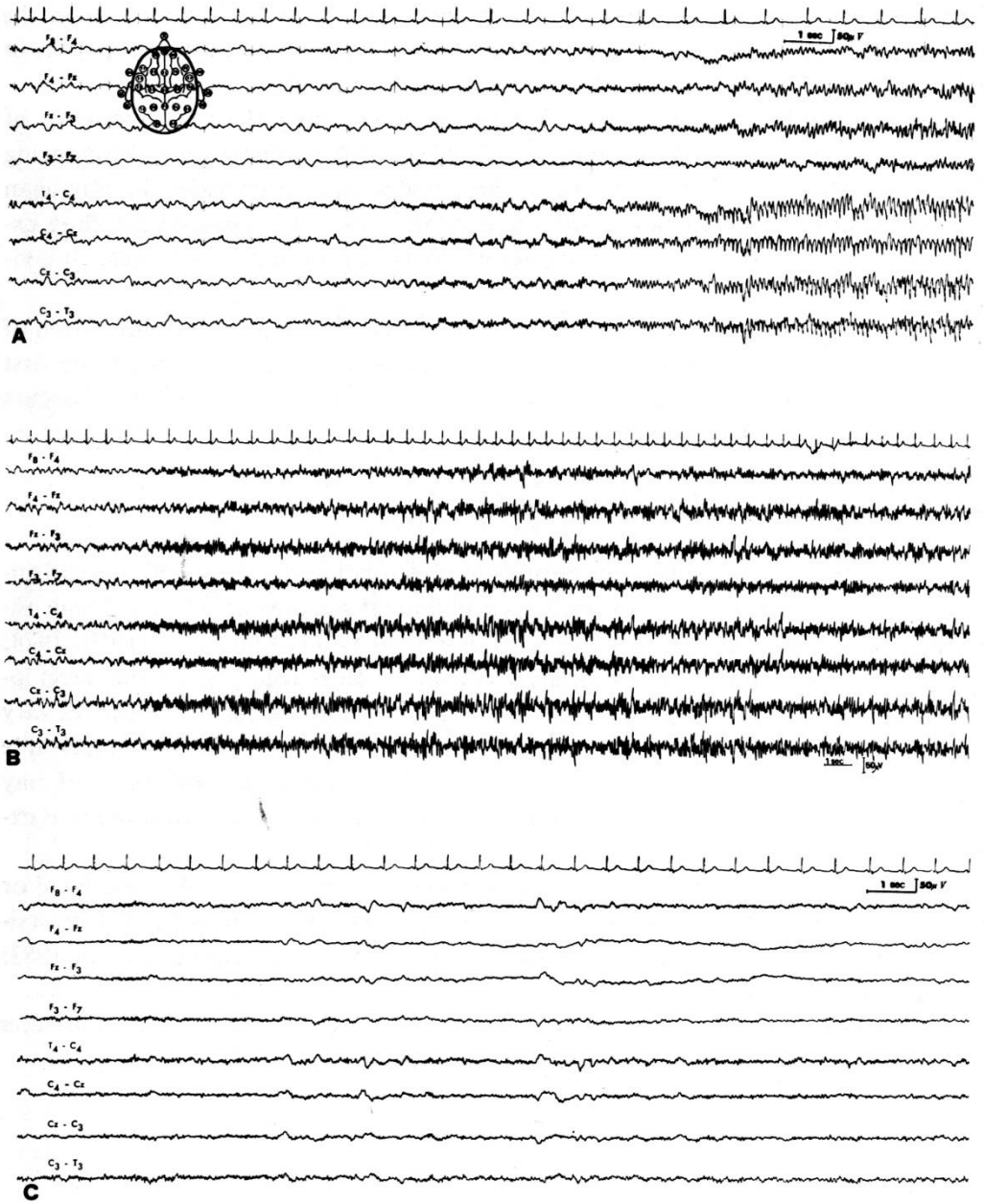
[redacted]

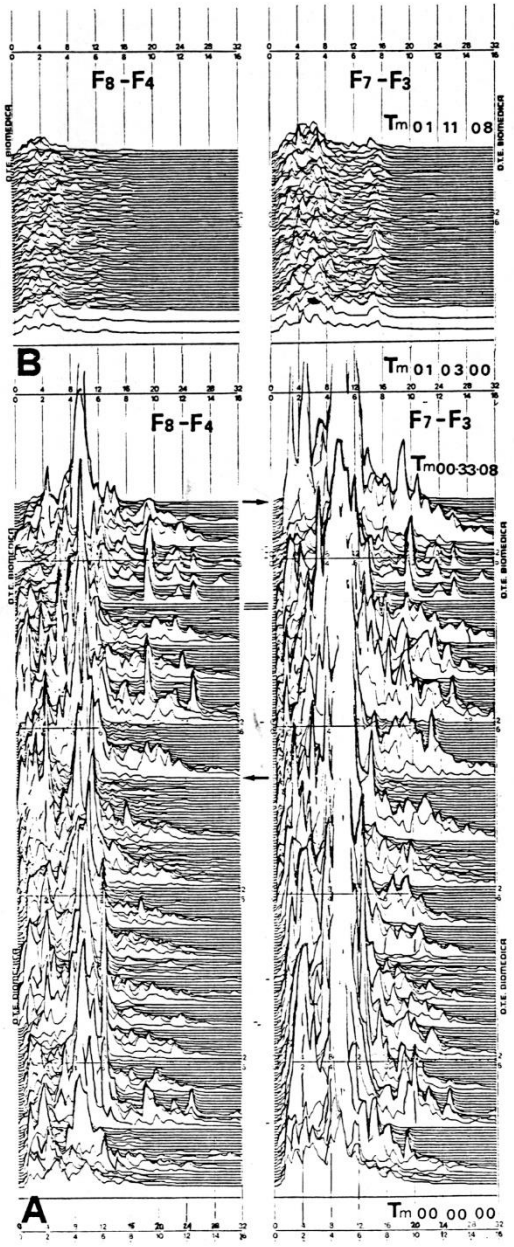
6. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours or who are being administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol
7. Subjects with a living will that does not allow heroic measures
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed
9. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll);

Stato di male non convulsivo in pazienti in coma

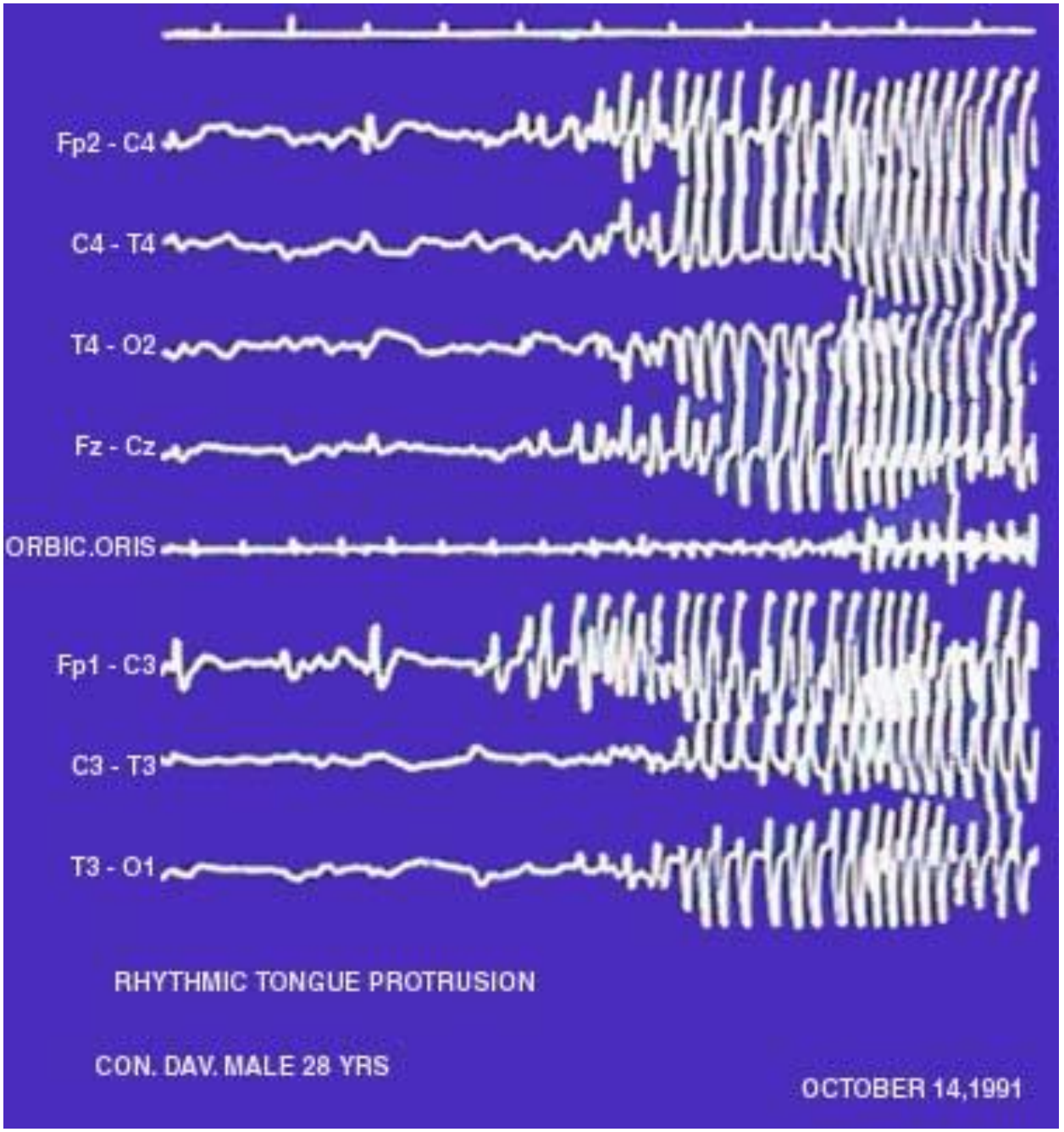
- Fino all'8% dei pazienti in coma senza evidenza clinica di crisi
- Come evoluzione di SE convulsivo, con o senza minime manifestazioni motorie (SE "subtle"), o come forma primitiva (SE vero o espressione di sofferenza cerebrale diffusa?)
- Ruolo del monitoraggio video-EEG
- Prognosi in genere sfavorevole (danno ipossico), **terapia aggressiva giustificata**

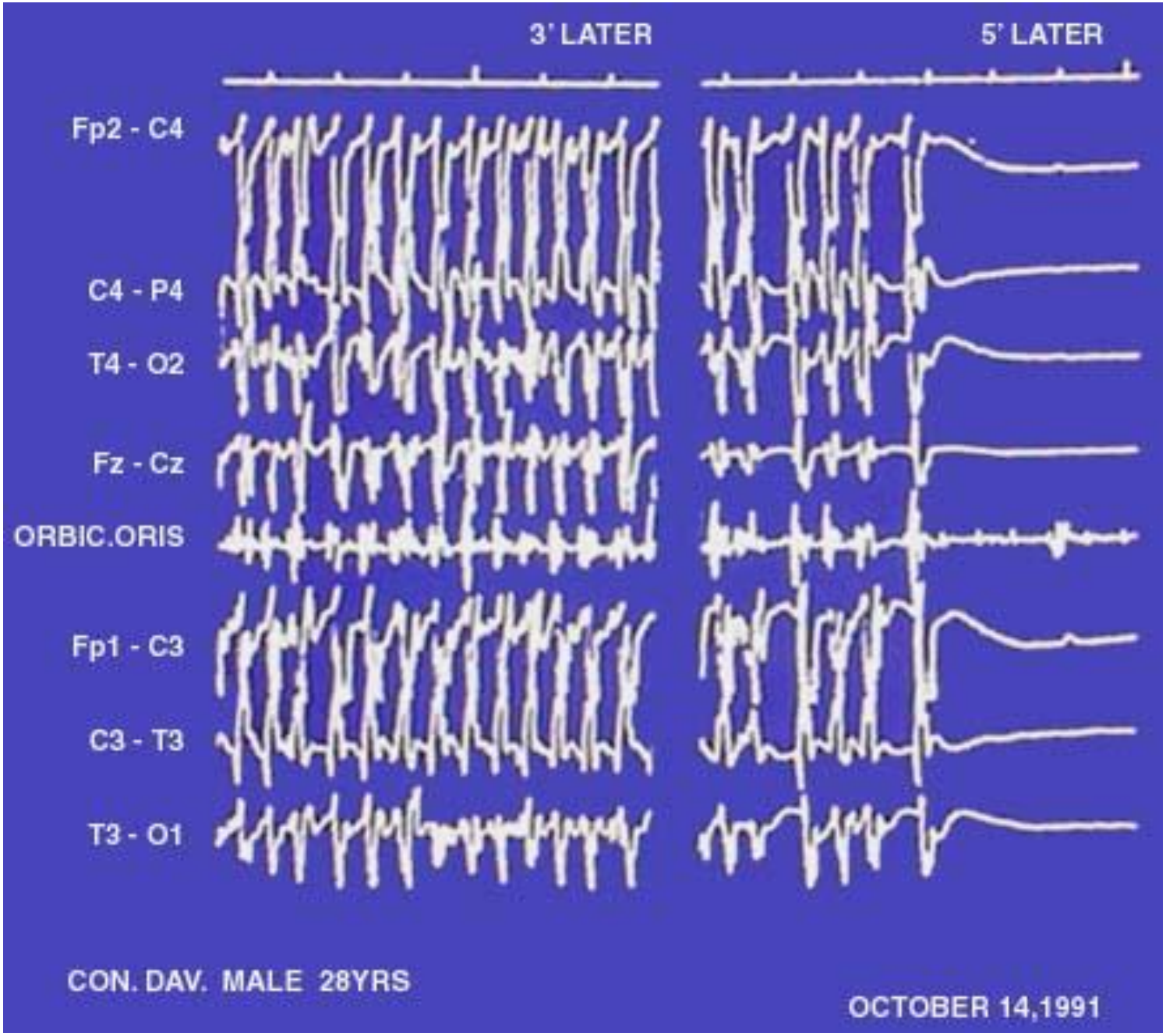
riconoscimento

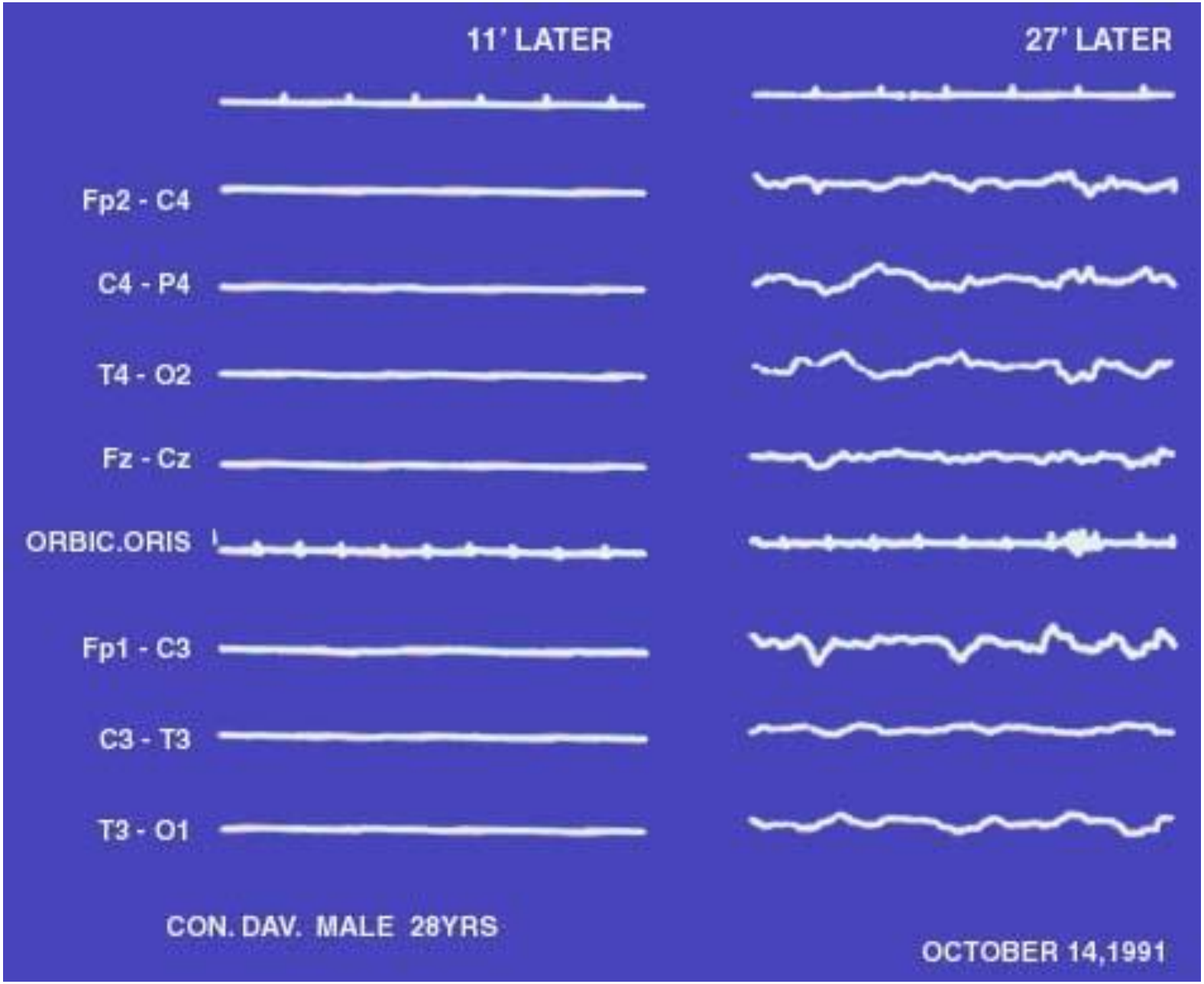




Michelucci et al 1985


Fp2 - C4
C4 - T4
T4 - O2
Fz - Cz
ORBIC.ORIS
Fp1 - C3
C3 - T3
T3 - O1
RHYTHMIC TONGUE PROTRUSION
CON. DAV. MALE 28 YRS
OCTOBER 14,1991


3' LATER
5' LATER
Fp2 - C4
C4 - P4
T4 - O2
Fz - Cz
ORBIC.ORIS
Fp1 - C3
C3 - T3
T3 - O1
CON. DAV. MALE 28YRS
OCTOBER 14,1991


11' LATER
27' LATER
Fp2 - C4
C4 - P4
T4 - O2
Fz - Cz
ORBIC.ORIS
Fp1 - C3
C3 - T3
T3 - O1
CON. DAV. MALE 28YRS
OCTOBER 14,1991

Criteri EEG

Epilepsia, 51(2):177–190, 2010
doi: 10.1111/j.1528-1167.2009.02297.x

CRITICAL REVIEW AND INVITED COMMENTARY

Nonconvulsive status epilepticus and coma

Gerhard Bauer and Eugen Trinka

Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria

Table 1
Old and new terms of EEG patterns in the patients with critical illness, modified according to the 2012 version of the American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology [2].

Commonly used terminology	New terminology
Triphasic waves (TWs)	Continuous 2/s GPDs with triphasic morphology
Periodic lateralized epileptiform discharges (PLEDs)	Lateralized periodic discharges (LPDs)
Bilateral periodic epileptiform discharges (BiPLEDs)	Bilateral periodic discharges (BPDs)
Generalized periodic epileptiform discharges (GPEDs)	Generalized periodic discharges (PDs)
Frontal intermittent rhythmic delta activity (FIRDA)	Occasional frontally predominant brief 2/s generalized rhythmic delta activity
Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) with focal evolving rhythmic delta activity	Stimulus-induced-evolving lateralized rhythmic delta activity (SI-evolving LRDA)
Lateralized seizure, delta frequency range	Evolving lateralized rhythmic delta activity (LRDA)
Semirhythmic delta	Quasi RDA
Coma with lateralized epileptiform discharges (coma-LEDs) [14]	Coma with lateralized periodic discharges (coma-LPDs)
Coma with generalized epileptiform discharges (coma-GEDs)	Coma with generalized periodic discharges (coma-GPDs)

Patients without known epileptic encephalopathy
EDs > 2.5 Hz, or
EDs ≤ 2.5 Hz or rhythmic δ/θ activity (>0.5 Hz) AND one of the following:
EEG and clinical improvement after IV AED[a], or
Subtle clinical ictal phenomena, or
Typical spatiotemporal evolution[b]
Patients with known epileptic encephalopathy
Increase in prominence or frequency when compared with baseline with observable change in clinical state
Improvement of clinical and EEG[a] features with IV AEDs

EDs, epileptiform discharges (spikes, polyspikes, sharp-waves and sharp-and-slow-wave complexes); EEG, electroencephalography; IV AEDs, intravenous antiepileptic drugs. Reproduced with permission from [41].
[a]If EEG improvement without clinical improvement, or if fluctuation without definite evolution, this should be considered possible NCSE.
[b]Incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency >1 Hz or change in location), or decrementing termination (voltage or frequency).

Recent advances in status epilepticus.
Trinka, Eugen; Brigo, Francesco; Shorvon, Simon

Current Opinion in Neurology. 29(2):189-198, April 2016.
DOI: 10.1097/WCO.0000000000000307

Table 2 Salzburg Electroencephalography Consensus Criteria for nonconvulsive status epilepticus

Pattern EEG critico o non critico?

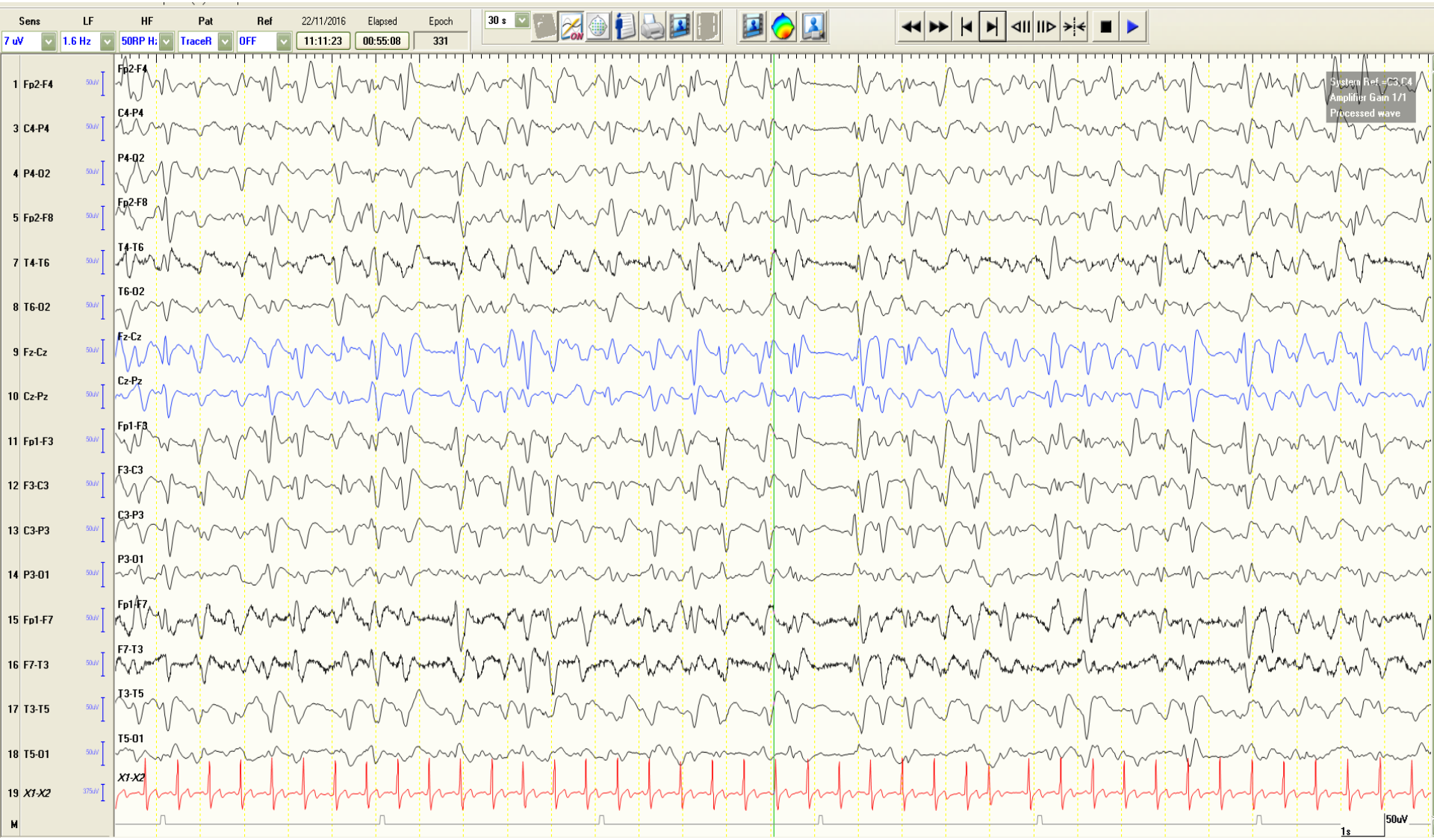
A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus

*†‡Eugen Trinka, §Hannah Cock, ¶Dale Hesdorffer, #Andrea O. Rossetti, **Ingrid E. Scheffer, ††Shlomo Shinnar, ‡‡Simon Shorvon, and §§Daniel H. Lowenstein

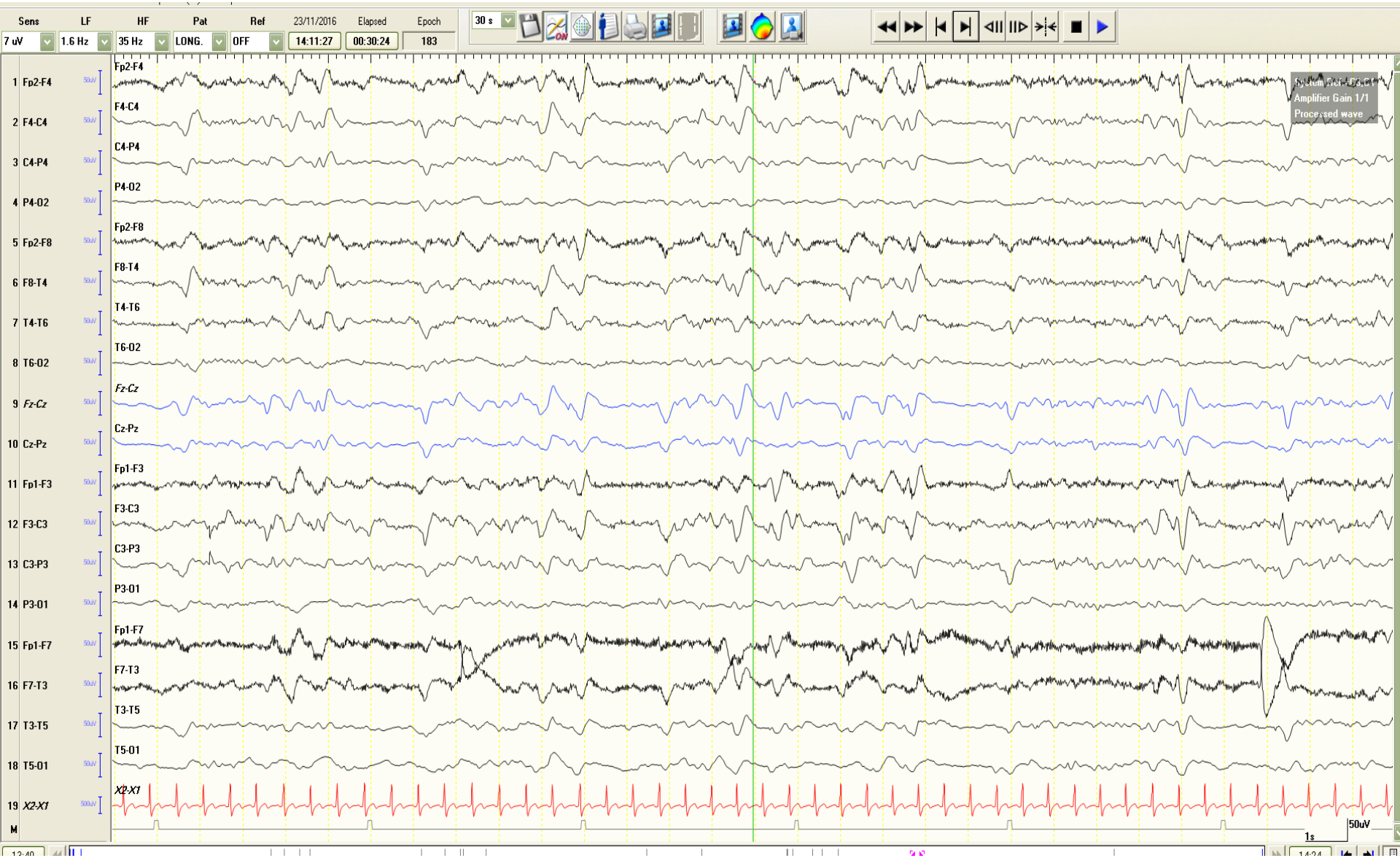
Epilepsia, **(*):1–9, 2015

"None of the ictal EEG patterns of any type of SE is specific. Epileptiform discharges are regarded as the hallmark, but with increasing duration of SE, the EEG changes and rhythmic non-epileptiform patterns may prevail. Similar EEG-patterns, such as triphasic waves, can be recorded in various pathologic conditions, leading to substantial confusion in the literature"

FF, 74 aa, coma persistente dopo emorragia intraparenchimale TO sn



Dopo lorazepam



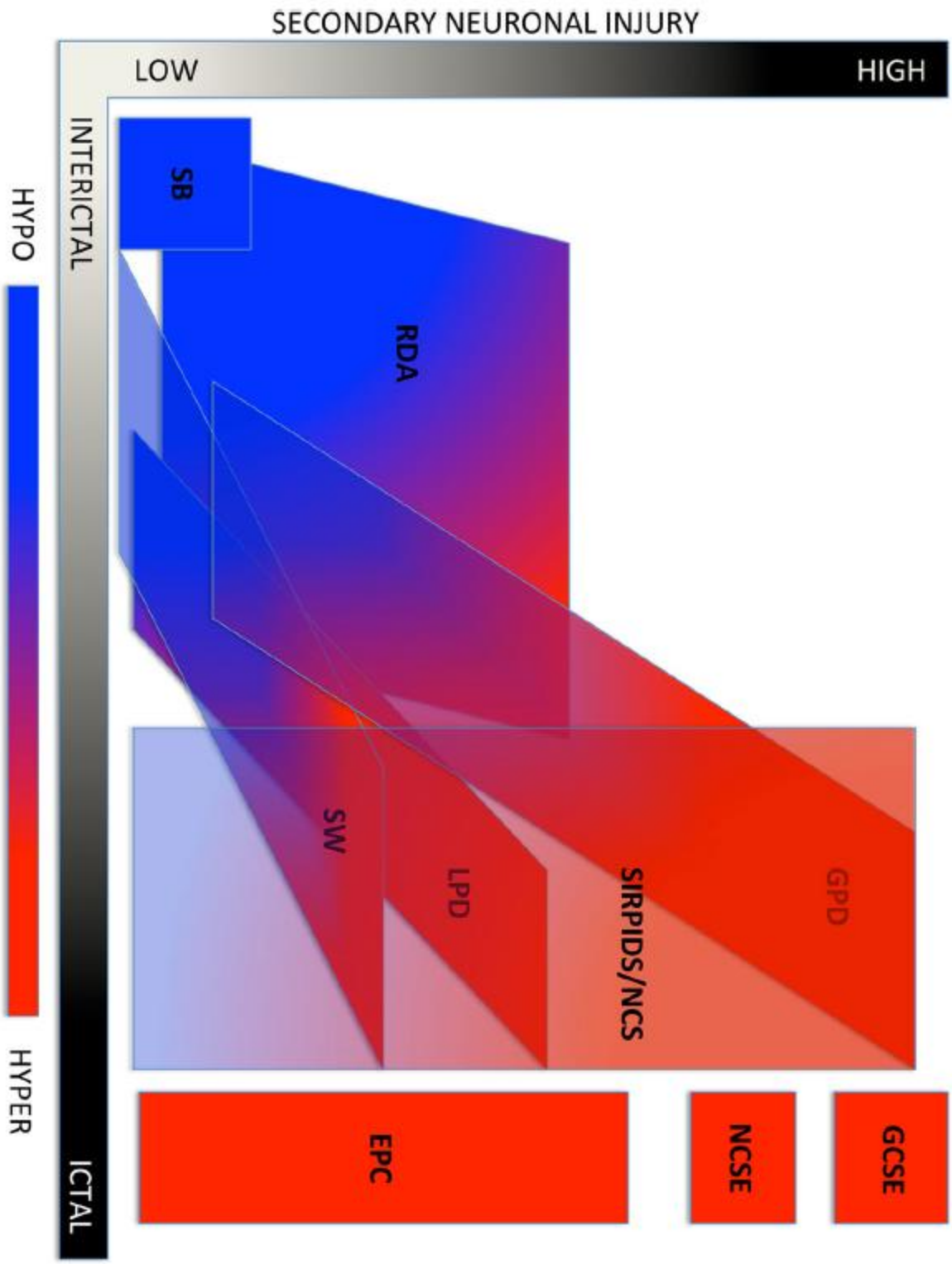
neurocritical care society Neurocrit Care (2016) 24:324–331
DOI 10.1007/s12028-016-0245-y

ORIGINAL ARTICLE

Metabolic Correlates of the Ictal-Interictal Continuum: FDG-PET During Continuous EEG

Aaron F. Struck[1] · M. Brandon Westover[1] · Lance T. Hall[2] · Gina M. Deck[1] · Andrew J. Cole[1] · Eric S. Rosenthal[1]

The ictal-interictal-injury-metabolism continuum



Conclusioni

- Vuoto normativo per l'uso off-label in urgenza/emergenza
- Usare in prima battuta i farmaci con indicazione registrata a parte condizioni specifiche in cui si possa ritenere più valido il farmaco off label
- Il consenso informato può essere procrastinato dopo la risoluzione del quadro
- La Commissione farmaco può essere «saltata» in emergenza ma deve comunque ricevere la richiesta
- Comportamento medico supportato da evidenze scientifiche adeguate

Stato di male convulsivo

- Urgenza assoluta
- Può condurre a profonde modificazioni dei parametri vegetativi e vitali, a danno cerebrale e a complicanze a carico di altri organi
- Mortalità fino al 22% (De Lorenzo 1996) ↯ *eziologia, durata, età, qualità del trattamento* (Vignatelli 2008)

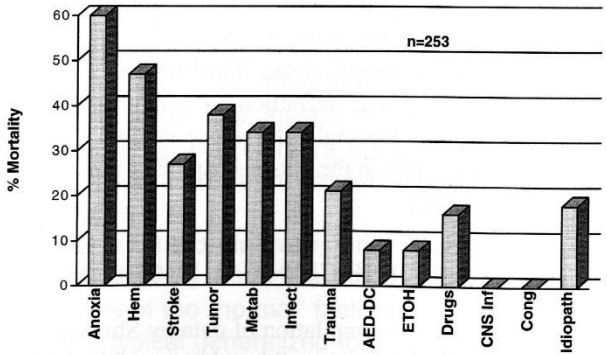


FIG. 5. Etiology/outcome of SE, Richmond, VA (1982–1986). From Towne et al., ref (21).

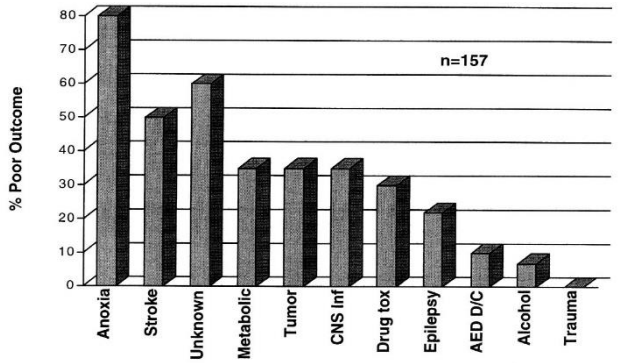


FIG. 4. Etiology/outcome of SE, SFGH (1980s). From Lowenstein and Alldredge, ref (18).

Trattamento dello stato di male

Il trattamento può svolgersi in 4 fasi diverse:

1) trattamento prima dell'arrivo al pronto soccorso

2) trattamento di prima linea al pronto soccorso

3) trattamento di seconda linea in pronto soccorso o medicina d'urgenza se i primi trattamenti sono stati inefficaci

4) trattamento in Rianimazione con anestesia generale

Stato di male convulsivo

Stadio dello SE iniziale

Stadio dello SE definito

neurologo

Stadio dello SE refrattario → ***rianimatore***

Trattamento prima dell'arrivo in PS

- **Obiettivo**: Interrompere il prima possibile crisi seriali/prolungate/stati di male
- ***Familiari*** (se epilessia già nota) → diazepam rettale, lorazepam sublinguale, clobazam orale, midazolam buccale o nasale (5-10 mg 0,3 mg/kg)
- ***Personale sanitario*** (ambulanza) → lorazepam 4 mg e.v. (0.1 mg/kg) o diazepam 10 mg e.v. (0.3 mg/kg). Midazolam nasale, e.v. o i.m. 5-10 mg (0,1-0,3 mg/kg).
- Aspetti organizzativi specifici

A comparison of lorazepam, diazepam, and placebo for the treatment of out of hospital status epilepticus

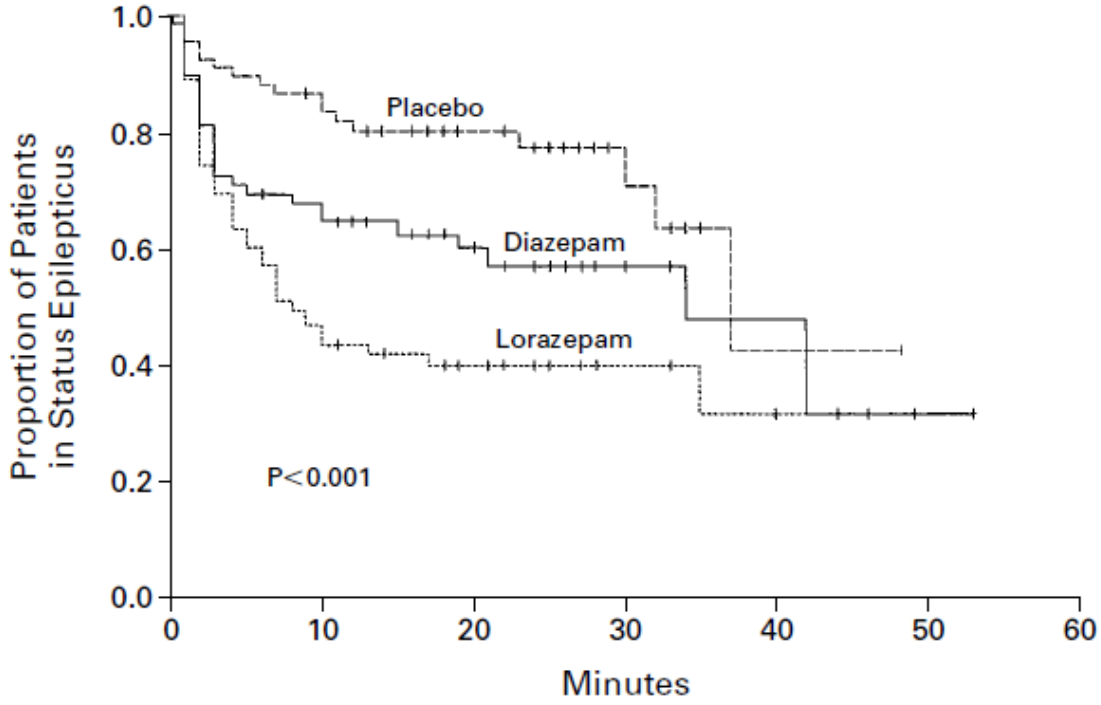
TABLE 2. STATUS EPILEPTICUS AT THE TIME OF ARRIVAL AT THE EMERGENCY DEPARTMENT.*

VARIABLE	LORAZEPAM GROUP (N=66) 2 mg	DIAZEPAM GROUP (N=68) 5 mg	PLACEBO GROUP (N=71)
		no. of patients (%)	
Status epilepticus terminated	39 (59.1)	29 (42.6)	15 (21.1)
Ongoing status epilepticus	27 (40.9)	39 (57.4)	56 (78.9)
	LORAZEPAM VS. PLACEBO	LORAZEPAM VS. DIAZEPAM	DIAZEPAM VS. PLACEBO
Odds ratio (simultaneous 95 percent CI) for termination of status epilepticus			
Unadjusted	5.4 (2.3–13.2)	1.9 (0.9–4.3)	2.8 (1.2–6.7)
Adjusted†	4.8 (1.9–13.0)	1.9 (0.8–4.4)	2.3 (1.0–5.9)

*CI denotes confidence interval.

†Each odds ratio was adjusted for race or ethnic group, the intervals from the onset of status epilepticus to study treatment and from study treatment to arrival at the emergency department, and cause of status epilepticus within each prognostic group.

Alldredge et al N Engl J Med 2001



No. at Risk						
Diazepam	68	41	21	8	2	1
Lorazepam	65	29	15	6	2	0
Placebo	67	53	26	10	1	0

Figure 2. Kaplan–Meier Curves Comparing the Durations of Out-of-Hospital Status Epilepticus after Treatment with Lorazepam, Diazepam, or Placebo.

Tick marks indicate censoring of data. The curves were significantly different from one another by the log-rank test ($P<0.001$).

trattamento di prima linea al PS
Stadio dello SE iniziale

- Misure generali (funzione cardio-respiratoria, O_2 etc)
- 50 ml di soluzione di Glucosio al 50% (in presenza di ipoglicemia) + 250 mg di tiamina i.m. (stati di denutrizione, alcoolismo)
- **Lorazepam** e.v. 4 mg (0.1 mg/kg età ped.) in bolo (vel. max. 2 mg/min) (possibile ripetere dopo 10 min)

  oppure

  Diazepam e.v. 10-20 mg (0.25-0.5 mg/kg età ped.) in bolo (vel. max. 2-5 mg/min)
- Pari efficacia e rapidità d'azione, ma il **lorazepam ha una maggiore durata d'azione** (Leppik 1983, Andermann 1992)

- Uso sempre più comune di **Midazolam** i.m. 5-10 mg o e.v. 0.1-0.3 mg/kg

Stadio dello SE definito
(benzodiazepine inefficaci)

- **Fenitoina** e.v.15-18 mg/kg in bolo (vel. max. 50 mg/min) (somm. per via e.v. diretta o diluita in soluzioni di salina alla conc. di 5-10 mg/ml)
- **Valproato** e.v. in bolo 15-30 mg/kg in 5-10 min, seguito da infusione continua di 1-2 mg/kg/ora
- **Levetiracetam** e.v. in bolo 30-50 mg/kg in 5-15 min
- **Lacosamide** e.v. in bolo (200-400 mg) (vel. max. 60 mg/min)

} 2ªs?

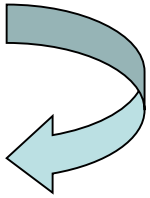
Stadio dello SE definito
(opzioni non in uso in Italia)

- **Fenobarbital** e.v. in bolo 10-20 mg/kg alla velocità di infusione di 100 mg/min*
- **Fosfenitoina** e.v in bolo 20 mg/kg a 150 mg/m

* la somministrazione richiede la presenza di rianimatore per la frequente depressione di coscienza e respiratoria

Stadio dello SE refrattario (lorazepam e fenitoina inefficaci)

- Lo SE diventa di competenza del **rianimatore**



- Intubazione e induzione di anestesia generale (propofol, tiopentone, midazolam)
- Ruolo dell'epilettologo: assistere il rianimatore nel monitoraggio clinico-EEG dello SE (induzione della anestesia, SE non convulsivo, SE "subtle")

Pharmacological characteristics of anesthetics used in refractory SE

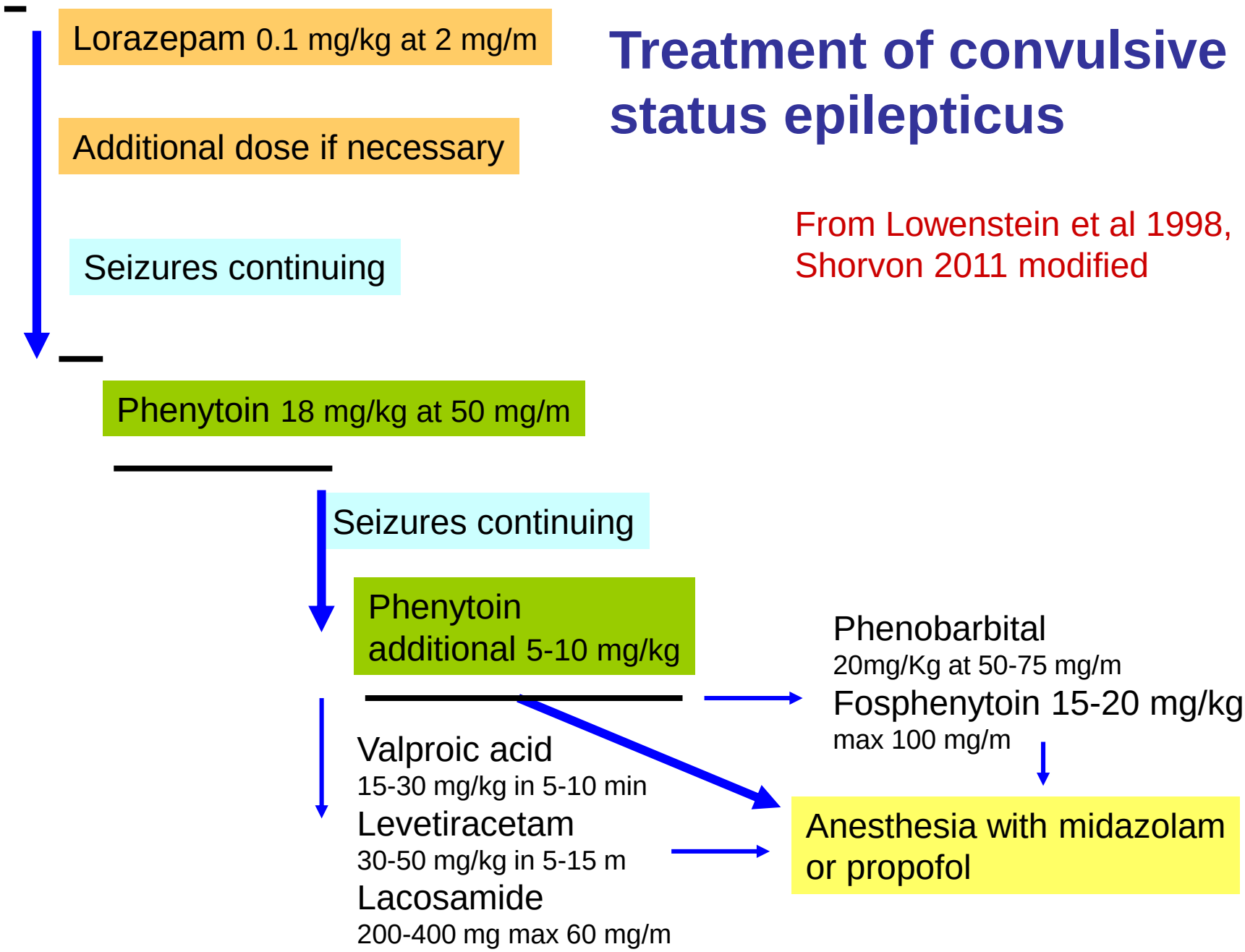
	Barbiturates	Propofol	Midazolam
Used since	Before 1960	End of 1980	Early1990
Mechanism of action			
GABA$_A$ agonistic	+++	+++	+++
NMDA antagonistic	+	(+)	
Ca channel modulation	(+)	(+)	
Na channel modulation		(+)	
Elimination half-life after prolonged administration			
	THP: 14–36 h PTB: 15–22 h	1–2 h	6–50 h
Accumulation	+++	(+)	++
Tachyphylaxis		(+)	+++
Hypotension	+++	+++	++
Other adverse effects	Immunological suppression	Infusion syndrome	
Administration			
Loading dose	THP: 2–7 mg/kg PTB: 5–15 mg/kg	2 mg/kg	0.1–0.3 mg/kg
Maintenance dose	THP: 3–5 mg/kg/h PTB: 1–5 mg/kg/h	2–10 mg/kg/h	0.05–0.6 mg/kg/h
Remarks	Long wash-out time	Limit to 48 h Combine with BDZ	Increasing doses needed with time

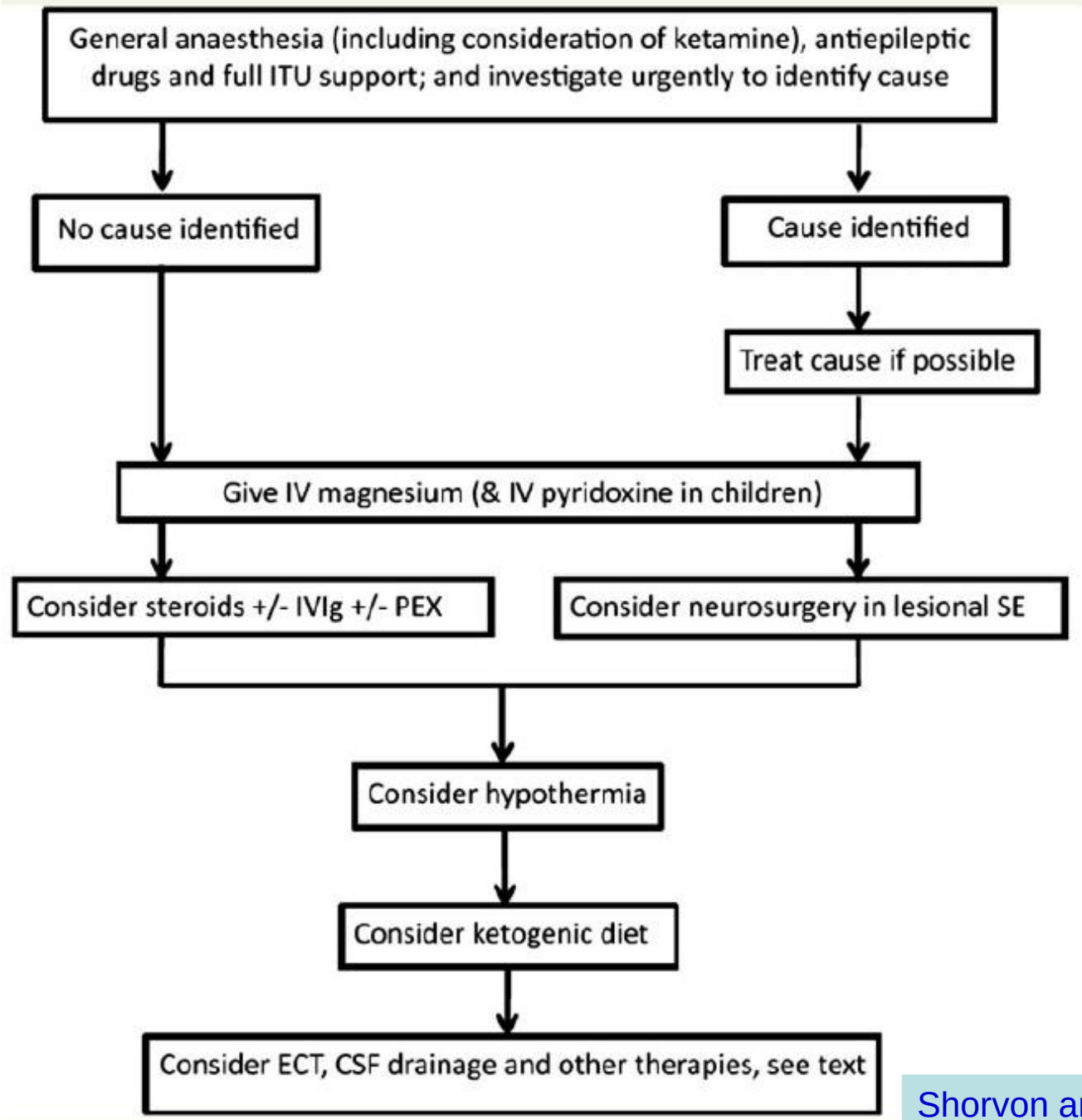
THP, thiopental; PTB, pentobarbital; BDZ, benzodiazepines

Rossetti 2007

Treatment of convulsive status epilepticus

From Lowenstein et al 1998, Shorvon 2011 modified





Shorvon and Ferlisi 2011

Stato di male non convulsivo nell'adulto

Ampia eterogeneità clinica, nosografica, eziologica, prognostica

Quadri convenzionali

- Stati di "assenza" (*epilessie generalizzate*)
- Stati di "assenza" de novo dell'anziano
- Stati di male focali a semeiologia "confusionale" (ad origine frontale e temporale) e a semeiologia sensoriale, dismnesica, psichica, autonomica ("aura continua", con ampia varietà di localizzazione della scarica). *Eterogeneità eziologica*

Stato di male non convulsivo nell'adulto

Ampia eterogeneità clinica, nosografica, eziologica, prognostica

Quadri non convenzionali

- Stati di male non convulsivi nei pazienti in coma (subtle) come fase di evoluzione di stato di male convulsivo/motorio
- Stati di male non convulsivi nei pazienti in coma (comatose Status Epilepticus), sintomatici di gravi alterazioni cerebrali focali o diffuse (es. anossia), a prognosi spesso infausta

Aspetti peculiari di trattamento relativi al NCSE

- Mancano linee guida universalmente accettate data l'eterogeneità delle condizioni denominate NCSE*
- Essenziale il ruolo dell'EEG per la diagnosi e la risposta alla terapia
- In generale, *a parte gli stati sintomatici di lesione cerebrale acuta o quelli osservati nei malati in coma*, l'atteggiamento terapeutico può essere meno aggressivo rispetto allo stato di male convulsivo

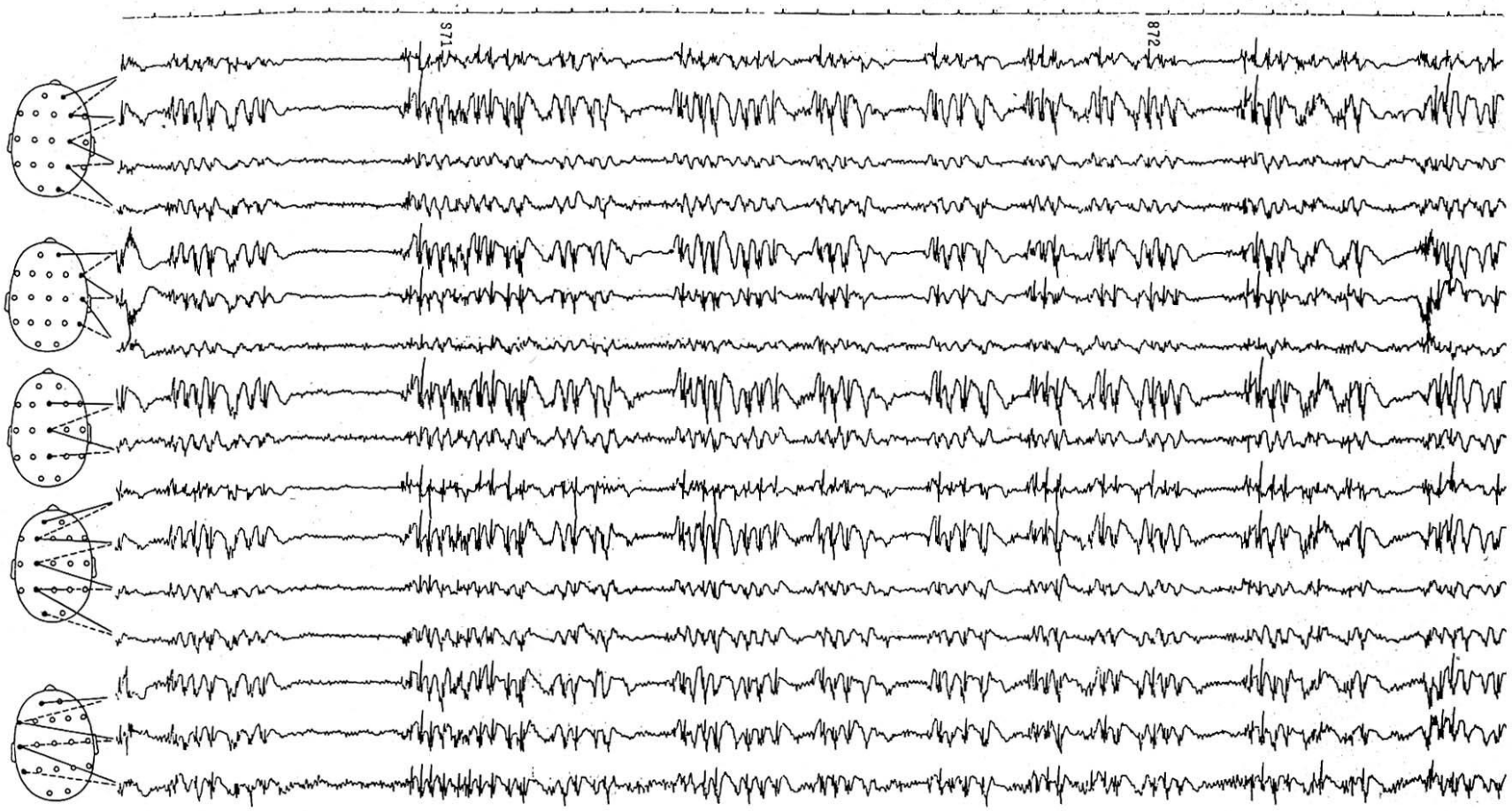
* Minicucci et al 2006, Shorvon et al 2008

Aspetti peculiari di terapia del NCSE relativi all'anziano

- La prognosi del NCSE nell'adulto in generale e nell'anziano in particolare può essere più correlata alla causa sottostante che alla persistenza del quadro elettro-grafico.
- La somministrazione e.v. di agenti antiepilettici (es. benzodiazepine) non è scevra da rischi per gli effetti ipotensivanti o sedativi.
- Atteggiamento conservativo spesso preferibile

Stato di assenza tipico

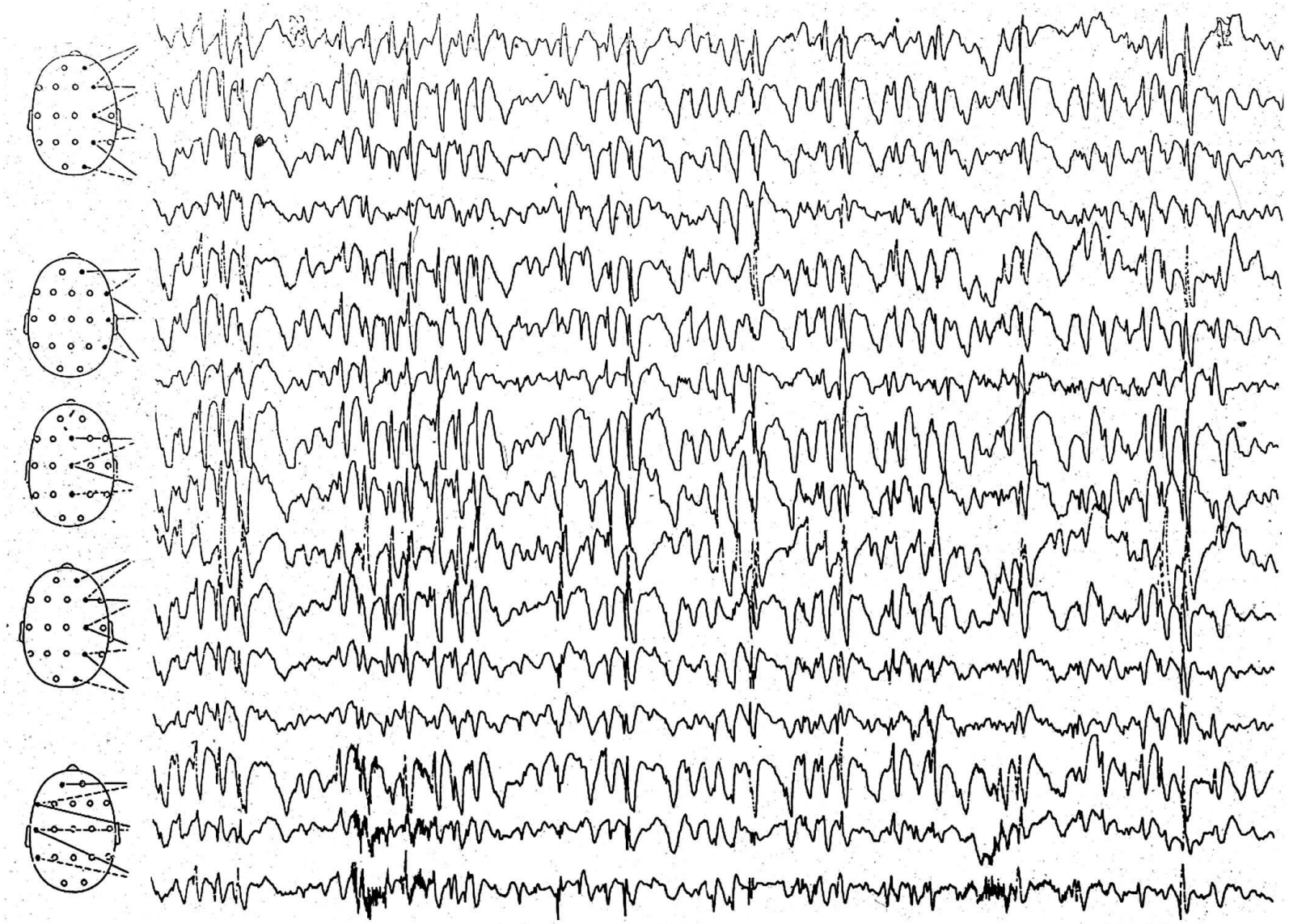
- Pazienti con epilessia generalizzata idiopatica, anche *adulti* *(absences persisting to adult life, Michelucci et al 1996; absence status epilepsy Genton et al 2008*)
- **La terapia non ha carattere d'urgenza (?)**
- **BZD per os (a domicilio)**
- **BZD e.v.**
- **Se persiste o talora come primo farmaco VPA e.v.**



C.V. male,53 yrs, Dec 1994

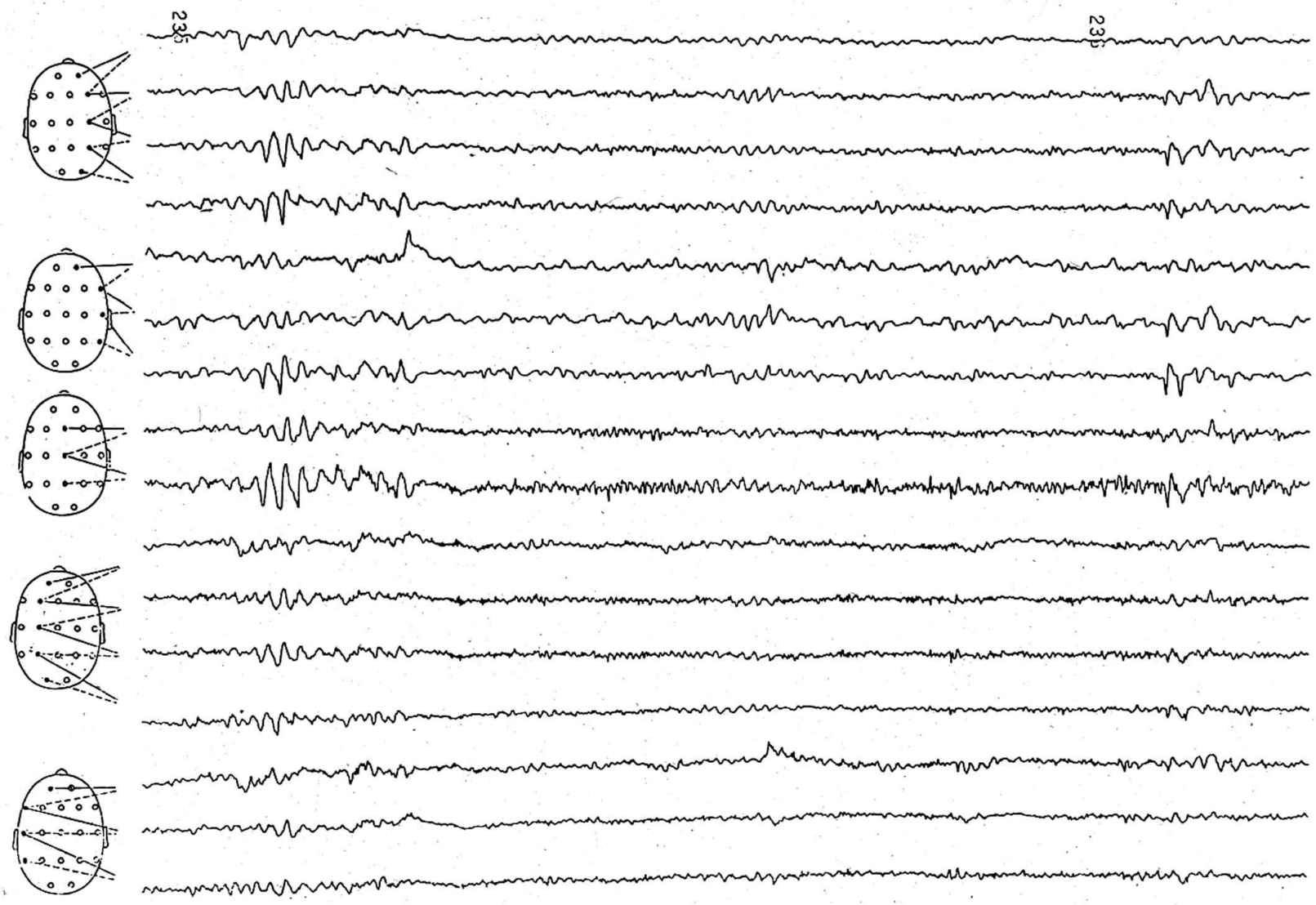
Stato di assenza atipico

- Caratteristico di encefalopatie epilettiche (es. s. di Lennox-Gastaut), che possono persistere in età adulta
- **La terapia non ha carattere d'urgenza**
- **Le BZD e.v. ⟹ risposta scarsa e transitoria, talora paradossa**
- **Preferibile VPA e.v. o p.o., BZD p.o. (con cautela), LTG (TPM? ZNS?)**



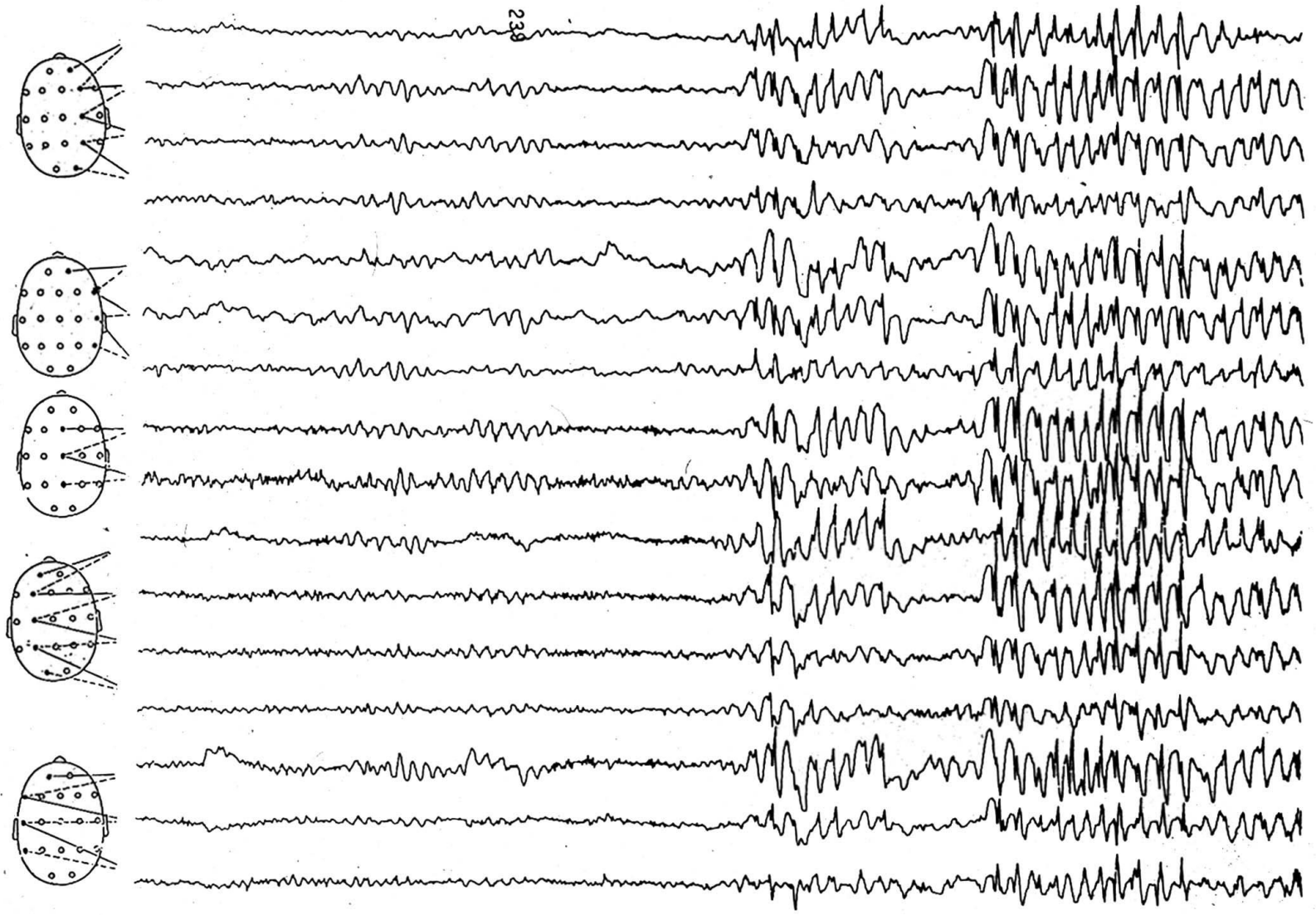
PAO. GIO., 22 yrs, female May 11, 1997

90 sec. later



PAO. GIO., 22 yrs, female May 11, 1997

3 min. later



PAO. GIO., 22 yrs, female May 11, 1997

100 uV
1 sec

DE NOVO ABSENCE STATUS AD ESORDIO TARDIVO

- **Quadro clinico:** stato confusionale fluttuante, abulia, alterazioni dell'umore, lievi mioclonie, rallentamento nel linguaggio; talora GTCS (mai all'inizio o alla fine dello status)
- **EEG:** punte-onda continue a 1-4 Hz; rallentamento diffuso
- **Fattori precipitanti:** sospensione di BZD, alterazioni tossico-metaboliche
- **Terapia: pronta risposta alle BZD e.v. (sufficiente una dose modesta – LRZ 1 mg, eventualmente da ripetere). Necessità monitoraggio video-EEG. Ambiente ospedaliero**

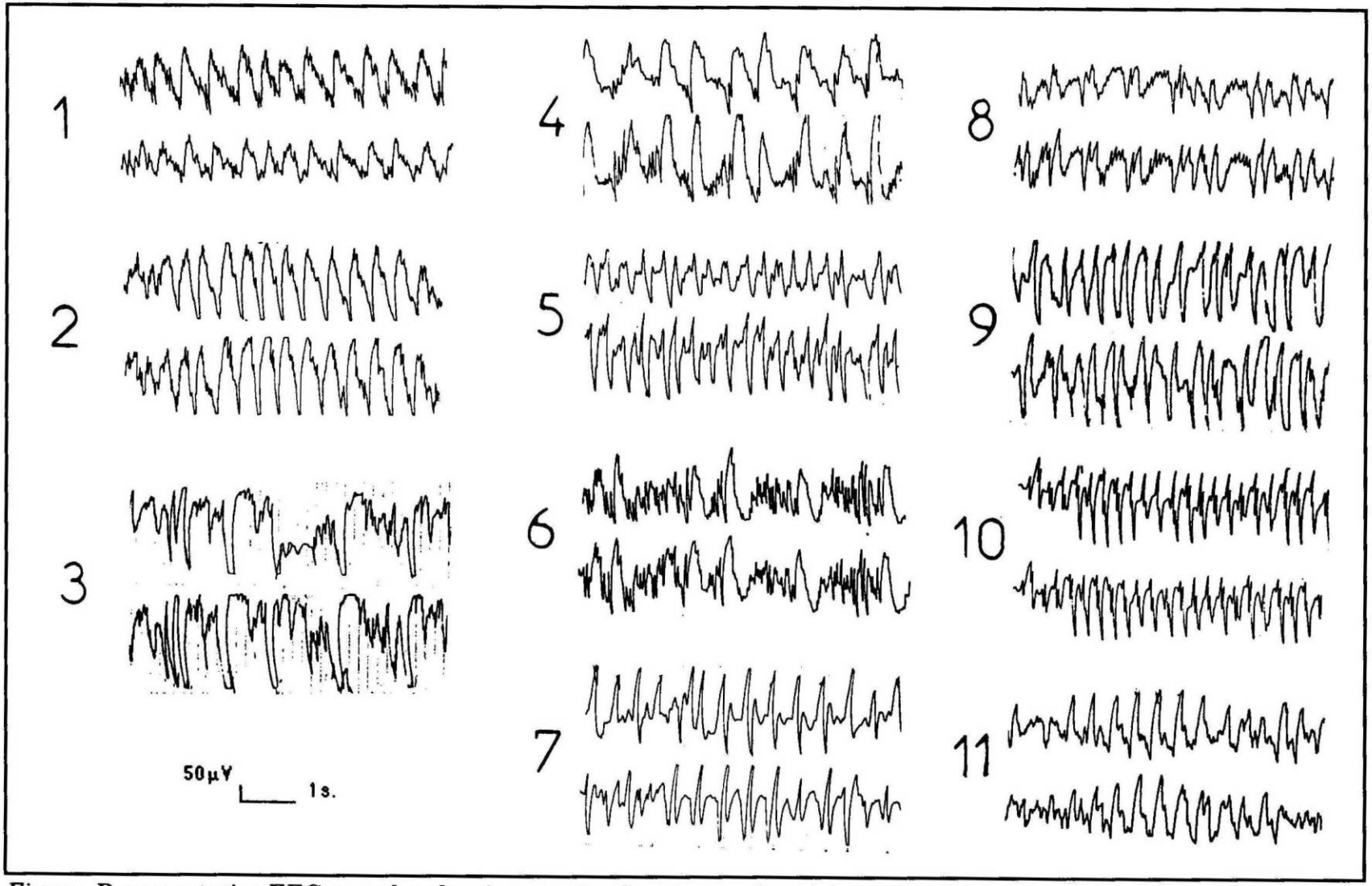


Figure. Representative EEG samples showing maximal paroxysmal activity, taken from symmetric right and left scalp areas. Leads: Fp2-C4, Fp1-C3 (patients 1 to 8, 10, and 11); Cz-T4 and T3-Cz (patient 9).

Thomas et al 1992

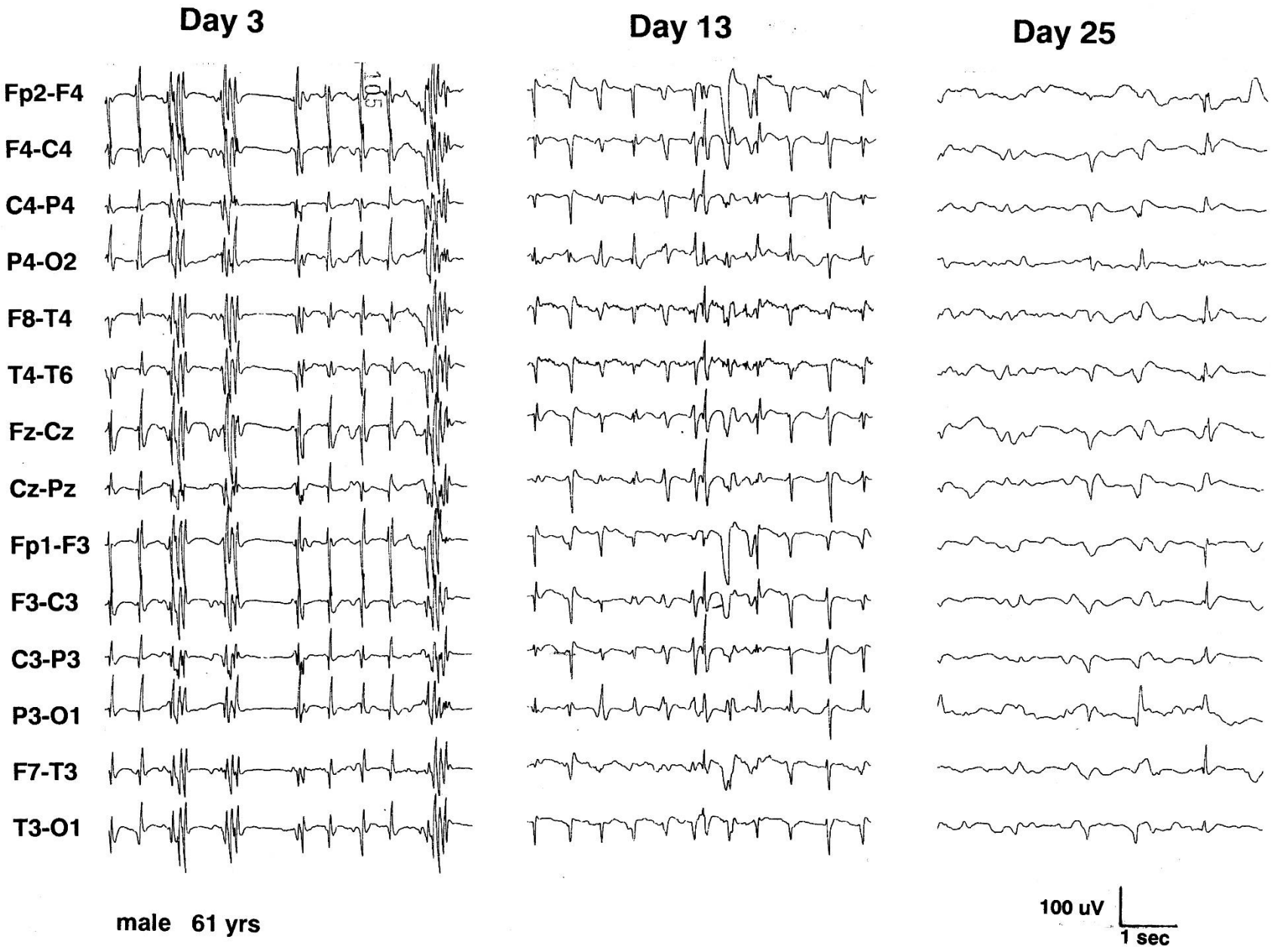
Trattamento dello stato di male non convulsivo

Tipo di stato	Trattamento di scelta	Trattamento addizionale
assenza tipica	Benzodiazepine e.v. o p.o.	Valproato e.v. (anche come 1° farmaco nell' absence status epilepsy) (Genton et al 2008)
assenza atipica	Valproato e.v. o p.o.	Benzodiazepine p.o. (con cautela), Lamotrigina p.o., Topiramato p.o.
parziale complesso	Benzodiazepine e.v. o p.o. (clobazam)	Fenitoina e.v., Valproato e.v., Levetiracetam e.v.,Topiramato p.o., Lacosamide e.v.

Stato di male non convulsivo in pazienti in coma (I)

- Come evoluzione di SE convulsivo, con o senza minime manifestazioni motorie (SE “subtle”)
- Dissociazione elettro-meccanica
- Ruolo del monitoraggio video-EEG
- Mortalità ~ 30%
- **terapia aggressiva giustificata (con fenitoina, levetiracetam, valproato…. e terapia anestesiologica → propofol, midazolam)**

Post-anoxic status epilepticus



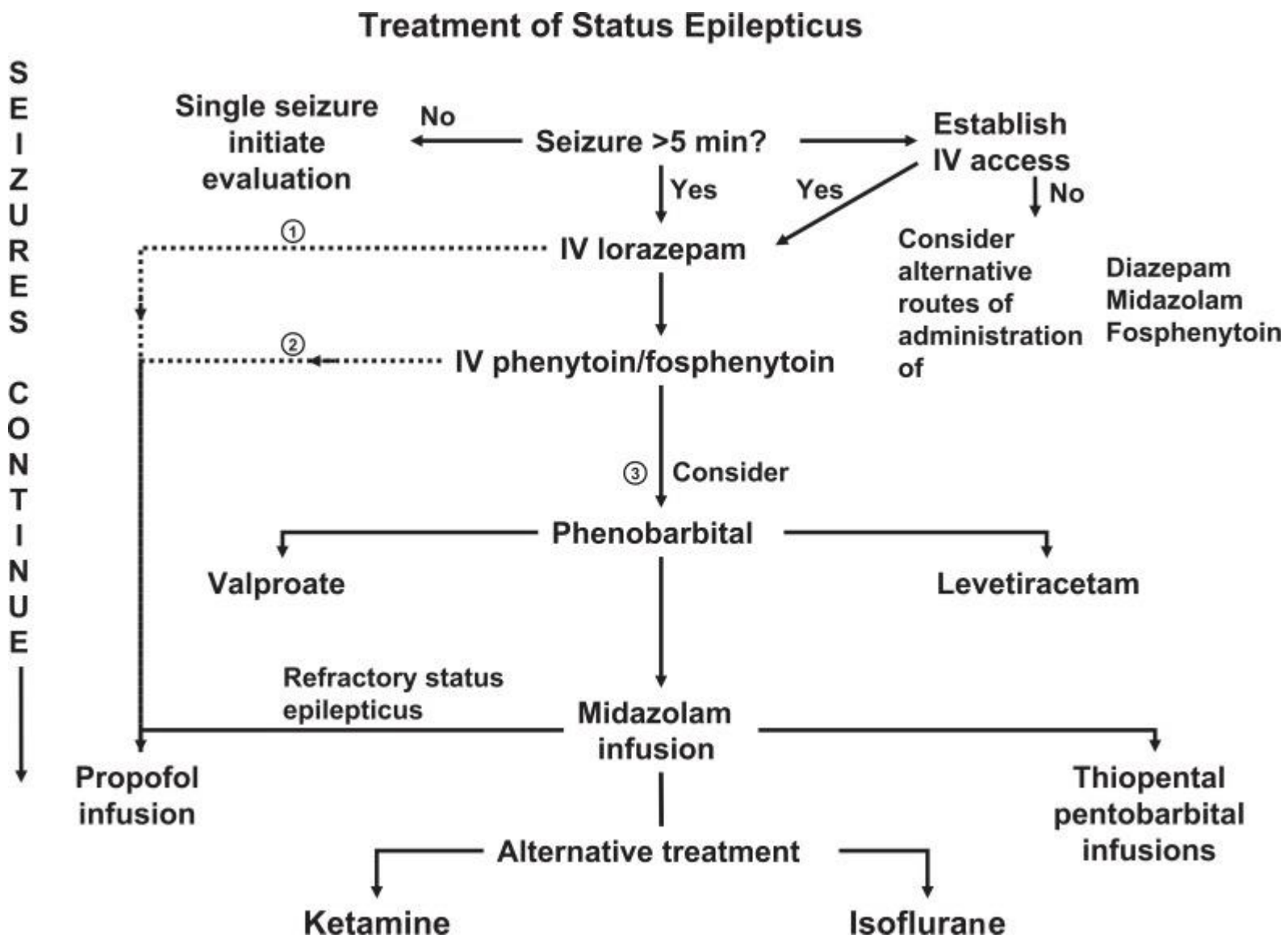
Nuove prospettive

- Migliore definizione del ruolo di LEV, LCM, VPA e.v. (studi controllati)
- Midazolam buccale e per via nasale
- TPM in sondino naso-gastrico (Reuber et al 2002, Towne et al 2003, Bensalem & Fakhouri 2003, Kahriman et al 2003)
- ***?*** antagonisti AMPA (perampanel)
- Osservazioni anedottiche: ECT (Shin et al 2009), musica (Miranda et al 2010, Kuester et al 2010)
- Casi superefrattari: immunomodulazione, chirurgia, ipotermia, dieta chetogenica,etc

Topiramato per s.n.g./os in stati refrattari: esperienza personale

- 4 casi
- S.M. focale motorio elementare (2)
- S.M. non convulsivo in pz in coma (2)
- Dose: 300-400 mg in bolo + terapia mantenimento
- Efficacia: 4/4 in 12-24 ore
- Tossicità: sedazione (1), instabilità (2), confusione (2)

.


Treatment of Status Epilepticus
SEIZURES CONTINUE
Single seizure initiate evaluation
No
Seizure >5 min?
Establish IV access
Yes
Yes
No
①
IV lorazepam
Consider alternative routes of administration of
Diazepam
Midazolam
Fosphenytoin
②
IV phenytoin/fosphenytoin
③ Consider
Phenobarbital
Valproate
Levetiracetam
Refractory status epilepticus
Midazolam infusion
Propofol infusion
Thiopental pentobarbital infusions
Alternative treatment
Ketamine
Isoflurane

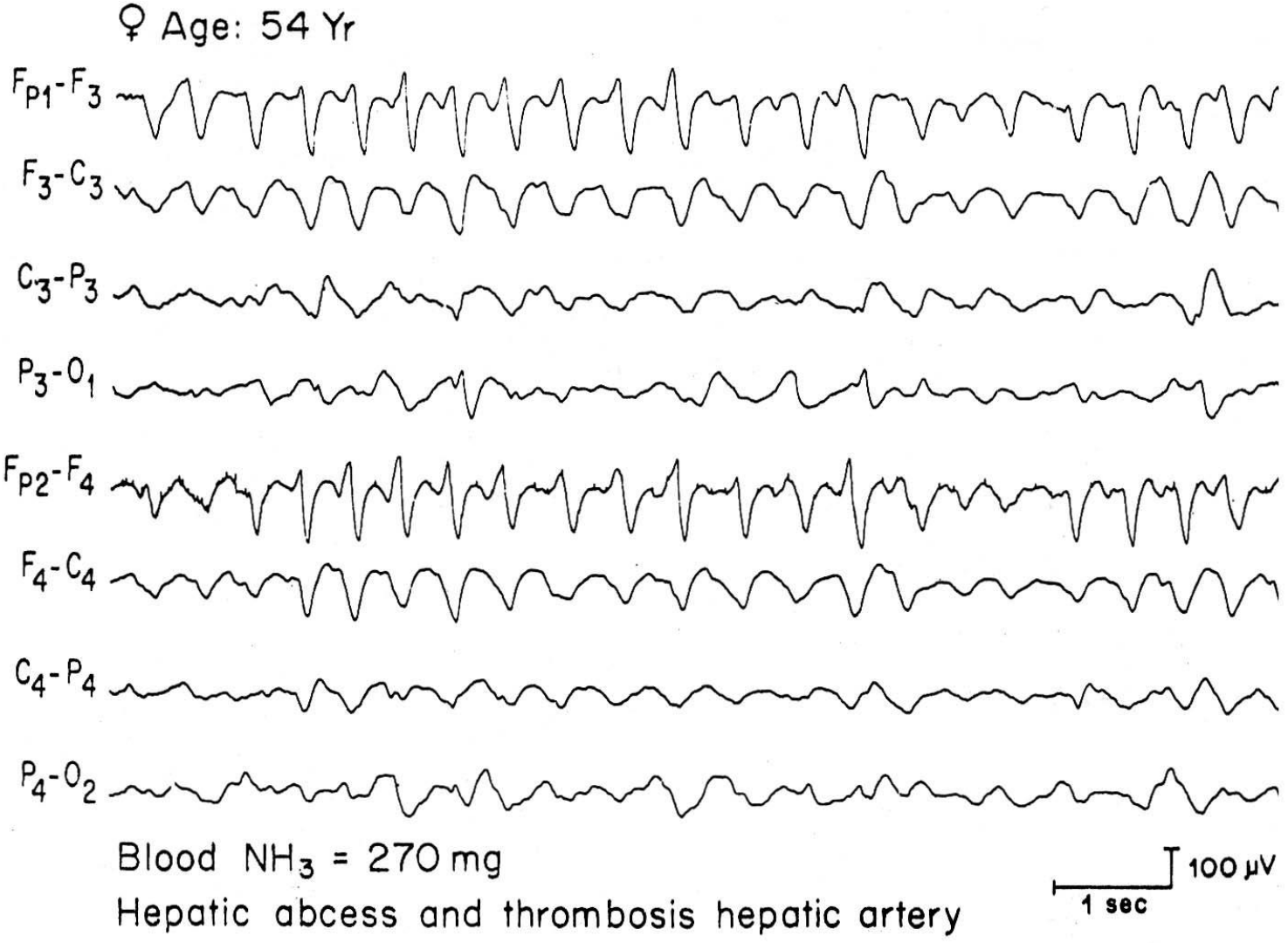
Annex I. Availability and licensing of drugs for SE in European countries.

	Valproate		Phenytoin		Lorazepam		Diazepam		Midazolam		Clonazepam	
	Available	Reg.f.SE	Available	Reg.f.SE	Available	Reg.f.SE	Available	Reg.f.SE	Available	Reg.f.SE	Available	Reg.f.SE
Australia	yes	no	yes	yes	yes	no	yes	yes	yes	no	yes	yes
Austria	yes	no	yes	yes	yes	yes	yes	yes	yes	no	yes	no
Belgium	yes	no	yes	yes	yes	no	yes	yes	yes	no	yes	no
Canada	no	no	yes	yes	yes	no	yes	yes	yes	no	yes	no
Czech Republic	no[a]	no	yes	yes	no	no	yes	yes	yes	no	yes	yes
Denmark	yes	no	yes	yes	—	—	—	—	—	—	—	—
Finland	yes	no	yes	yes	yes	no	yes	yes	yes	no	yes	no
France	yes	no	yes	yes	yes	no	yes	yes	yes	no	yes	yes
Germany	yes	no	yes	yes	yes	yes	yes	yes	yes	no	yes	yes
Greece	yes	no	yes	yes	—	—	—	—	—	—	—	—
Hungary	yes	yes	yes	yes	no	no	yes	yes	yes	no	yes	no
Ireland	yes	no	yes	yes	yes	no	yes	no	no	no	yes	yes
Italy	yes	no	yes	no	yes	yes	yes	yes	yes	no	yes	yes
Japan	no	no	yes	yes	yes	no	yes	yes	yes	no	yes	no
Korea	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
The Netherlands	yes	no	yes	yes	yes	no	yes	no	yes	no	yes	yes
Norway	yes	yes	yes	yes	no	no	yes	yes	yes	no	yes	no
Poland	yes	no	yes	yes	yes	yes	yes	no	yes	yes	yes	no
Portugal	yes	no	yes	yes	yes	no	yes	no	yes	no	yes	no
Russia	yes	no	no	no	—	—	—	—	—	—	—	—
South Africa	yes	no	yes	yes	yes	no	yes	yes	yes	no	yes	yes
Spain	yes	no	yes	yes	yes	no	yes	yes	yes	no	yes	yes
Sweden	yes	no	yes	yes	yes	no	yes	yes	yes	no	yes	yes
Switzerland	yes	no	yes	yes	yes	no	yes	yes	yes	no	yes	yes
Turkey	—	no	yes	yes	—	—	—	—	—	—	—	—
United Kingdom	yes	no	yes	yes	yes	yes	yes	yes	yes	no	yes	yes
United States of America	yes	no	yes	yes	yes	no	yes	yes	yes	no	yes	no

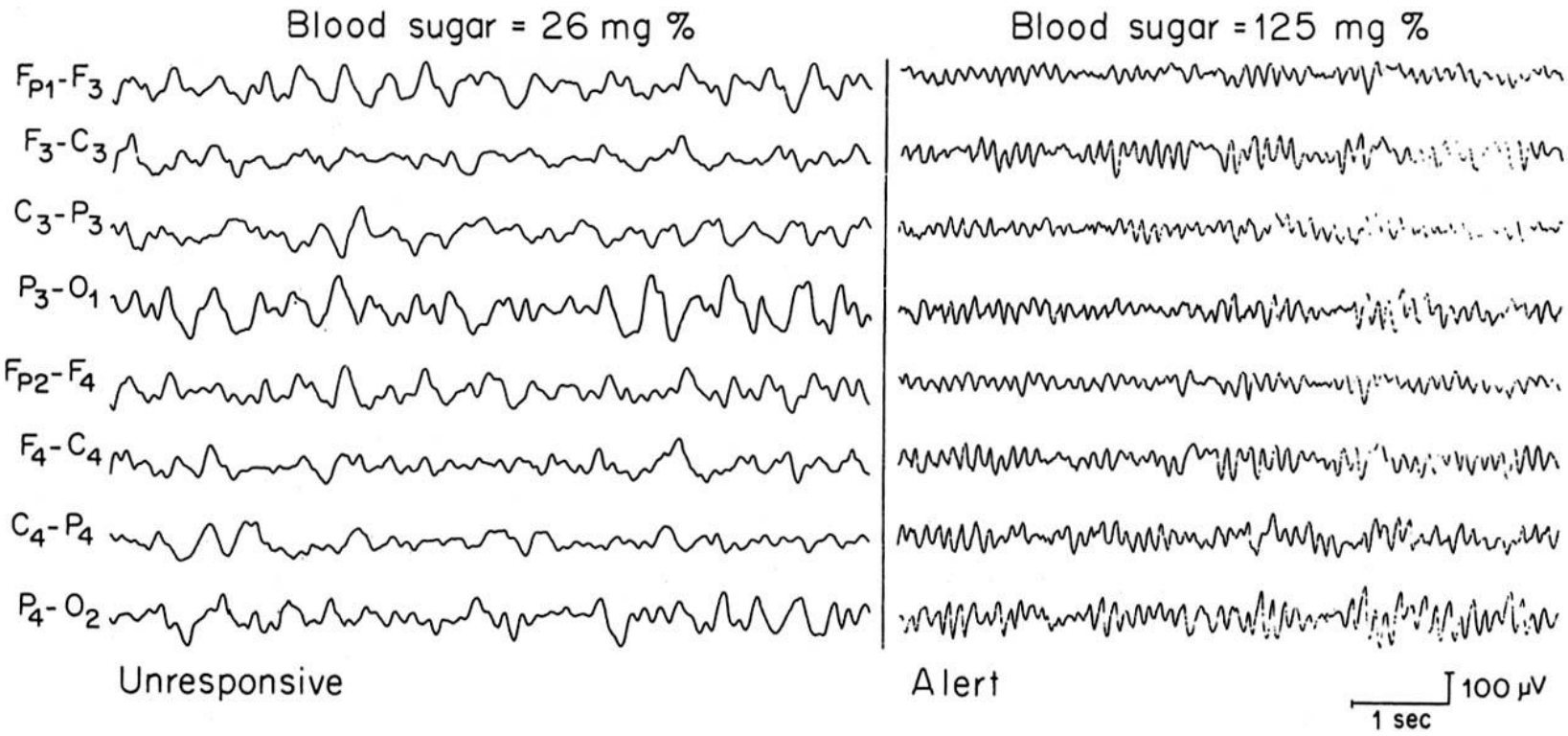
Reg.f.SE, registered for use in SE.
[a]Valproate intravenous (IV) is licensed but not marketed.

Shorvon 2008

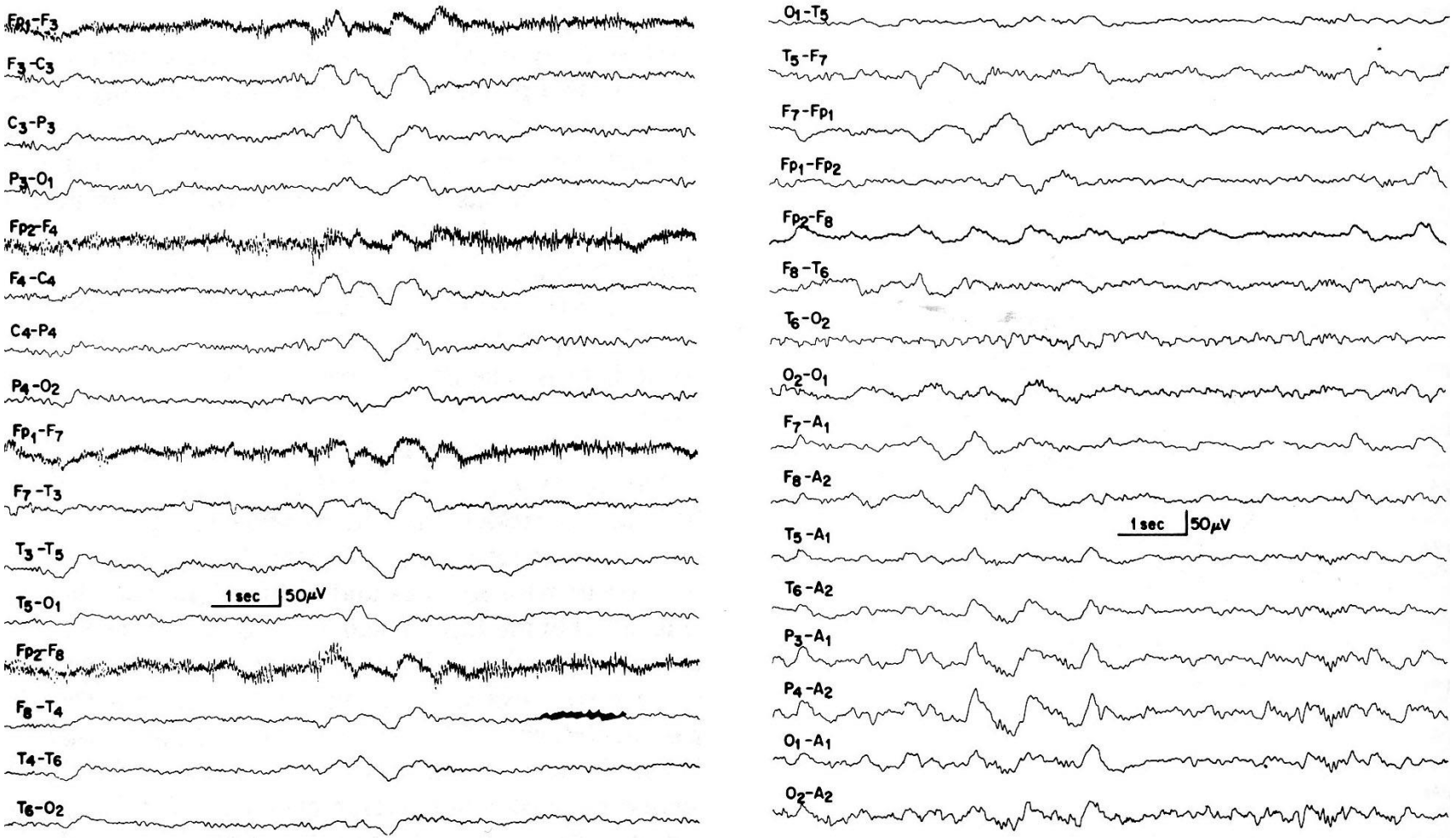
Encefalopatia epatica



Ipoglicemia

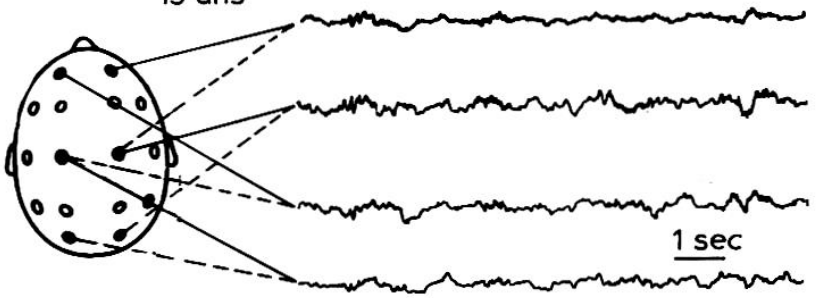


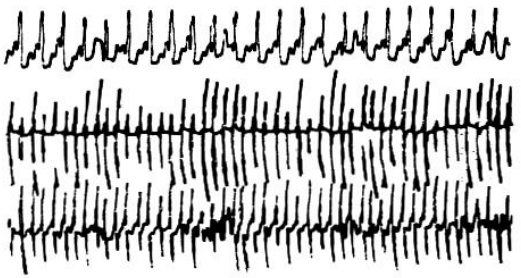
Encefalopatia uremica

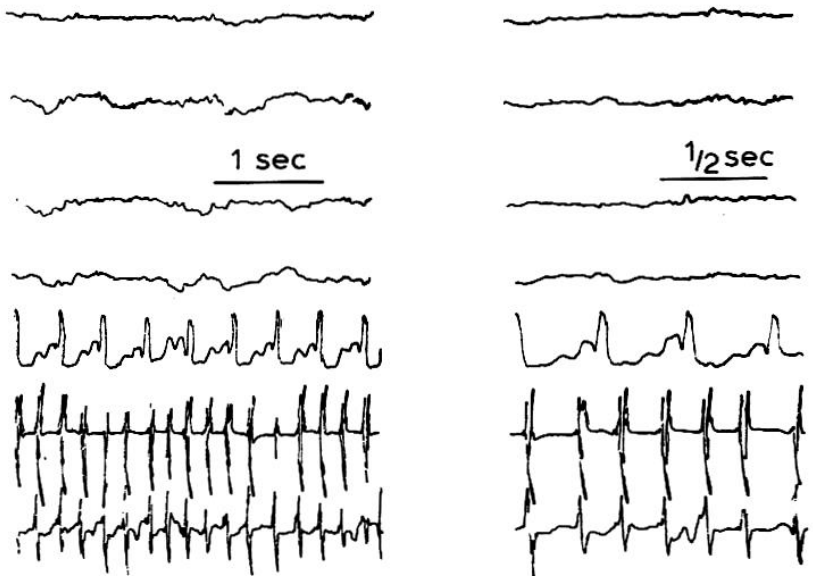


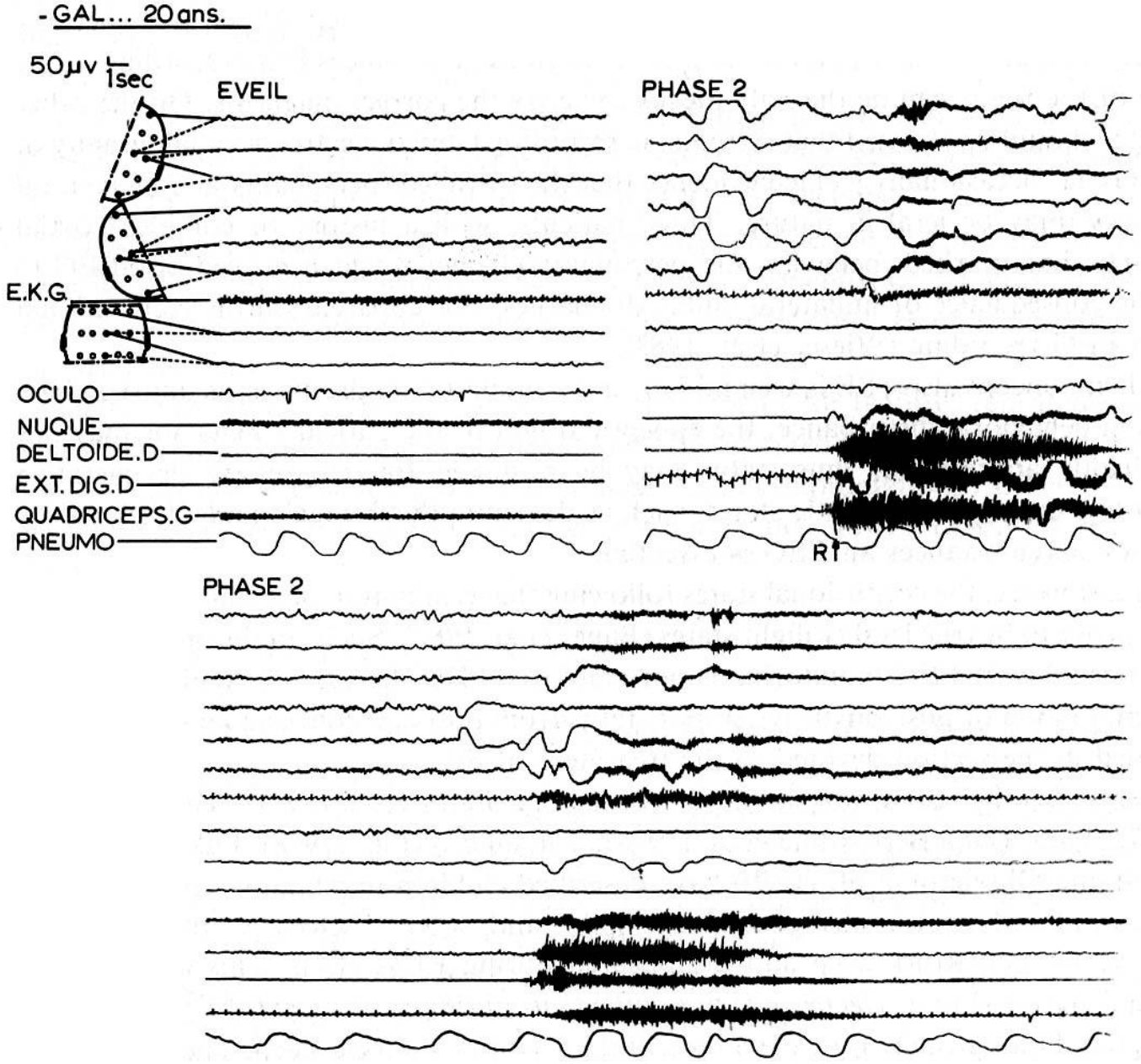
MAR... J.M.

19 ans








- GAL... 20 ans.
50µv
1sec
EVEIL
PHASE 2
E.K.G.
OCULO
NUQUE
DELTOIDE.D
EXT. DIG.D
QUADRICEPS.G
PNEUMO
R
PHASE 2

Conclusioni

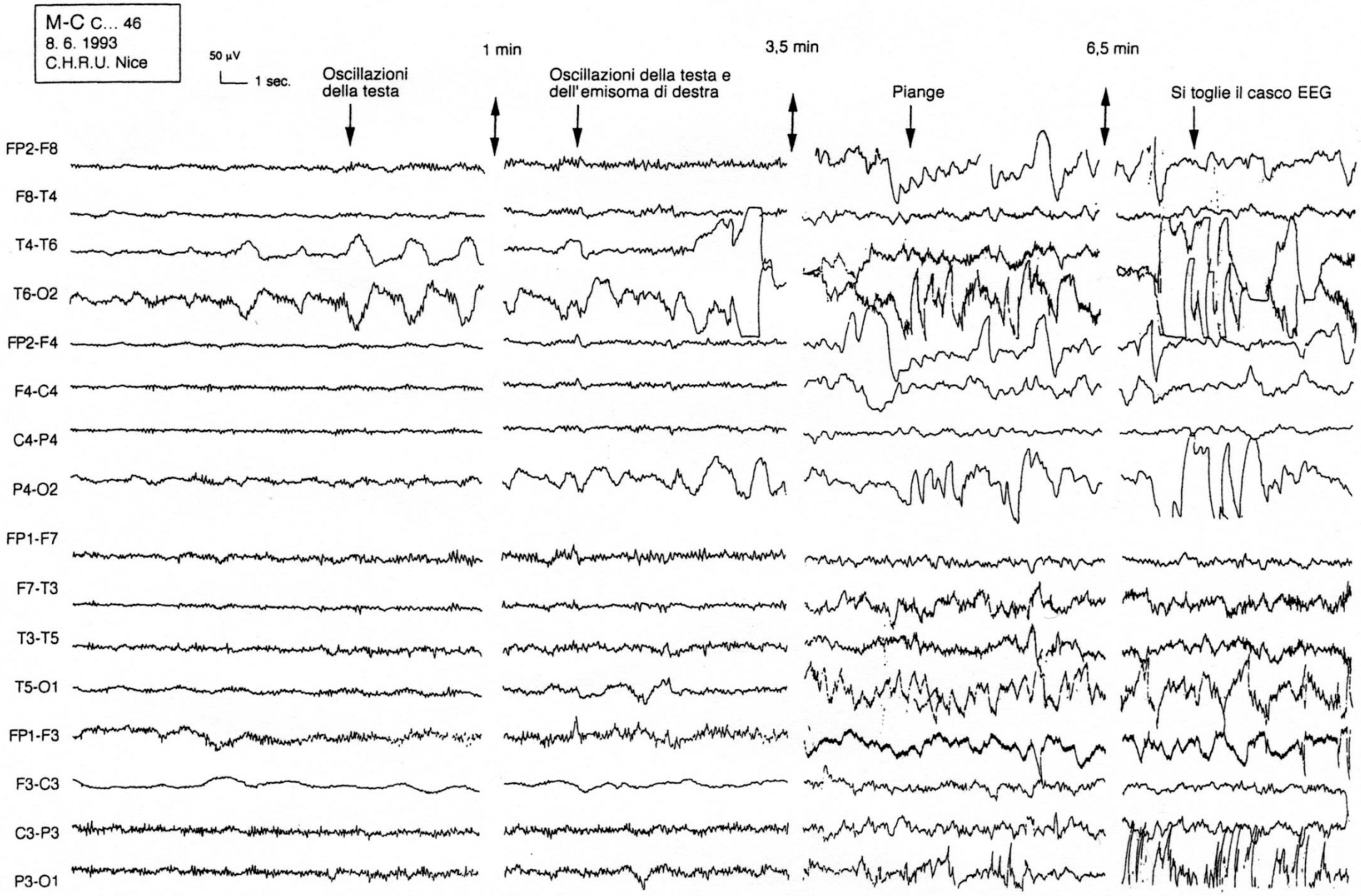
Obiettivo giungere alla diagnosi in tempi rapidi

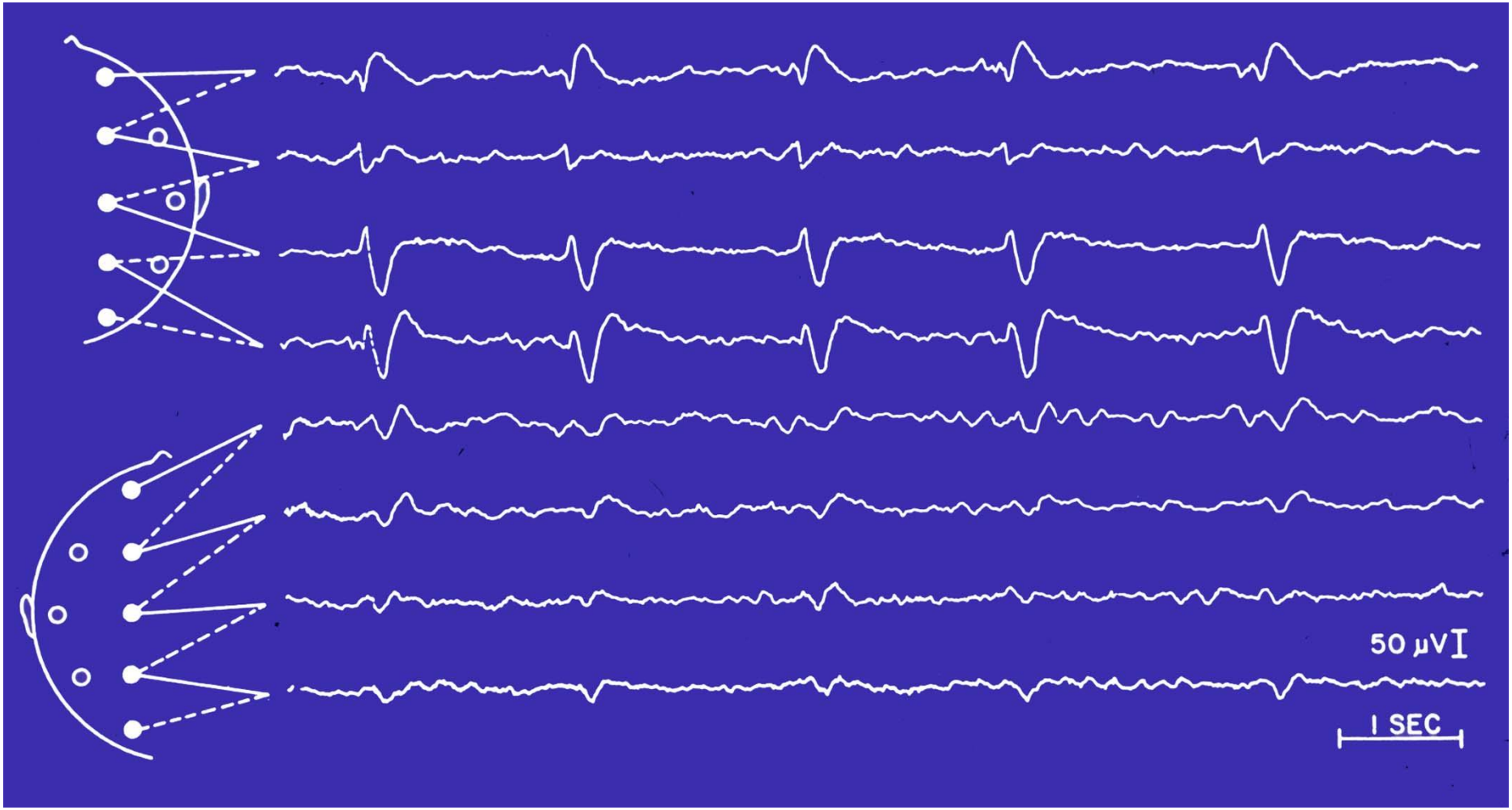
- Utilità/necessità del monitoraggio EEG e video-EEG:

❖ diagnosi (SM vs altre condizioni)

❖ riconoscimento del tipo di status (implicazioni eziologiche?)

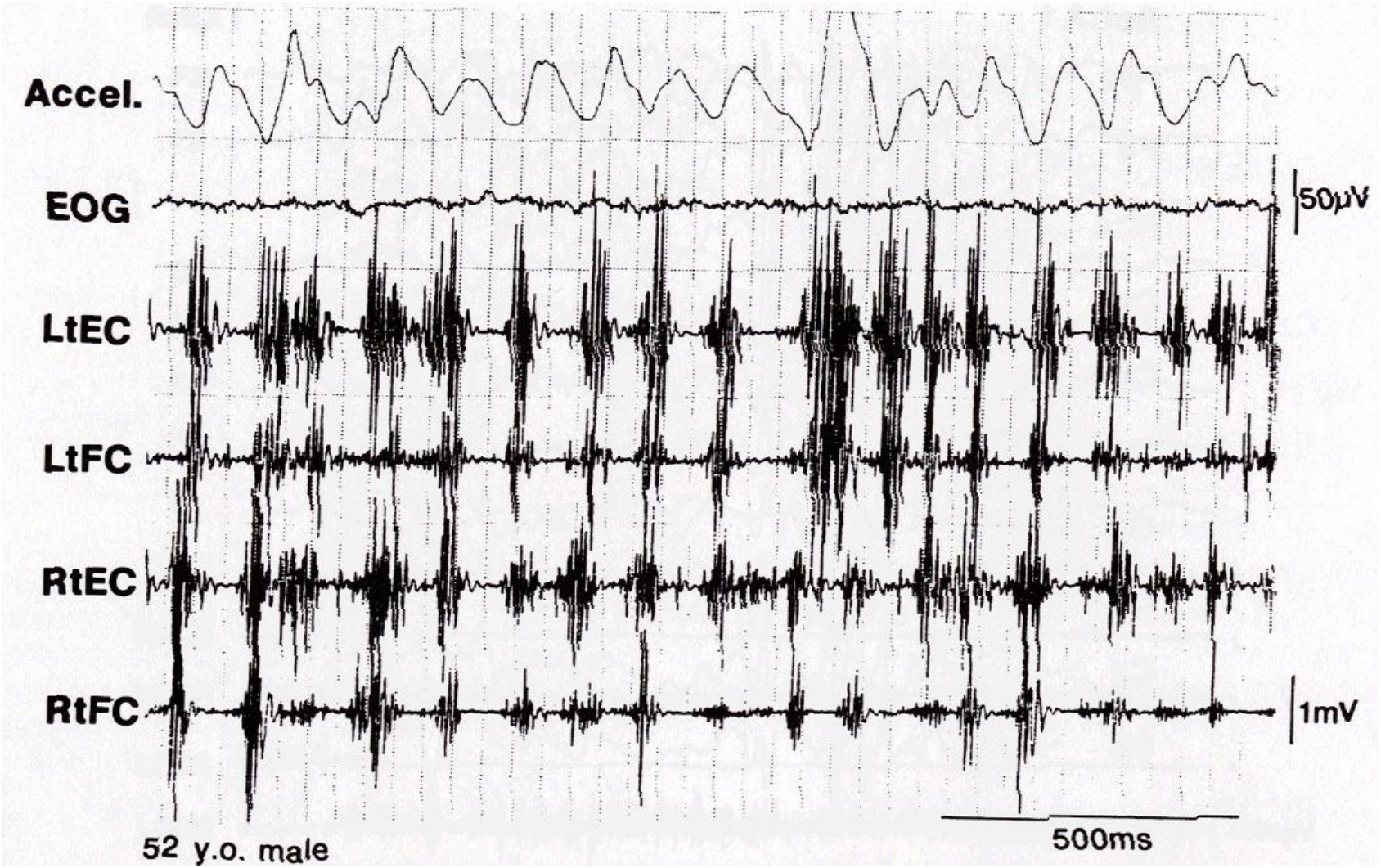
❖ guida alla terapia (++ in ER)


M-C C... 46
8. 6. 1993
C.H.R.U. Nice
50 µV
1 sec.
Oscillazioni della testa
1 min
Oscillazioni della testa e dell'emisoma di destra
3,5 min
Piange
6,5 min
Si toglie il casco EEG
FP2-F8
F8-T4
T4-T6
T6-O2
FP2-F4
F4-C4
C4-P4
P4-O2
FP1-F7
F7-T3
T3-T5
T5-O1
FP1-F3
F3-C3
C3-P3
P3-O1

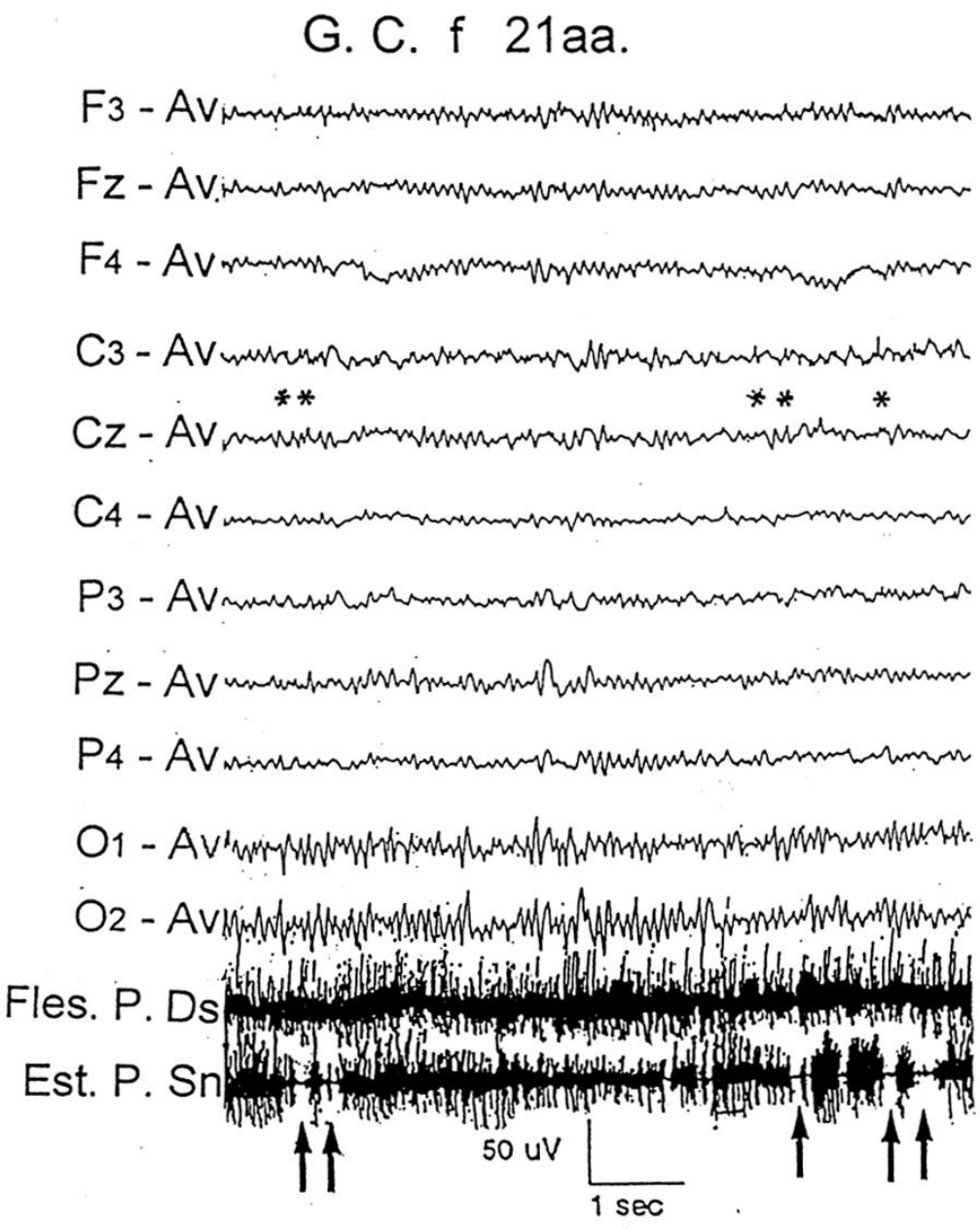


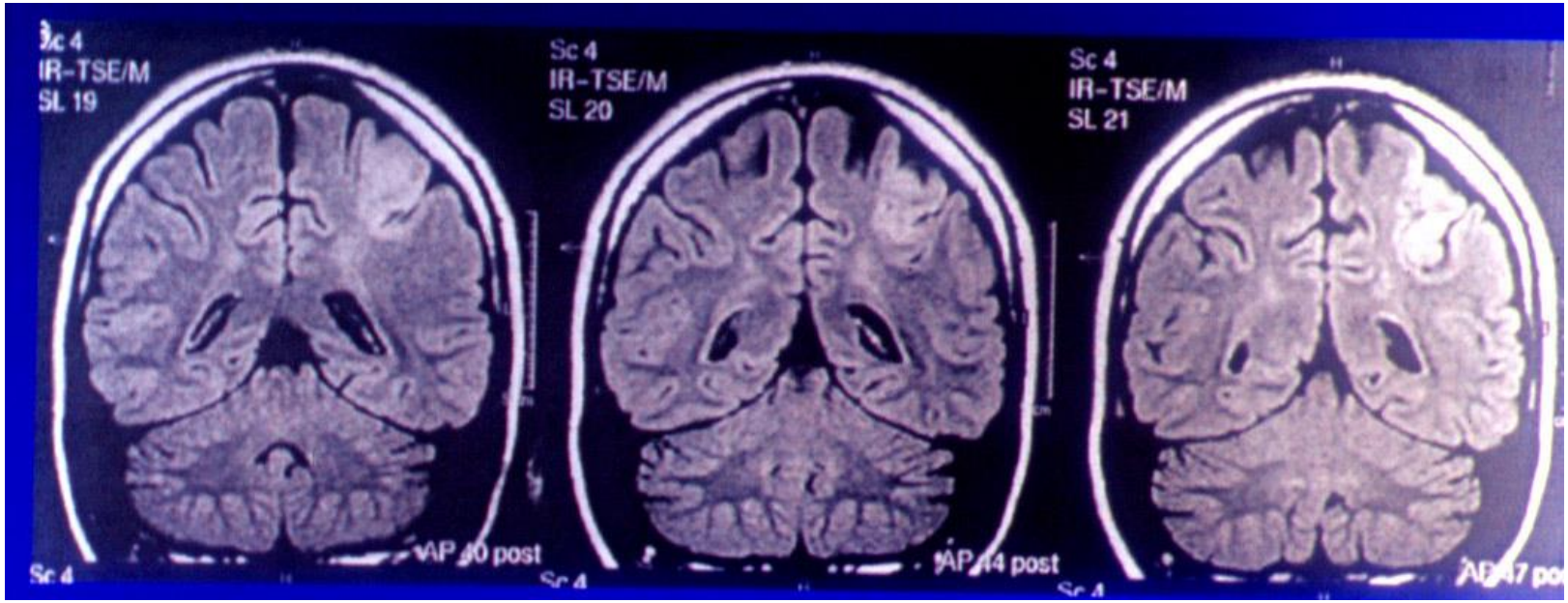
Pz di 64 aa con vasta lesione ischemica parieto-temporo-occipitale dx: PLEDs

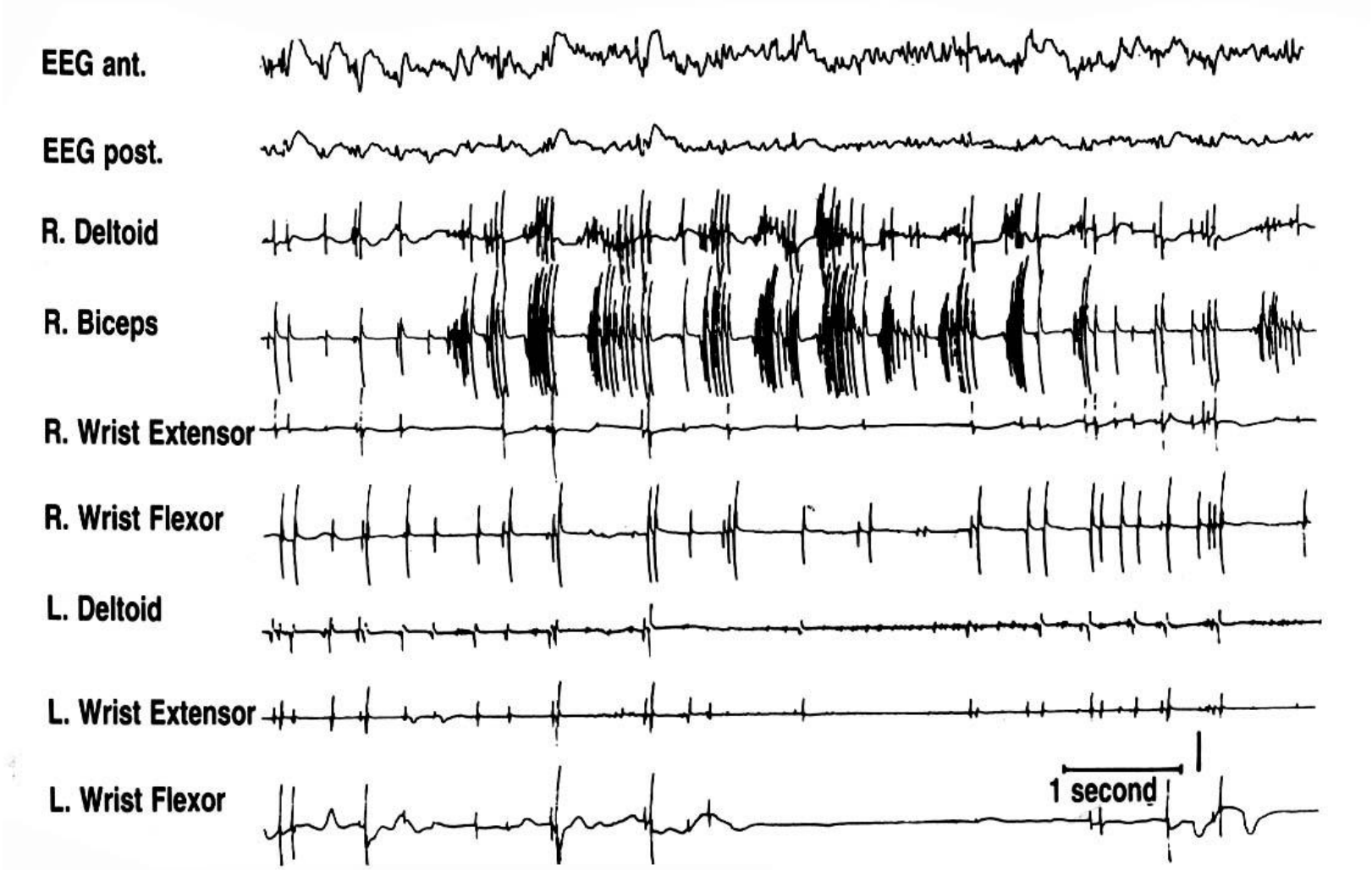
ASTERIXIS

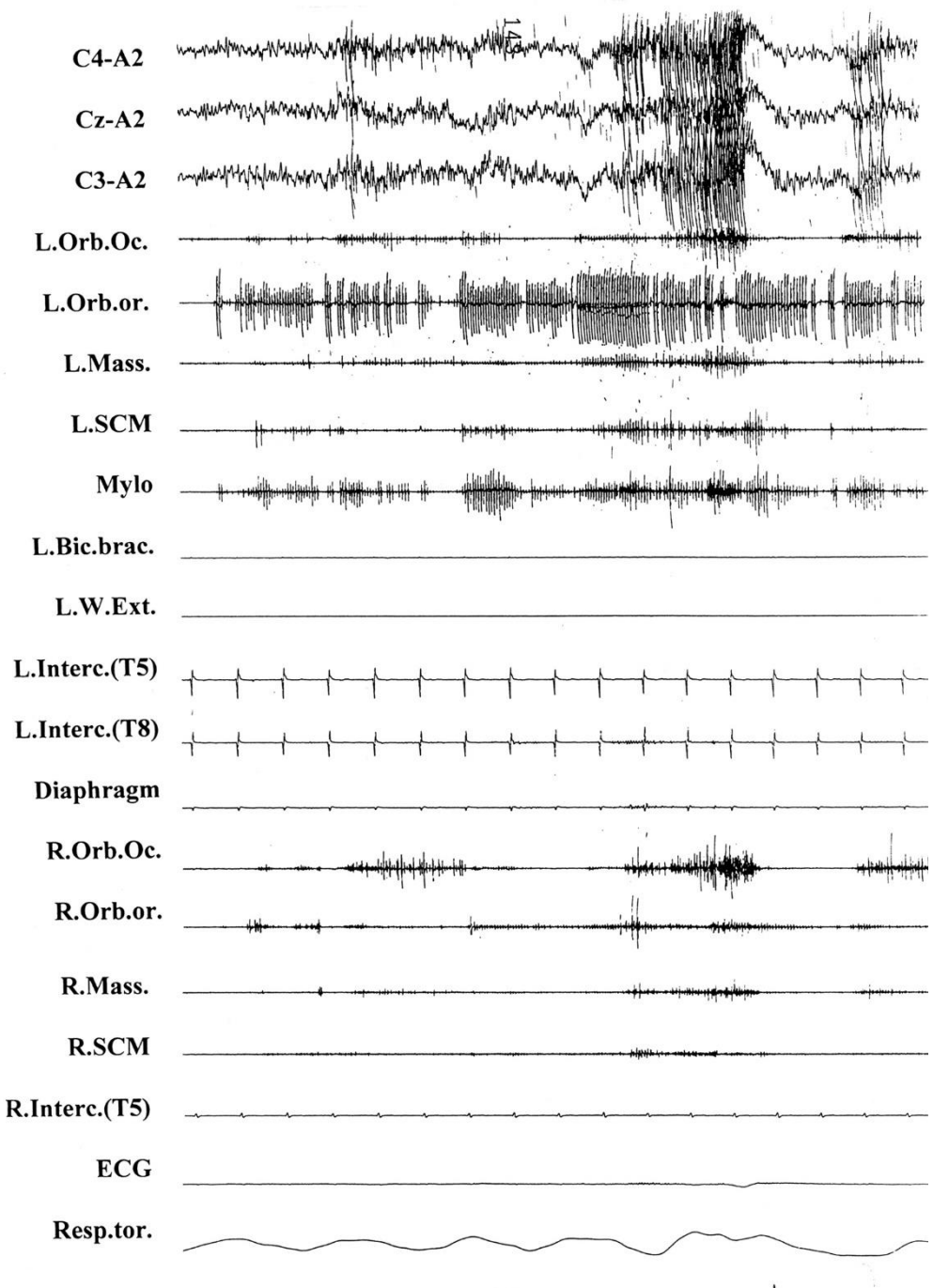


(Shibasaki, 1995)

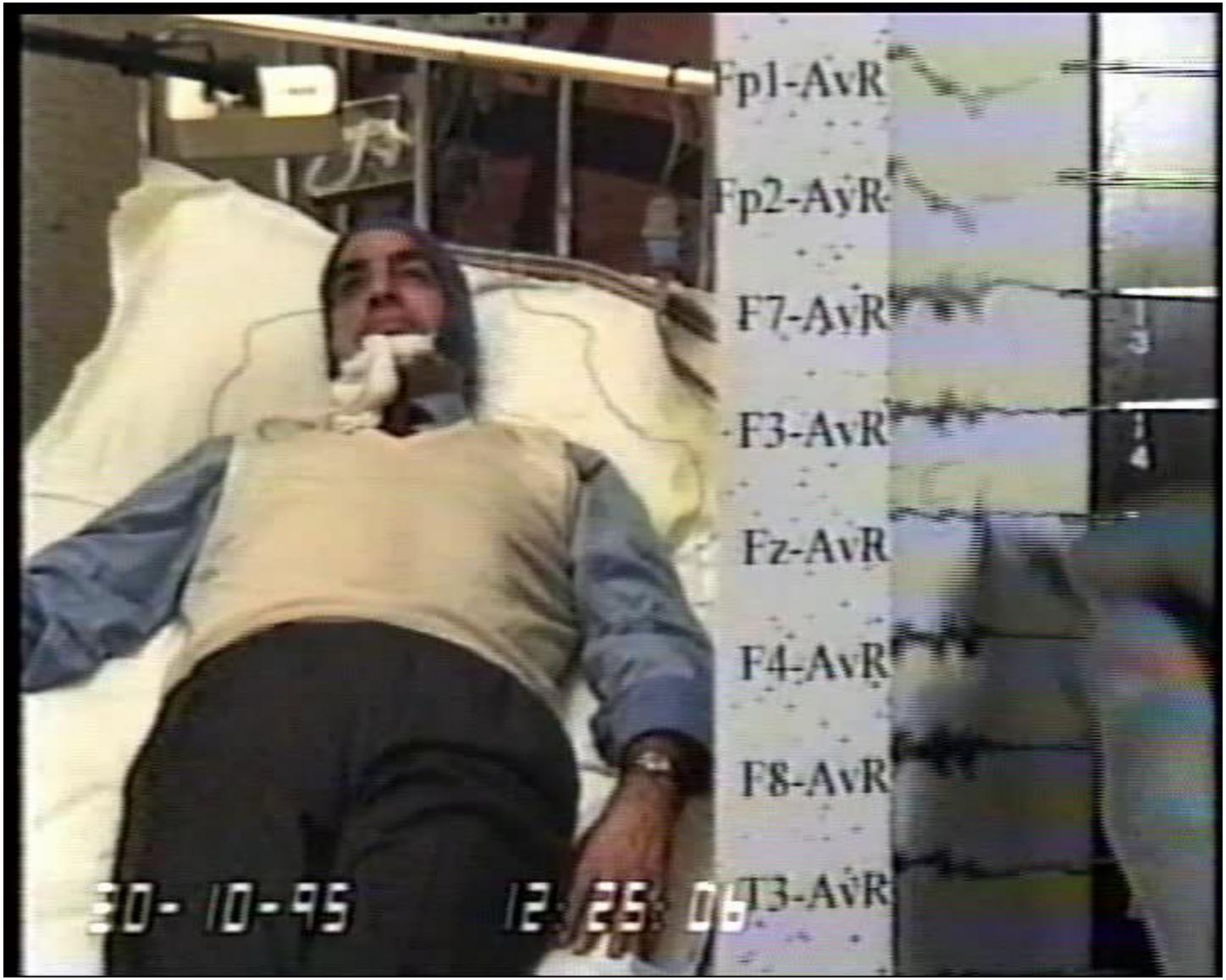

G. C. f 21aa.
F3 - Av
Fz - Av
F4 - Av
C3 - Av
Cz - Av
C4 - Av
P3 - Av
Pz - Av
P4 - Av
O1 - Av
O2 - Av
Fles. P. Ds
Est. P. Sn
50 uV
1 sec

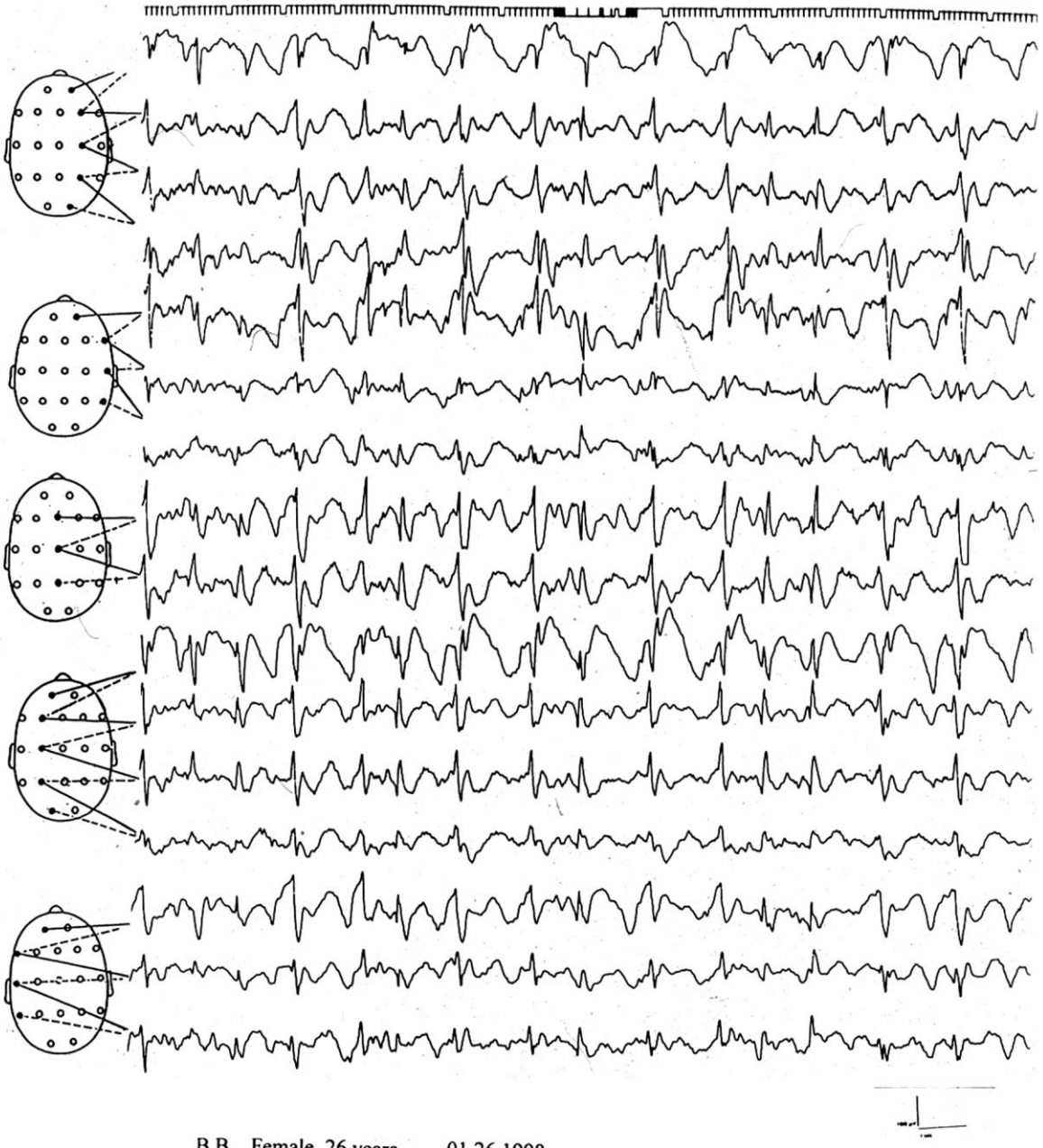

Sc 4
IR-TSE/M
SL 19
Sc 4
IR-TSE/M
SL 20
Sc 4
IR-TSE/M
SL 21


EEG ant.
EEG post.
R. Deltoid
R. Biceps
R. Wrist Extensor
R. Wrist Flexor
L. Deltoid
L. Wrist Extensor
L. Wrist Flexor
1 second

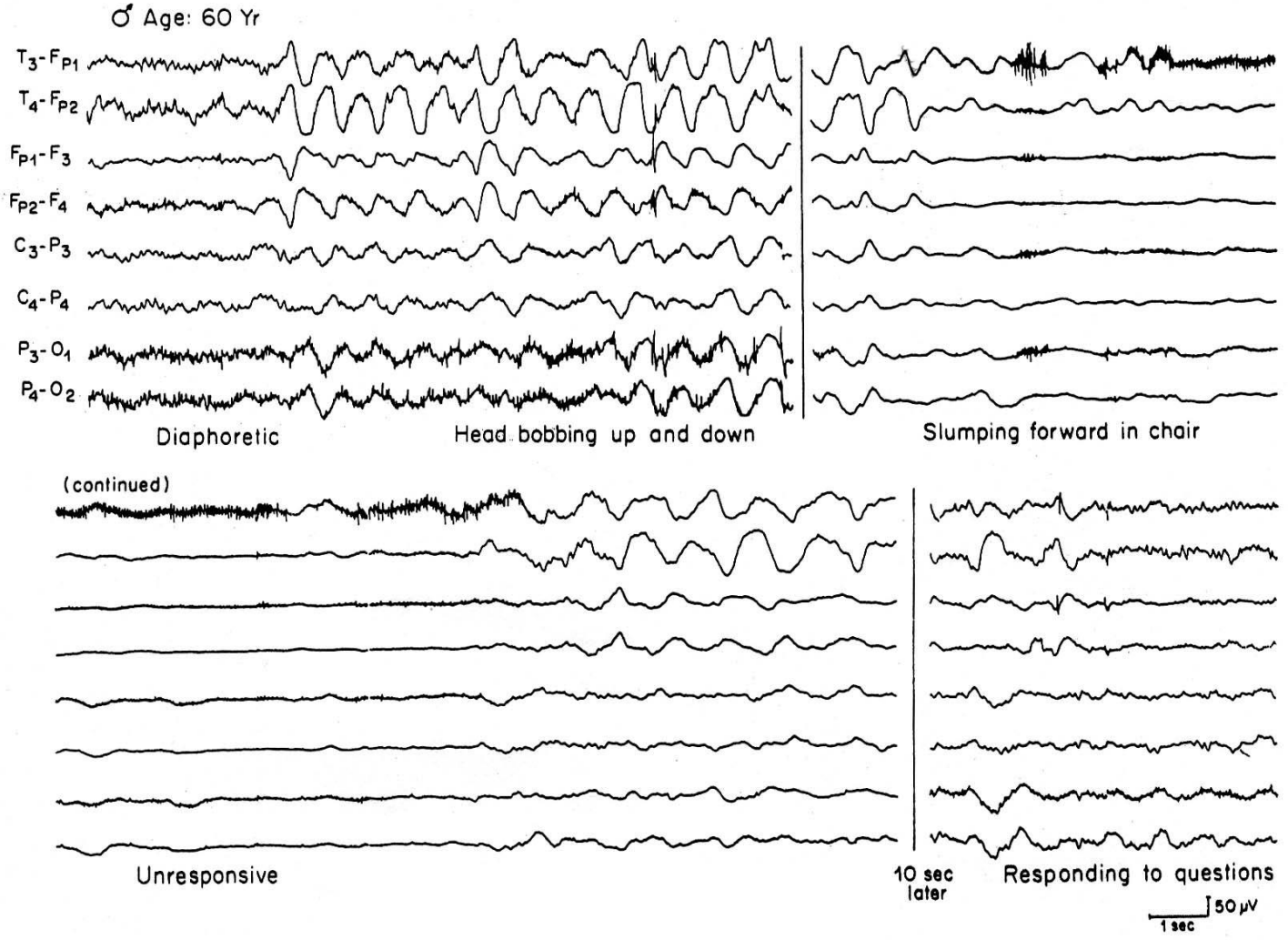


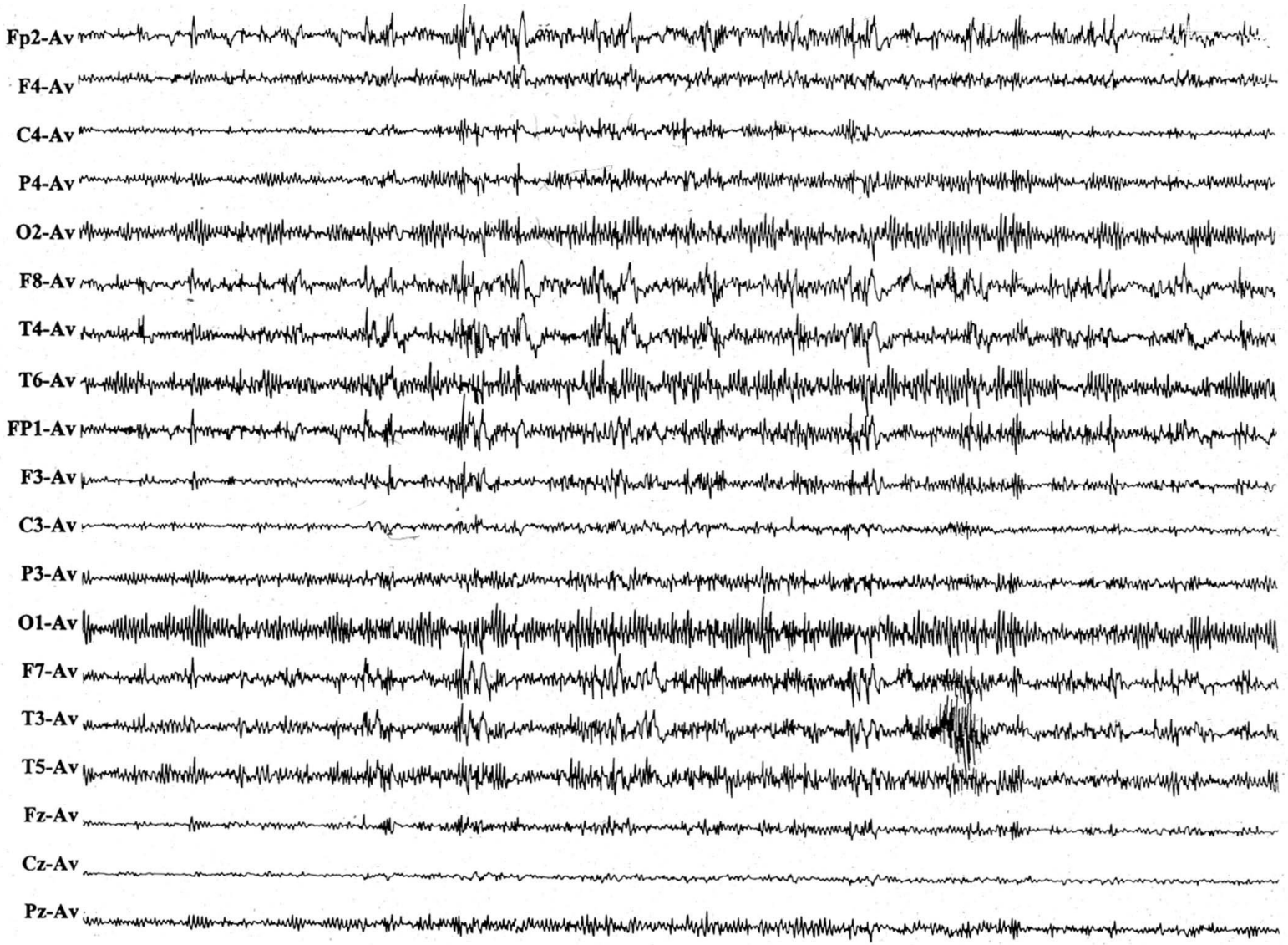
C.E.R. 70 yrs male 31-8-01

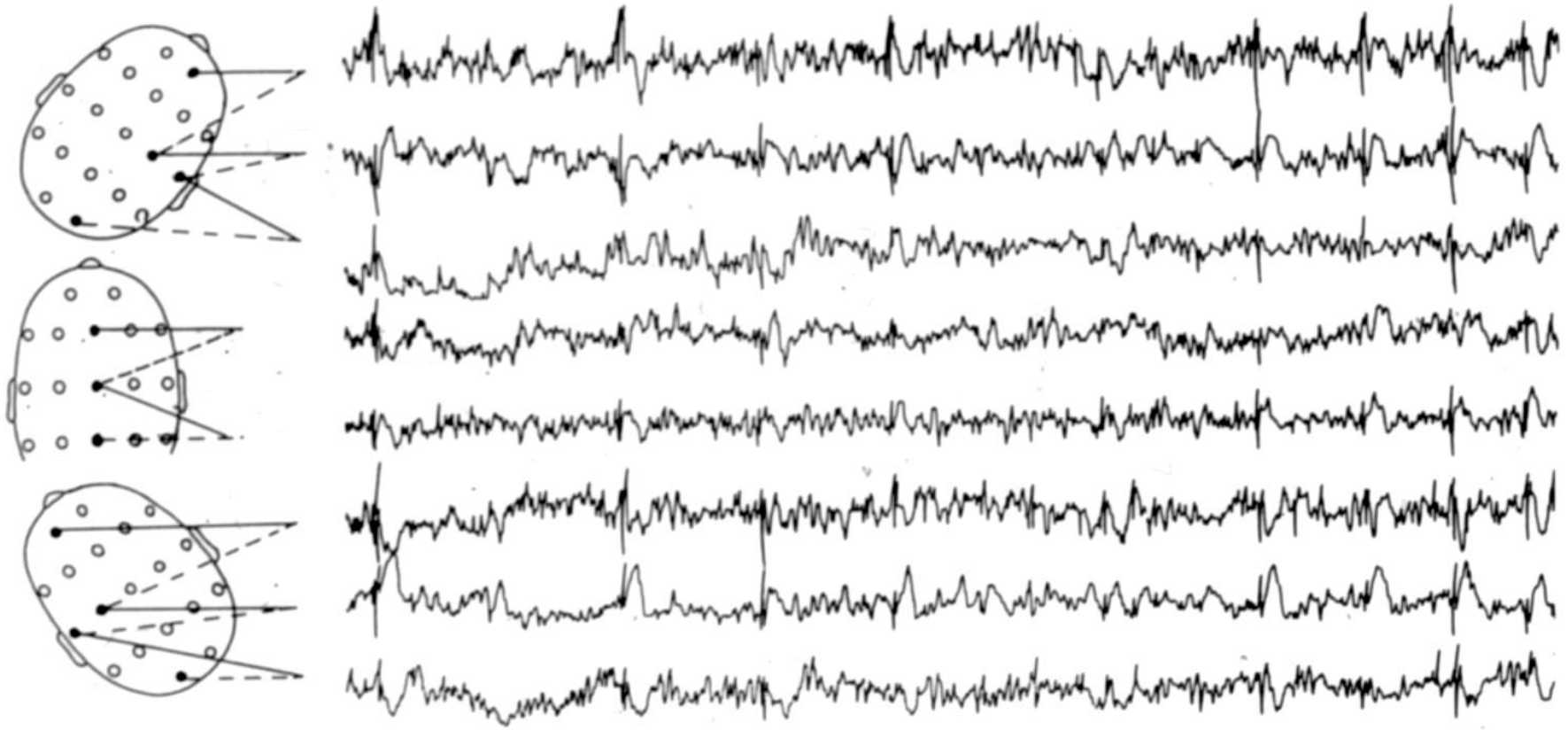

Fp1-AvR
Fp2-AvR
F7-AvR
F3-AvR
Fz-AvR
F4-AvR
F8-AvR
T3-AvR
30-10-95
12:25:06



B.B. Female 26 years 01.26.1998


♂ Age: 60 Yr
T3-FP1
T4-FP2
FP1-F3
FP2-F4
C3-P3
C4-P4
P3-O1
P4-O2
Diaphoretic
Head bobbing up and down
Slumping forward in chair
(continued)
Unresponsive
10 sec later
Responding to questions
50 μV
1 sec


Fp2-Av
F4-Av
C4-Av
P4-Av
O2-Av
F8-Av
T4-Av
T6-Av
FP1-Av
F3-Av
C3-Av
P3-Av
O1-Av
F7-Av
T3-Av
T5-Av
Fz-Av
Cz-Av
Pz-Av
M.M. 42 aa F. 14/10/98
100 µV
1 sec



G.V. 84 yrs female

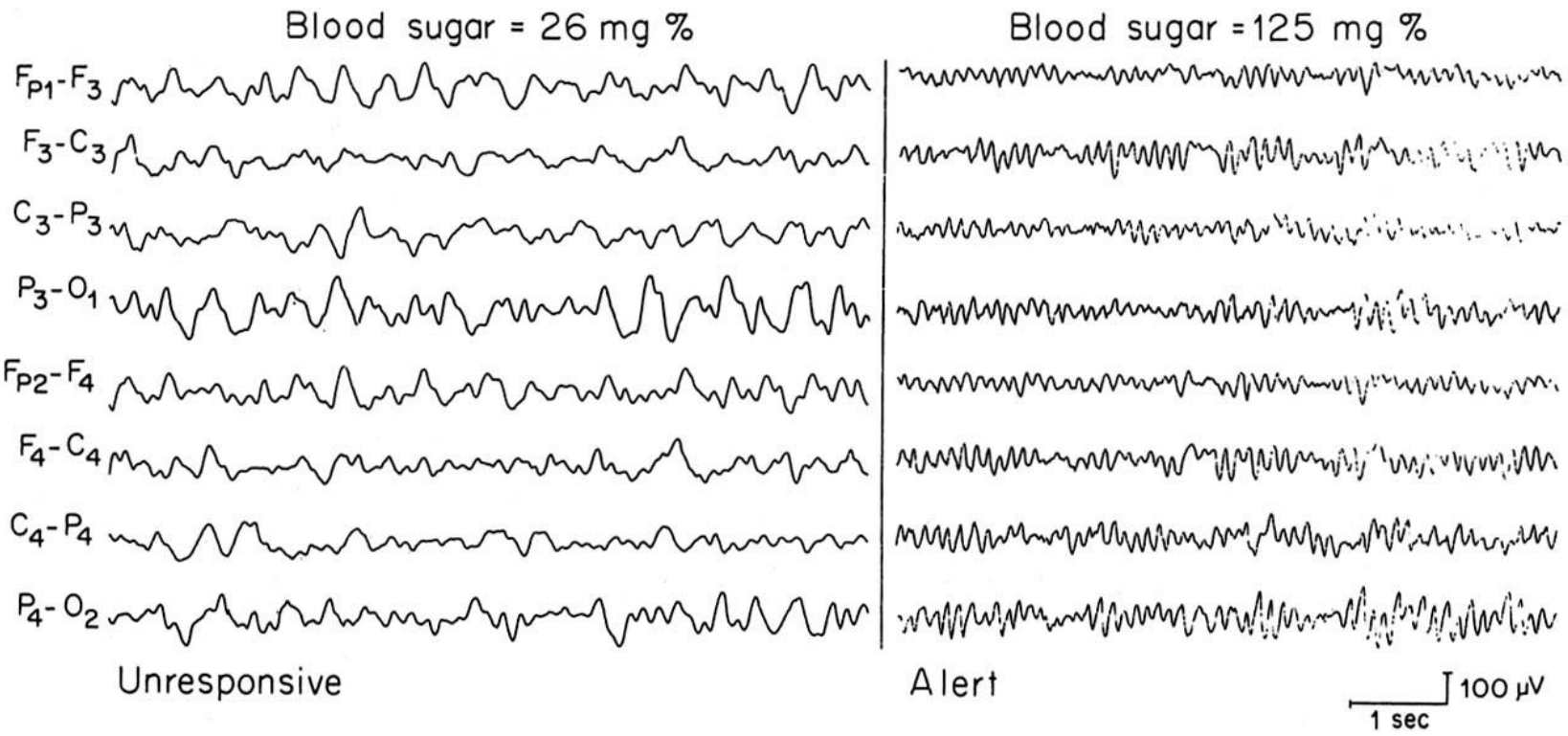

Blood sugar = 26 mg %
Blood sugar = 125 mg %
FP1-F3
F3-C3
C3-P3
P3-O1
FP2-F4
F4-C4
C4-P4
P4-O2
Unresponsive
Alert
100 µV
1 sec

TABLE 2. *Pharmacokinetics of clonazepam and diazepam*

	Clonazepam	Diazepam
Time to enter brain (i.v.)	10 s–1 min	<10 s
Time to peak brain (i.v.)	10 min	6 min
Distribution half-life (min)	30	20
Elimination half-life (h)	18–49	20–40
% Protein binding	47–80	90–99
Volume of distribution (L/kg)	1.5–4.4	0.8–2.0

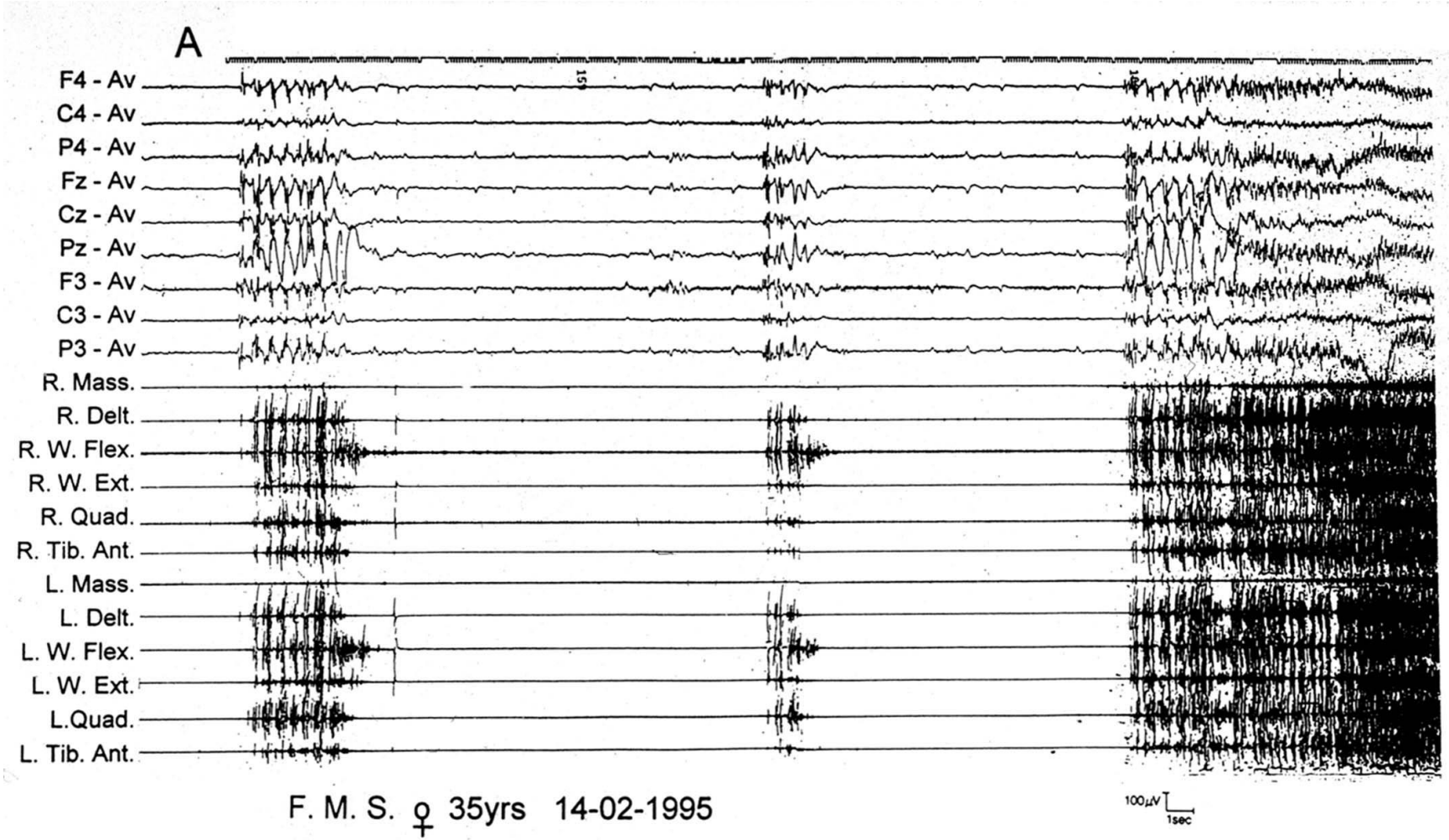
Adapted from refs. 9 and 23.

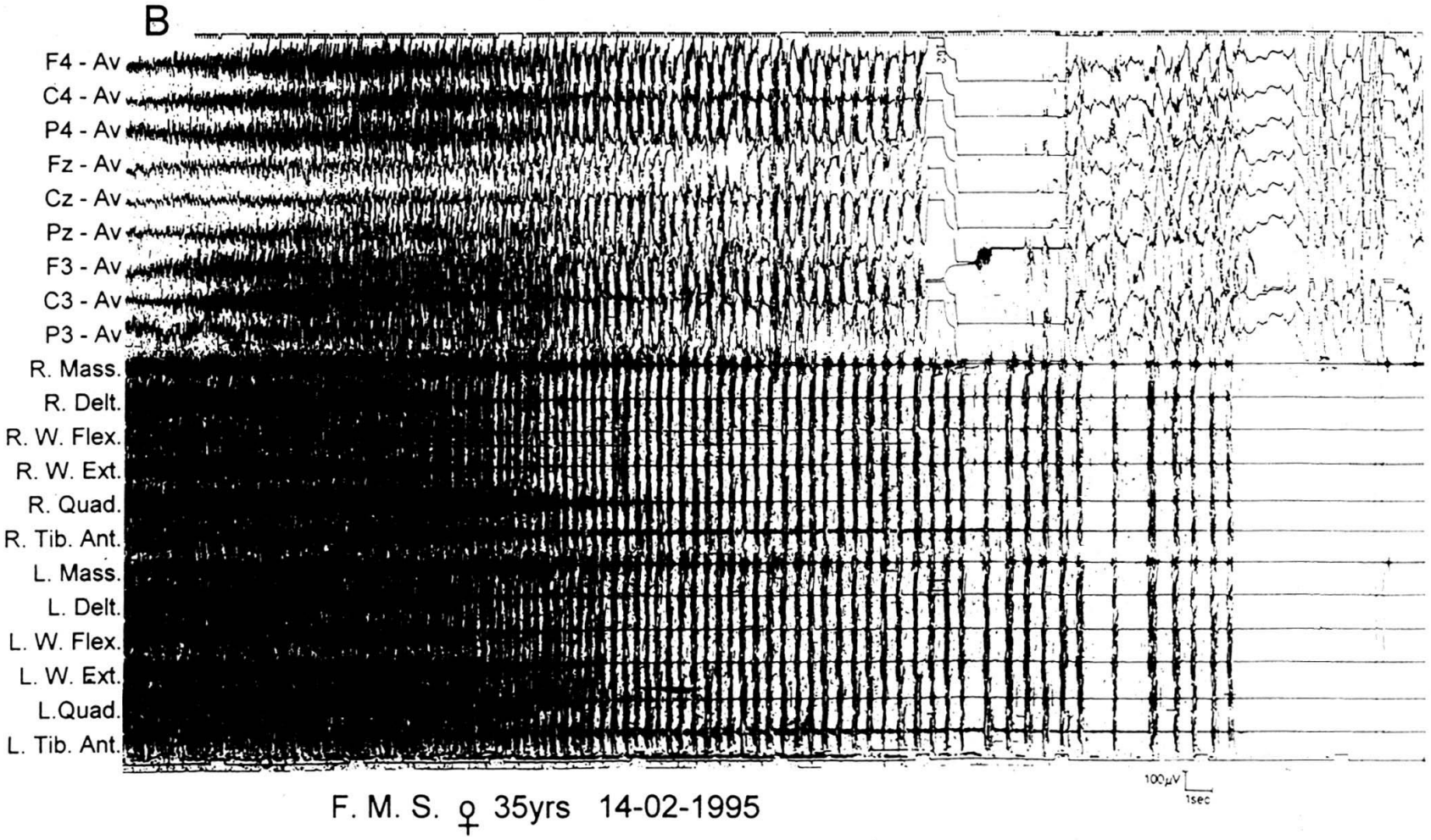
Table 3.8. *The causes of status epilepticus as the presenting symptom of epilepsy, or as an intercurrent event in established epilepsy*[a] *(in 554 patients from 5 case series)*

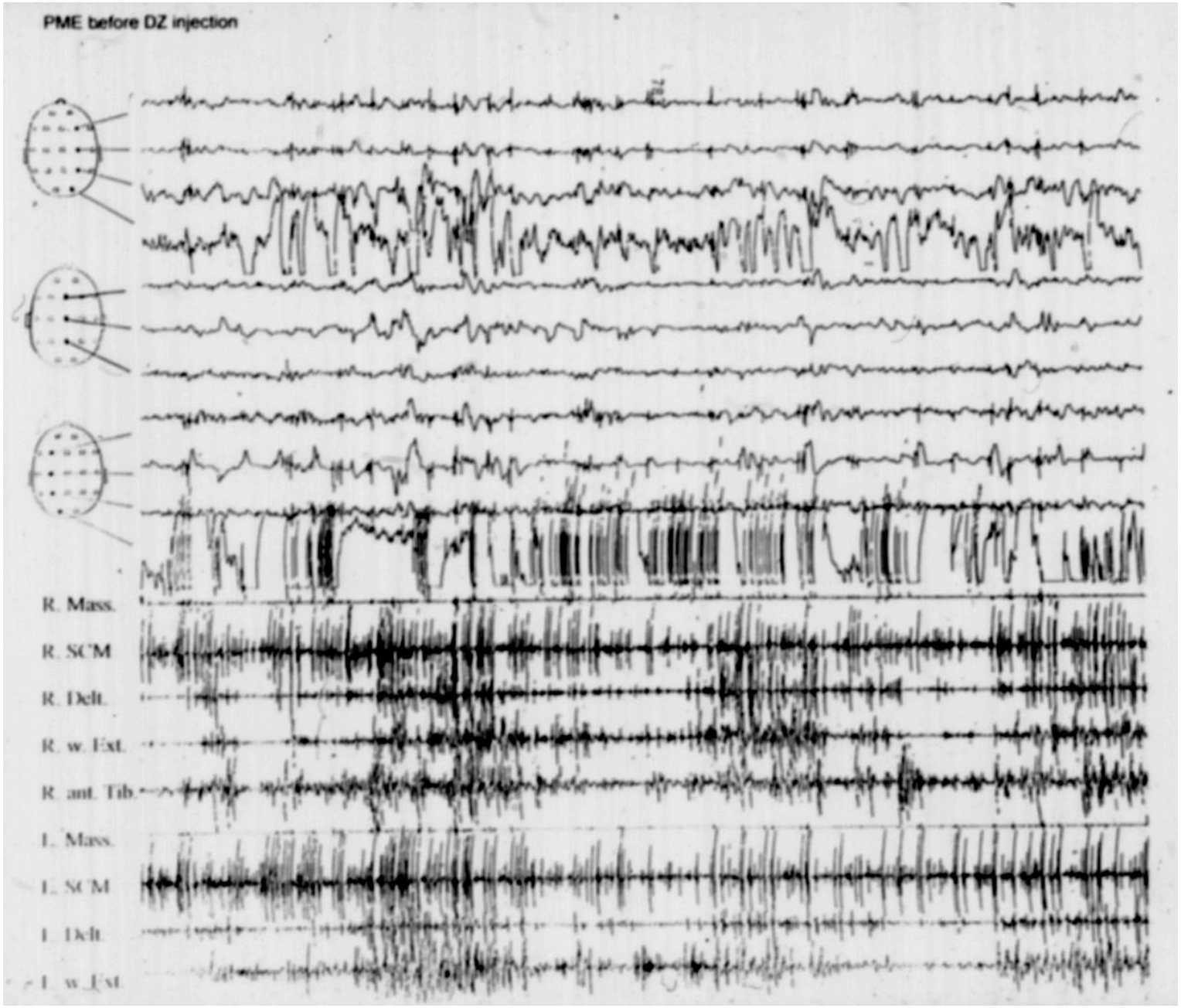
	Status as presenting symptom of epilepsy (%) (n = 327)	Status as an intercurrent event (%) (n = 227)
Cerebral trauma	12	17
Cerebral tumour	16	10
Cerebrovascular disease	20	19
Intracranial infection	15	6
Acute metabolic disturbance	12	5
Other acute event	14	3
No cause found	11	41

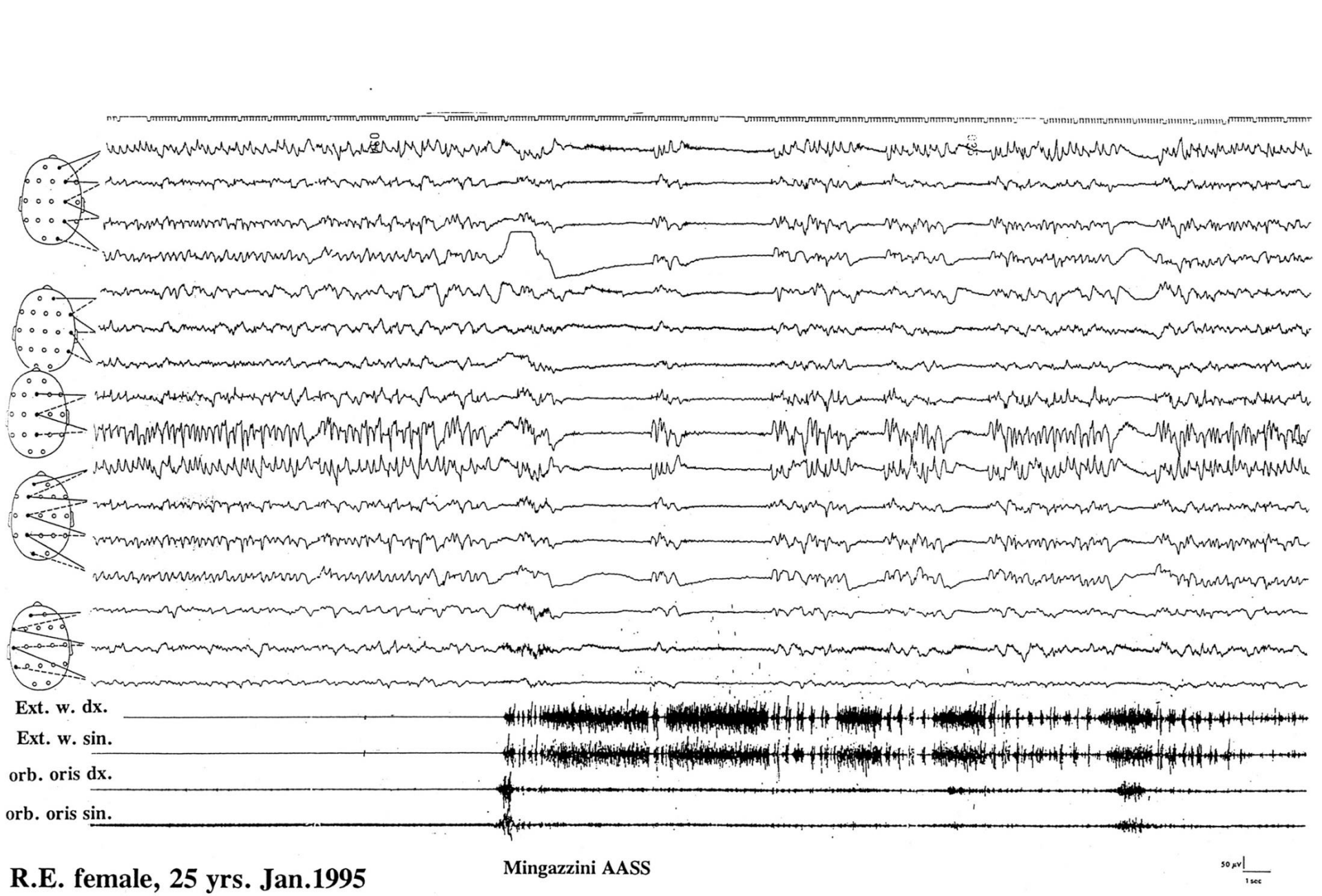
[a] Excluding precipitating causes.

From Janz 1961; Oxbury & Whitty 1971*a*; Aminoff & Simon 1980; Goulon *et al.* 1985; Dunn 1988.


A
F4 - Av
C4 - Av
P4 - Av
Fz - Av
Cz - Av
Pz - Av
F3 - Av
C3 - Av
P3 - Av
R. Mass.
R. Delt.
R. W. Flex.
R. W. Ext.
R. Quad.
R. Tib. Ant.
L. Mass.
L. Delt.
L. W. Flex.
L. W. Ext.
L.Quad.
L. Tib. Ant.
F. M. S. ♀ 35yrs 14-02-1995
100µV
1sec


B
F4 - Av
C4 - Av
P4 - Av
Fz - Av
Cz - Av
Pz - Av
F3 - Av
C3 - Av
P3 - Av
R. Mass.
R. Delt.
R. W. Flex.
R. W. Ext.
R. Quad.
R. Tib. Ant.
L. Mass.
L. Delt.
L. W. Flex.
L. W. Ext.
L.Quad.
L. Tib. Ant.
100µV
1sec
F. M. S. ♀ 35yrs 14-02-1995


PME before DZ injection
R. Mass.
R. SCM
R. Delt.
R. w. Ext.
R. ant. Tib.
L. Mass.
L. SCM
L. Delt.
L. w. Ext.



R.E. female, 25 yrs. Jan.1995

Mingazzini AASS

TABLE 4

Differential Diagnosis of CPSE

Neurologic
Mitochrondrial encephalopathies
Transient global amnesia
Organic brain syndrome
Posttraumatic amnesia
Complex migraine
Vascular compromise—ischemic, inflammatory
Toxic/metabolic
Toxic/metabolic encephalopathy
Alcohol withdrawal/benzodiazepine withdrawal
Hypoglycemia
Hypercalcemia
Neuroleptic malignant syndrome
Serotonin syndrome
Drugs: lithium, baclofen, tricyclics, tiagabine
Epilepsy/seizure-related
Typical absence status epilepticus
Atypical absence status epilepticus
Lennox–Gastaut syndrome with encephalopathy
Altered mental states with PLEDs/BPEDs/BiPLEDs
Prolonged postictal confusion
Epileptic fugue states/poriomania
Interictal/postictal psychosis
Psychiatric
Acute psychotic reactions
Somatoform disorders
Dissociative conversion reactions
Malingering

TABLE 5

Behavioral Distinctions among Absence, Temporal Lobe Complex Partial, and Frontal Lobe Complex Partial Status Epilepticus[a]

	ASE/AASE	TCPSE	FCPSE
Cognition			
Impaired consciouness	****	***	***
Fluctuating level of consciousness	****	**	**
Slowness	**	–	**
Verbal automatisms	–	*	–
Confabulation	–	–	*
Paranoia	–	**	–
Mood			
Indifferent, brooding	*	–	*
Puzzled, mute	*	–	**
Ironic	–	–	**
Smiling, laughing	–	–	**
Anxious, frightened	–	**	–
Angry	–	*	–
Aggressive, irritable		***	
Agitated	*	–	–
Movements			
Simple automatisms	*		
Complex automatisms	–	**	–
Wandering	–	*	–
Facial/global myoclonia	***	–	–

Source. Adapted with permission, from Rohr-le-Floch J., *et al.* (40).

[a] *Percentage of affected cases*: –, <10%; *, 11–25%; **, 26–50%; ***, >50% <90%; ****, ≥90%. ASE, absence status epilepticus; AASE, atypical absence status epilepticus; TCPSE, temporal lobe complex partial status epilepticus; FCPSE, frontal lobe complex partial status epilepticus.

CRISI NEONATALI FAMILIARI BENIGNE (BFNC): DATI CLINICI (1)

- Familiarità per convulsioni neonatali
- Esordio in 2ª o 3ª giornata, a cluster
- Crisi rare:
  - √ componente tonica iniziale
  - √ apnee, fenomeni autonomici
  - √ fenomeni clonici, simm. o asimm., bilat. o unilat.
- Scomparsa spontanea delle crisi entro 1 settimana
- Ricorrenza di epilessia nel 10%

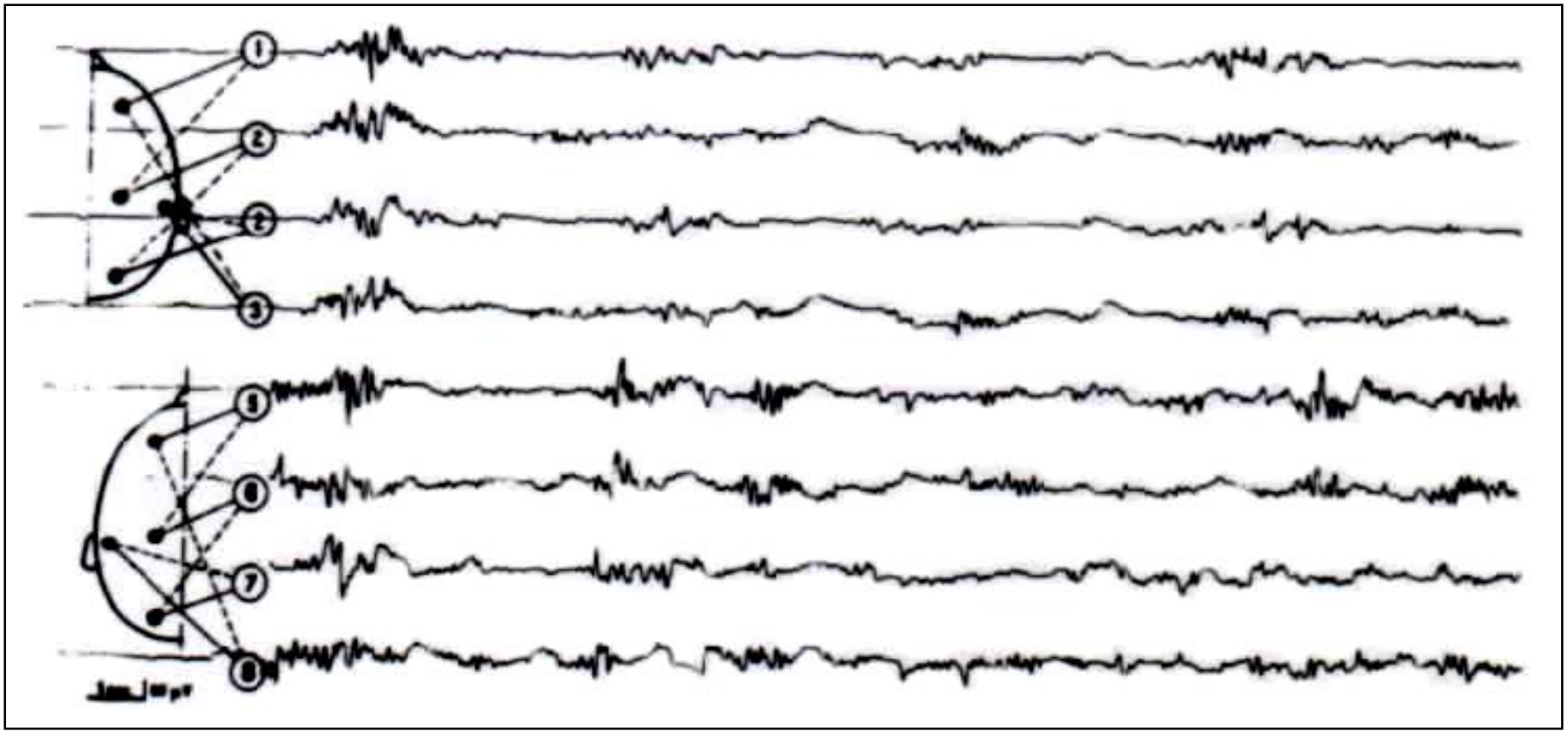


FIG. 2. Interictal EEG of a théta pointu alternant pattern in a baby with BINC.

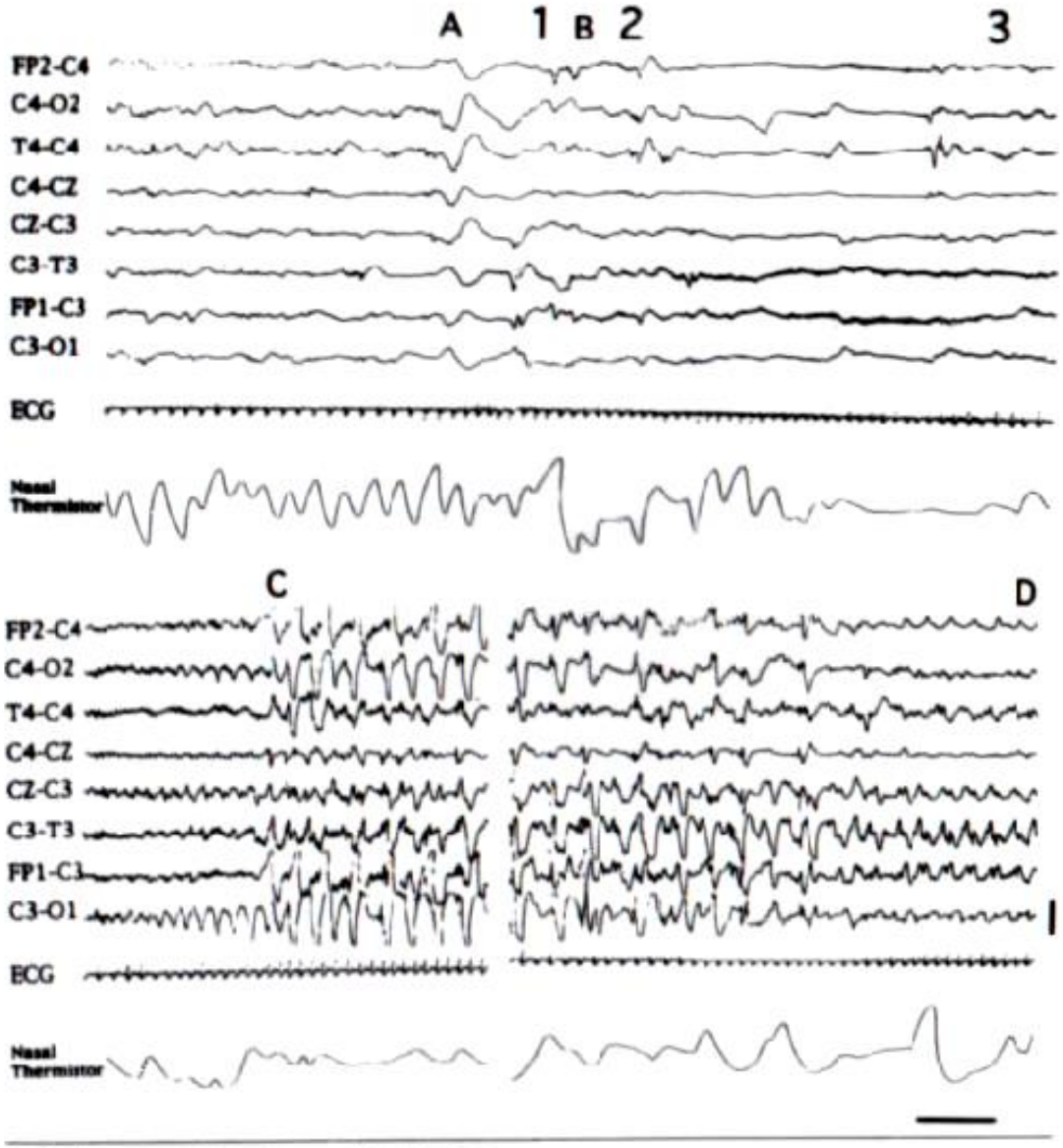


Fig 2. Electroencephalographic seizure recorded in Patient 3 on day 3 (the two parts of the figure are continuous; 7 seconds of clonic seizure were removed between C and D). A = arousal; B = tonic seizure onset; C = clonic seizure onset; D = left focal sharp waves (left discharge continues for 19 seconds). For explanation of 1, 2, and 3, see behavioral concomitants in Fig 4. Calibration: 100 uV, 2 seconds.

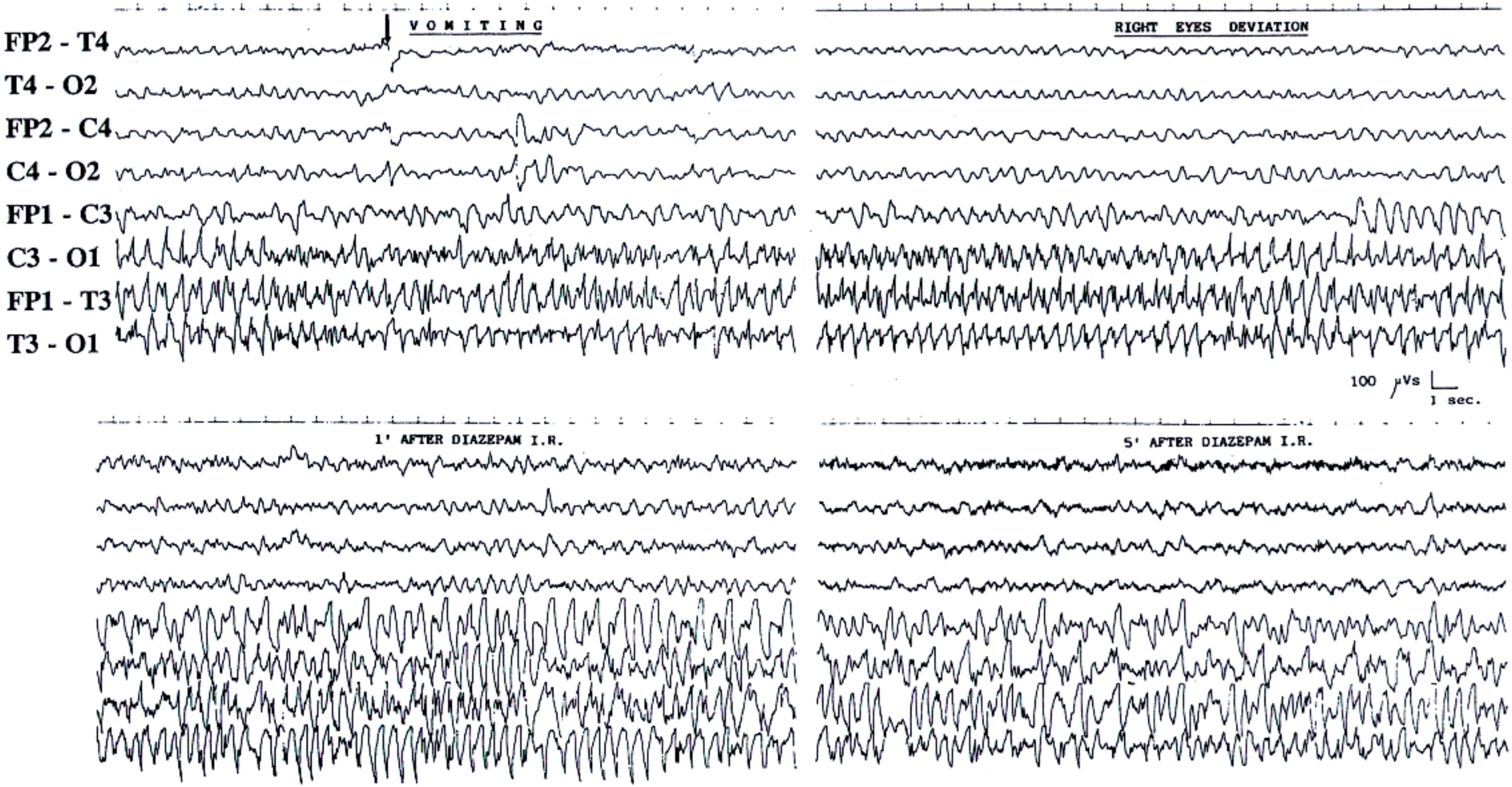
BFNC: DATI GENETICI

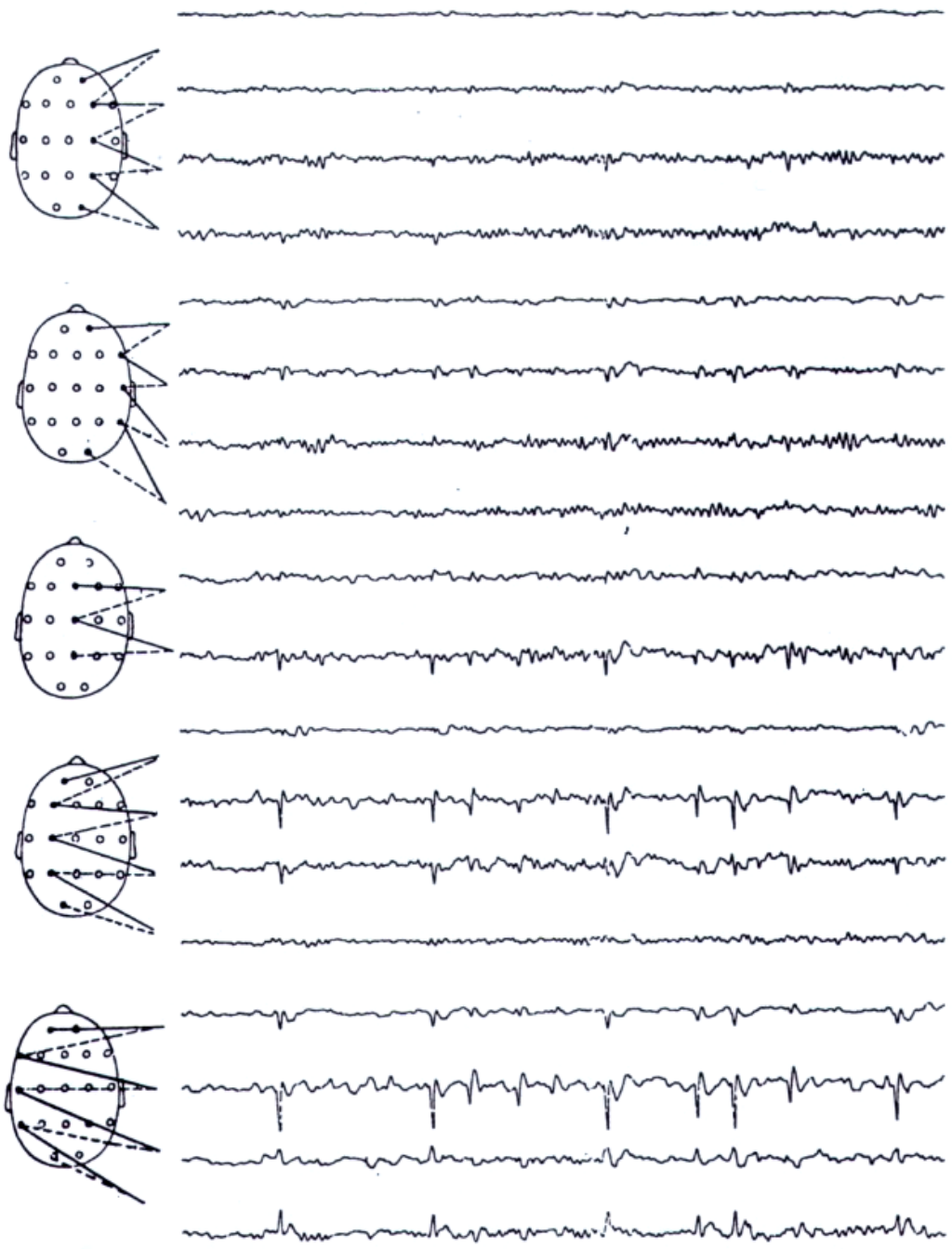
- Trasmissione autosomico-dominante (penetranza: 85%)
- Apparente eterogeneità (loci sui Cr.20, 8)
- Mutazioni a carico di 2 geni dei canali del K voltaggio-dipendenti:
  - KCNQ2
  - KCNQ3
- Mutazioni → difetto della ripolarizzazione di membrana

EARLY ONSET BENIGN CHILDHOOD OCCIPITAL EPILEPSY

- 28% of all benign childhood partial epilepsies
- Family history for epilepsy (7%) and FS (16-45%)
- Onset between 1 to 12 yrs (peak :5)
- Seizures are:
  - ✓ rare (mean total number : 3)
  - ✓ prolonged (5 to 10 min in 2/3^{ds} > 30 min in 1/3rd)
  - ✓ peculiar (ictal vomiting , eye deviation, autonomic features, impaired consciousness)
- High-amplitude occipital spikes, continuous on eye closure (fixation-off sensitivity)
- Remission within 1-2 years after onset
- Therapy is usually not needed

C. G. 2 years 7 months 4 / 4 / 1989

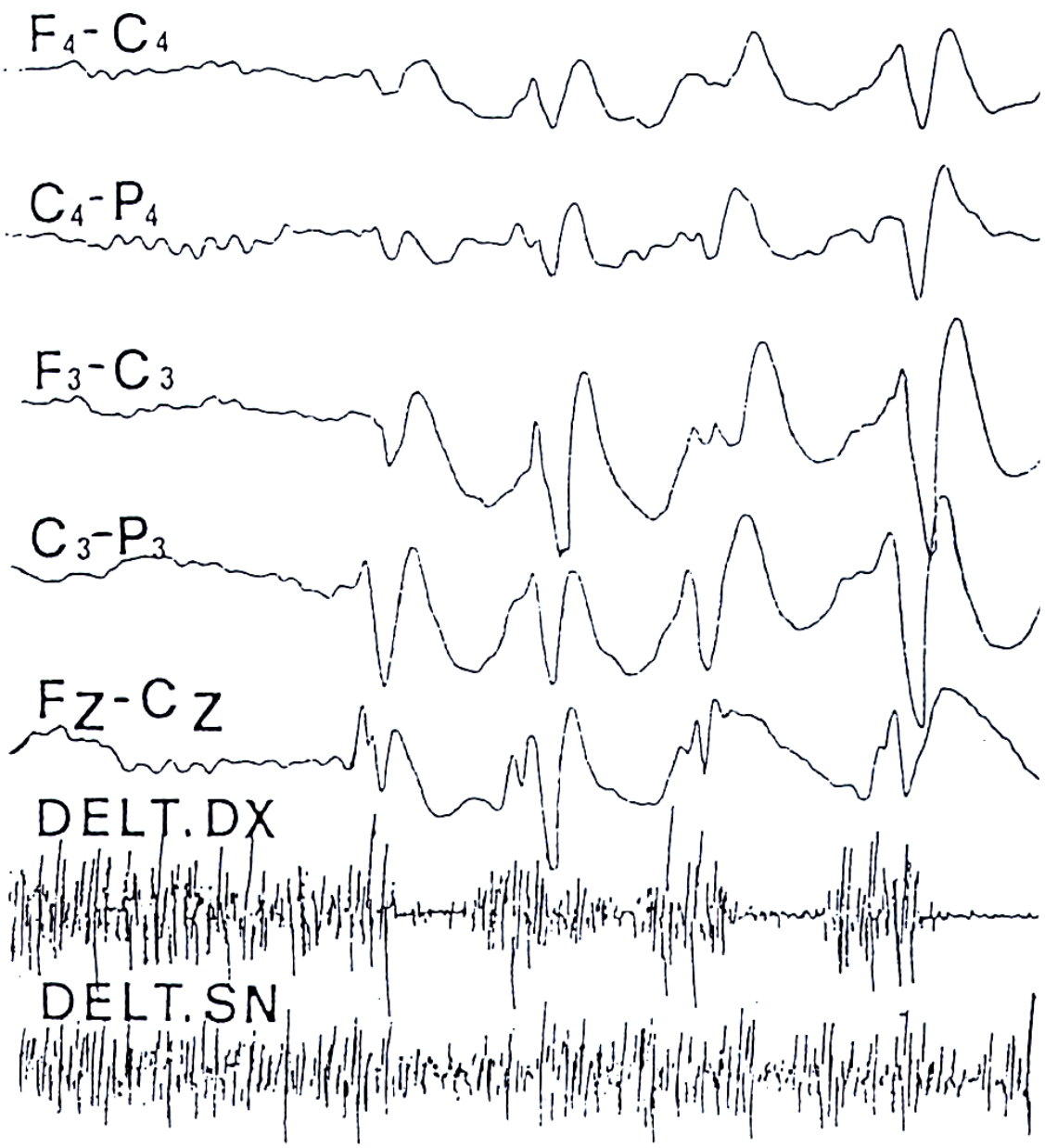




D.S. FEMALE 10 YRS

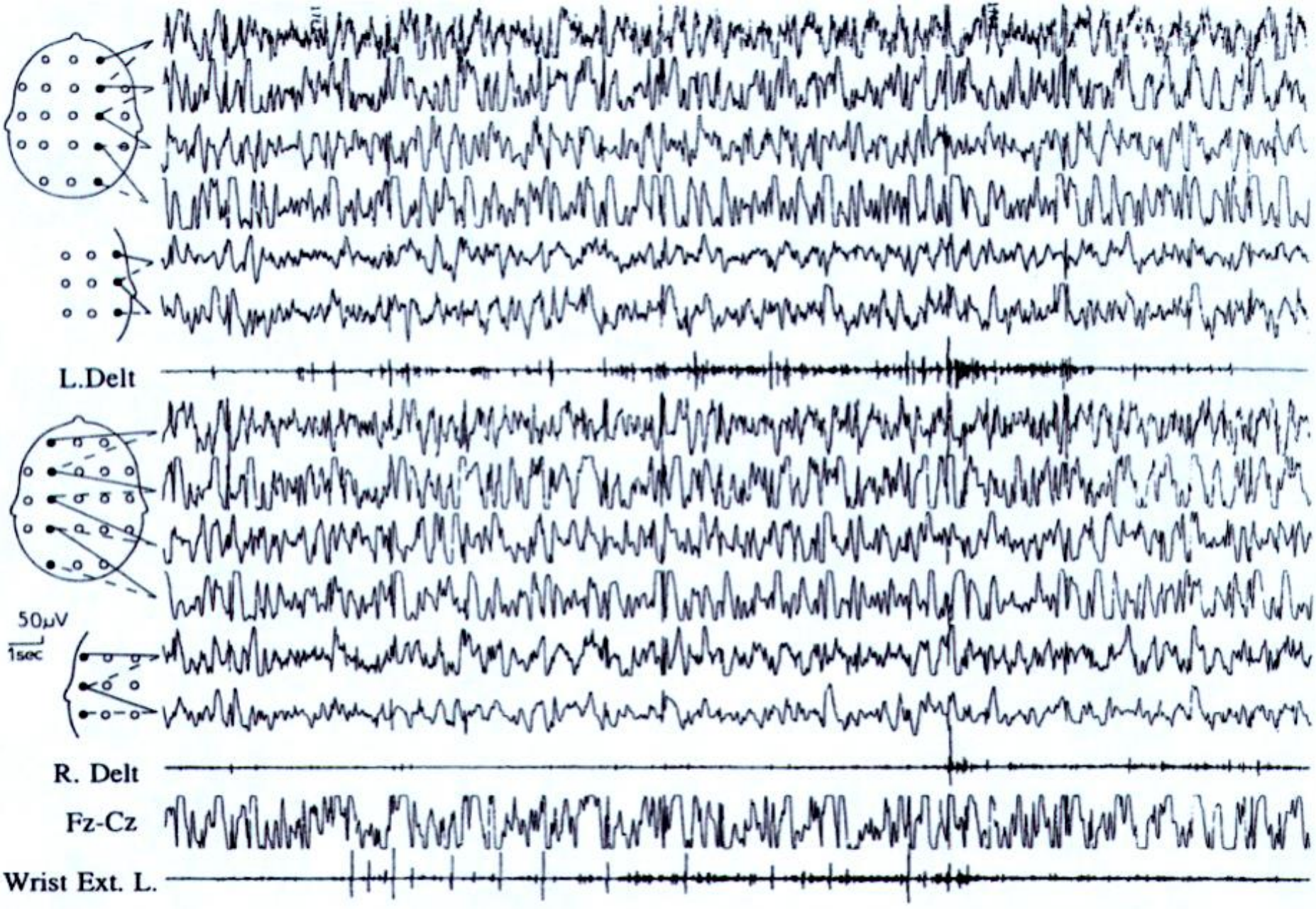
BENIGN CHILDHOOD EPILEPSY WITH CENTRO-TEMPORAL SPIKES

- Atypical features
  - ✓daytime only seizures (10-20%)
  - ✓post-ictal Todd's paralysis
  - ✓prolonged seizures
  - ✓spike morphology, location
- Complications
  - ✓status epilepticus
  - ✓negative myoclonus
  - ✓transient neuropsychological dysfunction
- Therapy
  - ❖is it necessary?


F4-C4
C4-P4
F3-C3
C3-P3
FZ-CZ
DELT.DX
DELT.SN
1 second

EPILEPSY WITH MYOCLONIC-ASTATIC SEIZURES

- Strong genetic component (link with GEFS +)
- Onset between 2 and 5 years
- Seizures : GTCS (at onset), myoclonic, astatic, myoclonic-astatic, drop-attacks
- Status epilepticus (“stupor-like”) ~ 36% of cases
- EEG : abnormal 4-7 Hz rhythms , bilateral SWs - PSWs
- Evolution: complete seizure control in > 50%. Mental deterioration and neurological signs in refractory cases

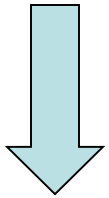

L.Delt
50μV
1sec
R. Delt
Fz-Cz
Wrist Ext. L.
Ma... E. 3y5m INPE-Pisa 10516 14. 1. 91

Encefalopatia con stato di male elettrico (punte-onda continue) durante il sonno lento

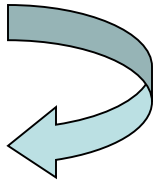
- Subclinical electrical status epilepticus induced by sleep (Patry et al, 1971)
- Encephalopathy related to electrical status epilepticus during slow sleep (Tassinari et al, 1977)
- Electrical status epilepticus during slow sleep (Tassinari et al, 1977)
- Continuous spike and waves during slow sleep (Morikawa et al, 1985)

Encefalopatia con stato di male elettrico (punte-onda continue) durante il sonno lento

- Stato di male elettrico nel sonno lento



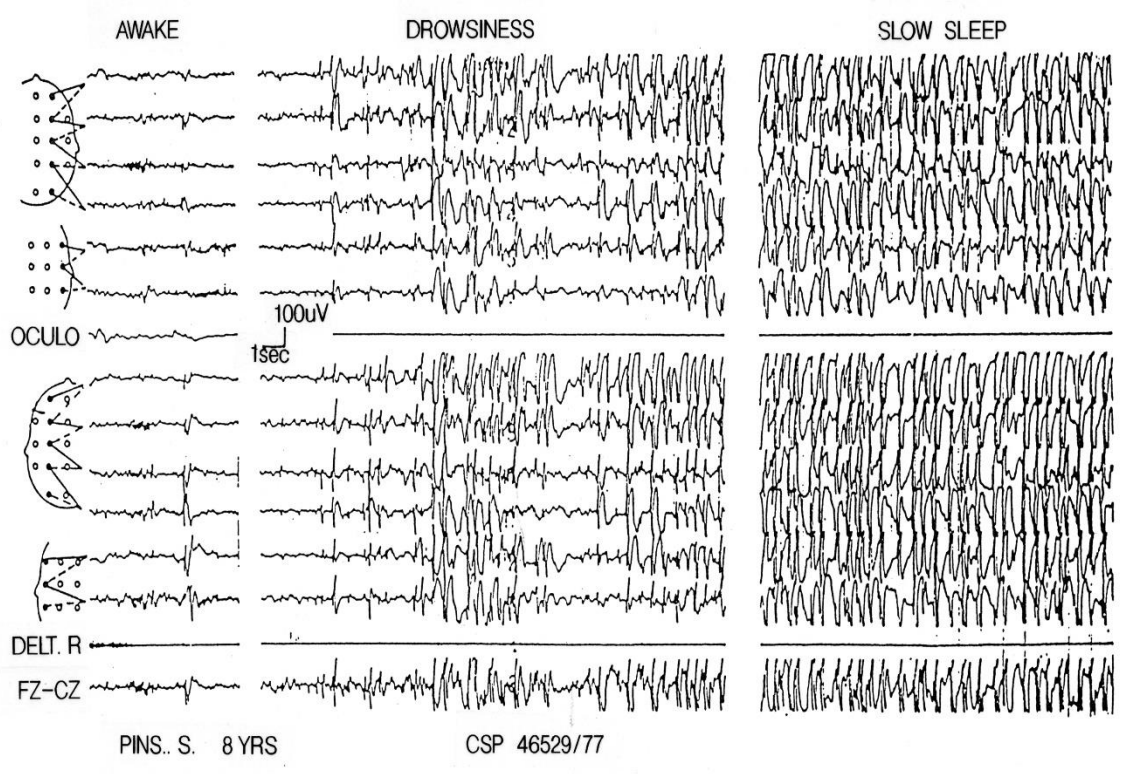
Pattern EEG + Epilessia +
Encefalopatia



sindrome clinica

ESES: il pattern EEG

Appena il paziente si addormenta, compaiono punte onda continue, diffuse, a varia predominanza (frontale, centrale, temporale)…….



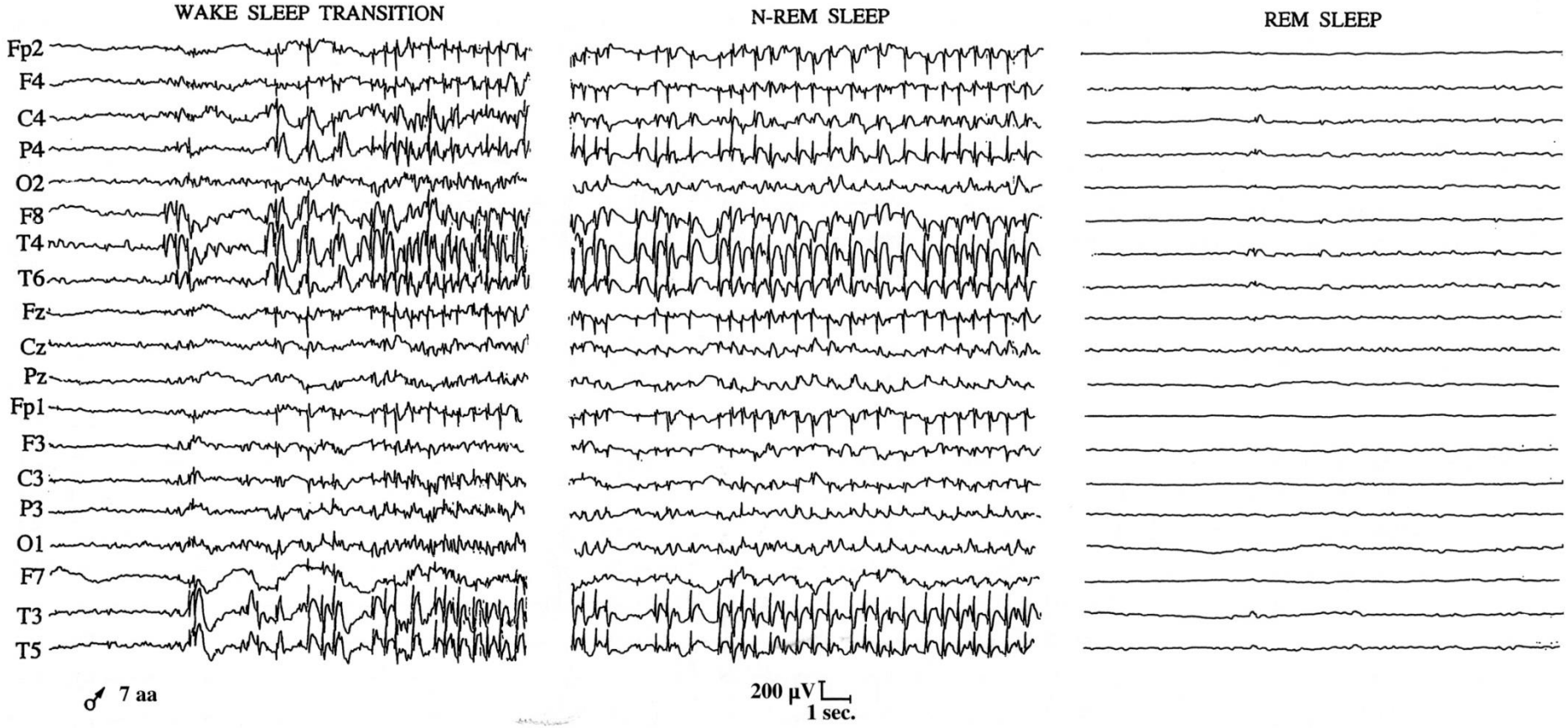
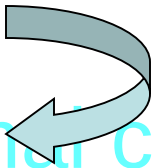


Fig. 2. Male of 7 years with LKS. In the wake–sleep transition phase, right temporal spike–wave activity spread to homologous contralateral areas, and tended to become more continuous. N-REM sleep was characterized by continuous, asymmetric spike–wave activity, predominant on the right temporal leads. During REM sleep, focal, right temporal spike–waves were evident.

La sindrome clinica con ESES: l'epilessia

- Esordio fra 1 e 12 anni
- All'inizio : crisi notturne, unilaterali e/o crisi parziali motorie, complesse, tonico-cloniche, assenze
- Alla comparsa dell'ESES: peggioramento delle crisi (assenze atipiche, cadute, stato di male, mioclono negativo, etc)



mai crisi toniche

La sindrome clinica con ESES: l'epilessia

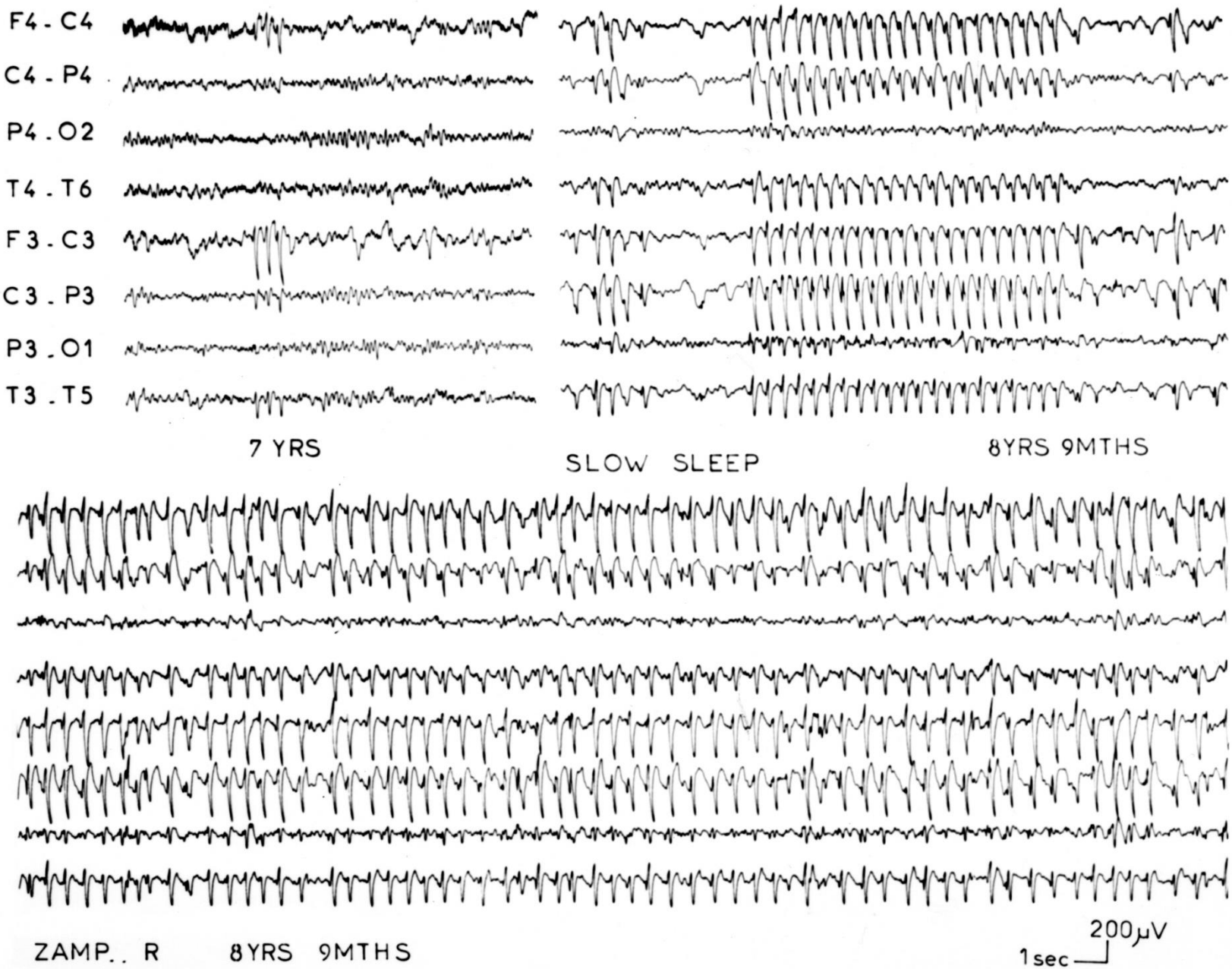
- In base al tipo di crisi, 3 gruppi:

  1) crisi motorie notturne rare per tutta l'evoluzione (12%)

  2) crisi motorie notturne + assenze (44%)

  3) crisi motorie notturne + assenze atipiche

     + cadute toniche o atoniche (44%)


AWAKE
F4 - C4
C4 - P4
P4 - O2
T4 - T6
F3 - C3
C3 - P3
P3 - O1
T3 - T5
7 YRS
8YRS 9MTHS
SLOW SLEEP
ZAMP.. R
8YRS 9MTHS
200μV
1sec

La sindrome clinica con ESES: l'encefalopatia

- Afasia acquisita (sindrome di Landau-Kleffner) PO regioni temporali
- Disturbi comportamentali e ritardo mentale PO regioni frontali
- Disturbi motori: distonia, disprassia, atassia, mioclono negativo PO regioni centrali

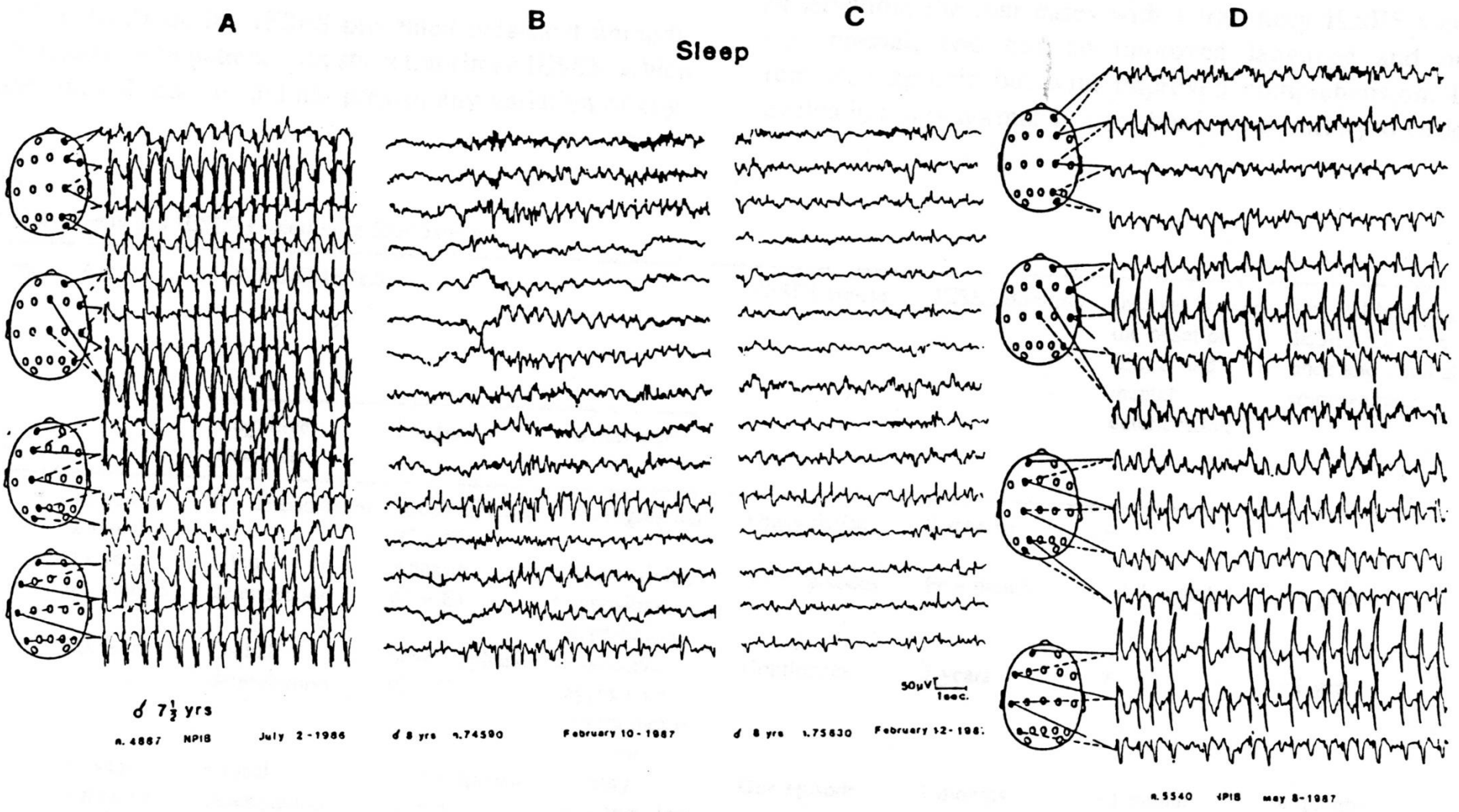
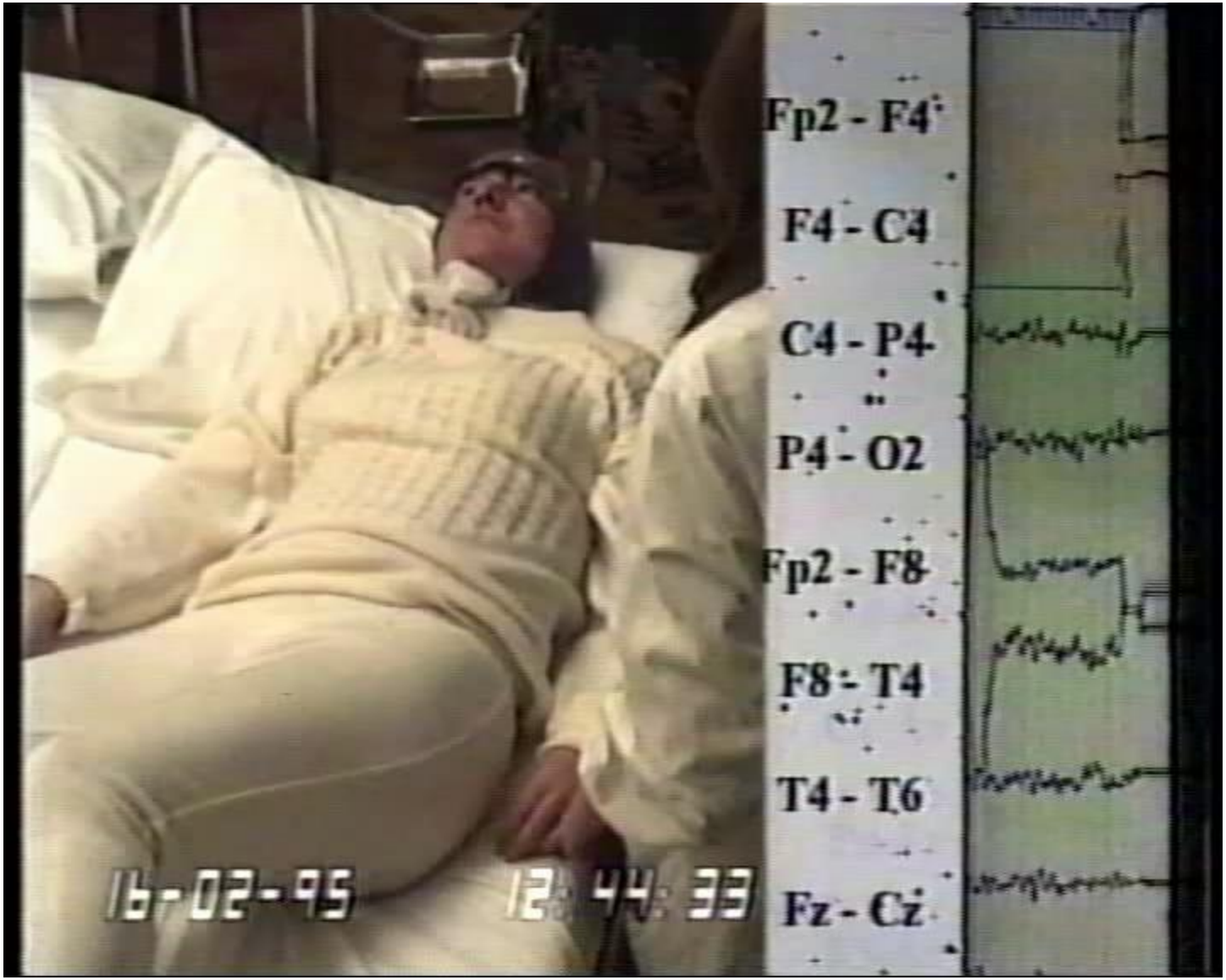
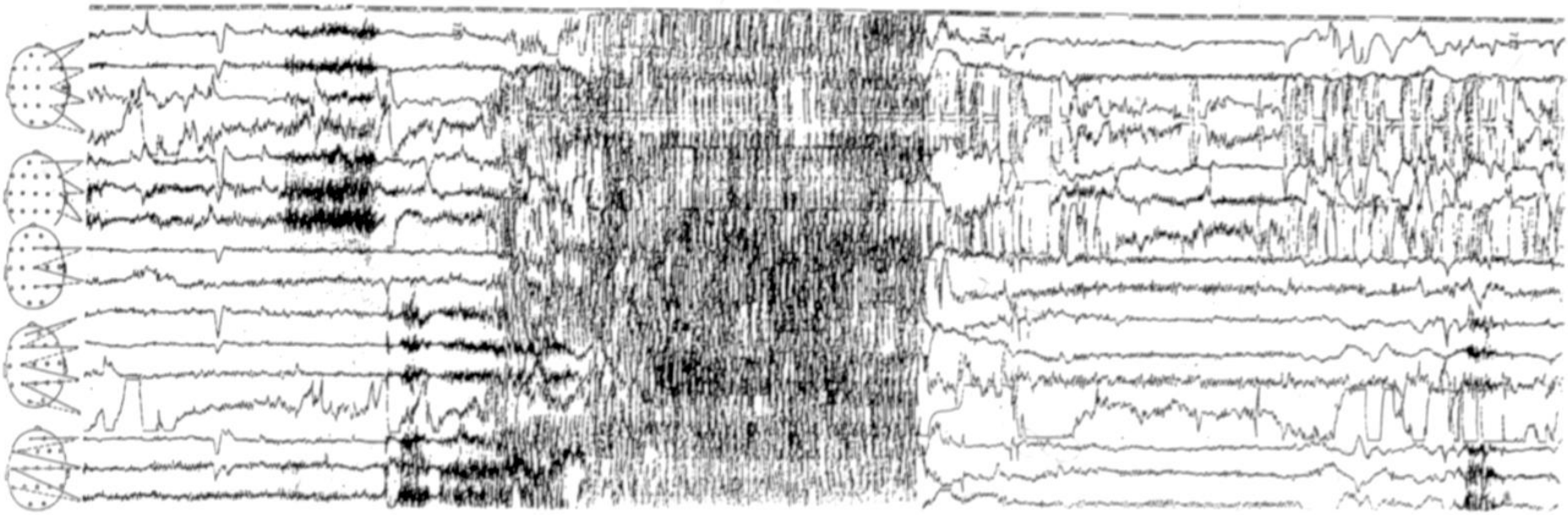


Fig. 4. Case 11 EEG recordings showing during the follow-up in NREM sleep the shift from IESES (A) to BTESES (B–D).


Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp2 - F8
F8 - T4
T4 - T6
Fz - Cz
16-02-95
12:44:33

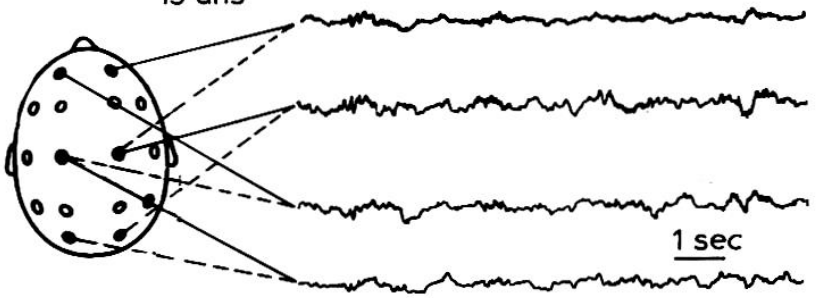
Pseudoseizure

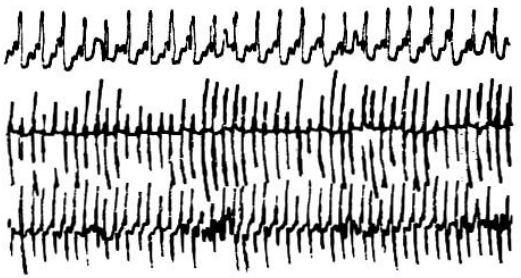


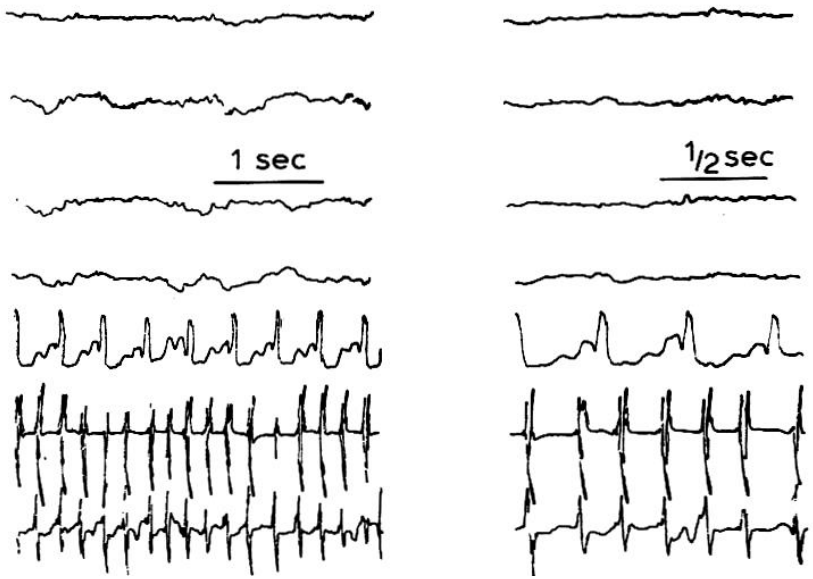
G.G. female, Feb.1995

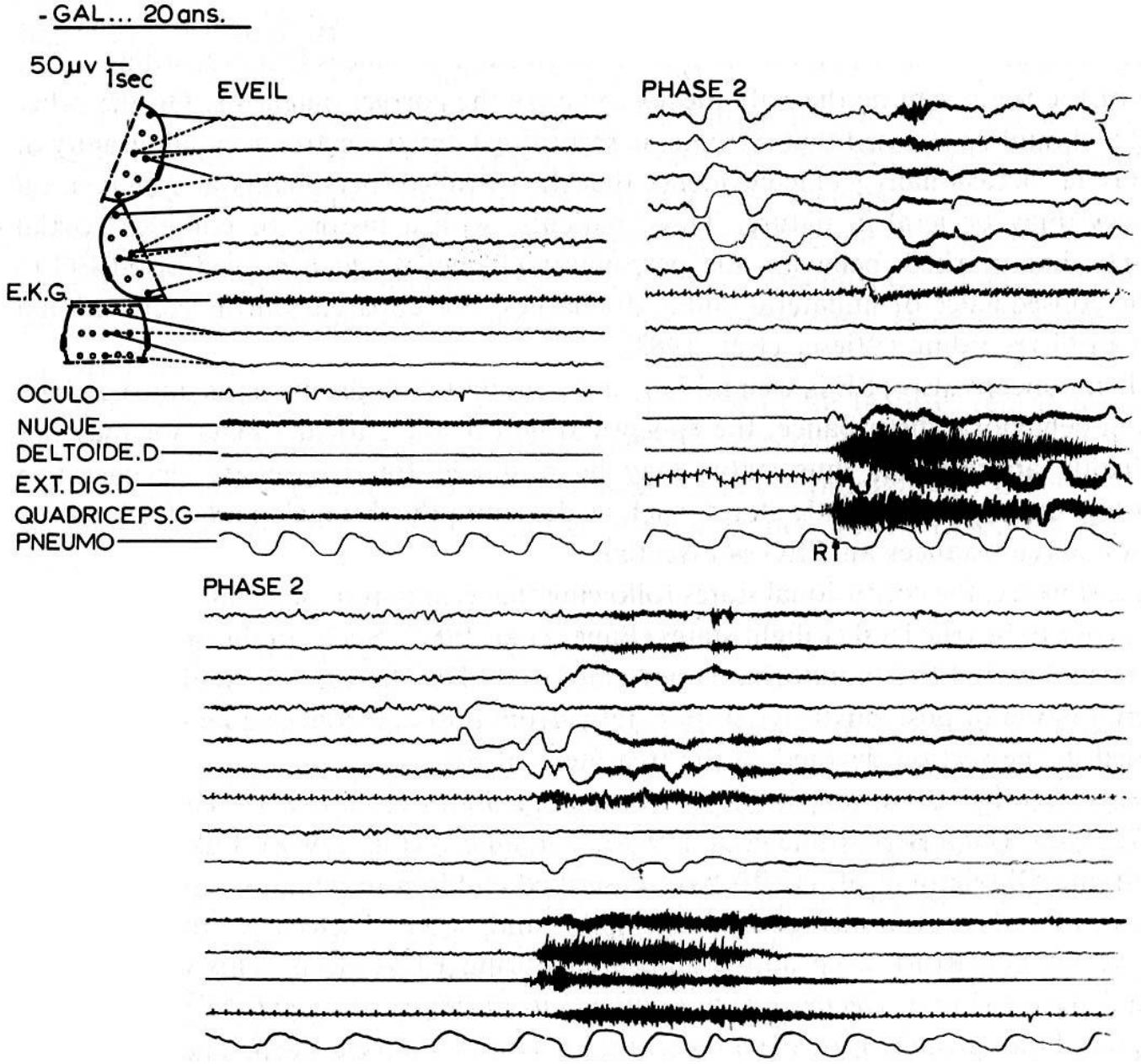
MAR... J.M.

19 ans








- GAL... 20 ans.
50µv
1sec
EVEIL
PHASE 2
E.K.G.
OCULO
NUQUE
DELTOIDE.D
EXT. DIG.D
QUADRICEPS.G
PNEUMO
R
PHASE 2

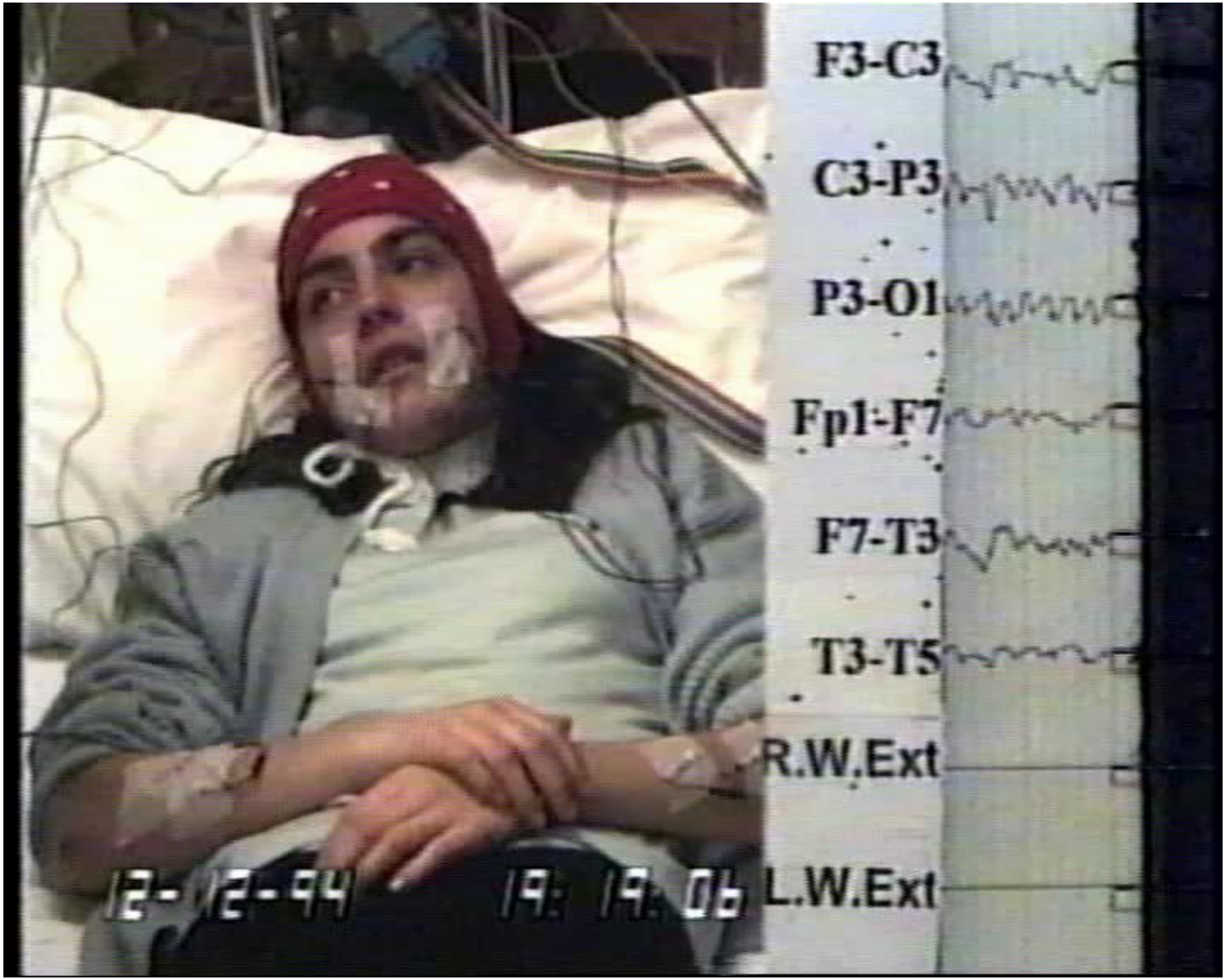

F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
R.W.Ext
L.W.Ext
12-12-94
19:19:06

TABLE 1. *1980 Santa Monica International Symposium classification of status epilepticus*

Primary generalized convulsive status
Tonic–clonic status
Myoclonic status
Clonic–tonic–clonic status
Secondary generalized convulsive status
Tonic–clonic status with partial onset
Tonic status
Subtle generalized convulsive status
Simple partial status
Partial motor status
Unilateral status
Epilepsia partialis continua
Partial sensory status
Partial status with vegetative, autonomic, or affective symptoms
Nonconvulsive status
Absence status—typical or atypical
Complex partial status

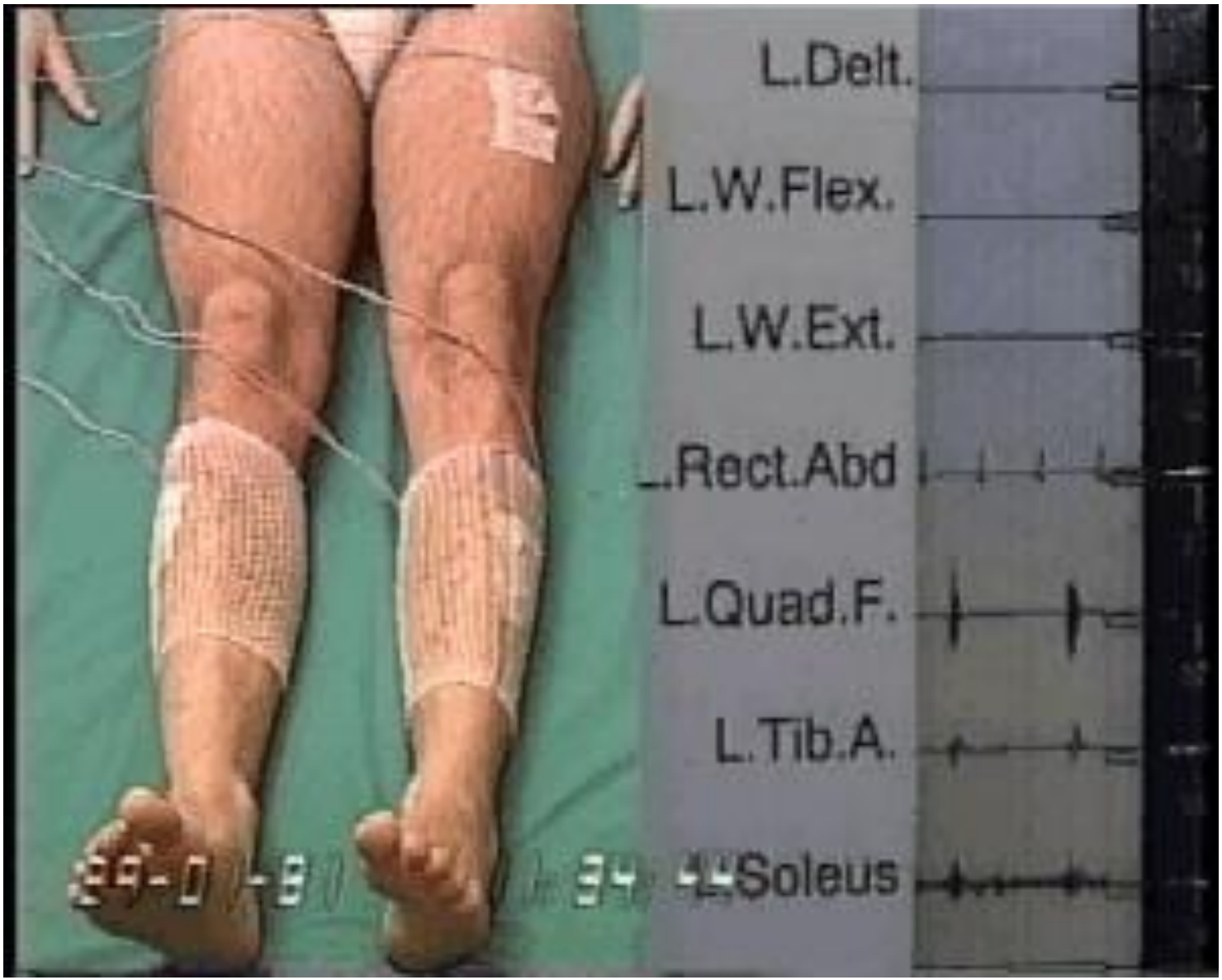
SE NON CONVULSIVO A SEMEIOLOGIA CONFUSIONALE

- **Generalizzato**
  - **stato di assenza tipico**
  - **stato di assenza atipico**

- **Focale**
  - **stato parziale complesso (temporale, frontale)**

- **Stato di assenza “de novo” ad esordio tardivo**

Gennaio 2001 (a)



Revised classification of SE

(Shorvon 1994)

- 1) S.E. confinato al periodo neonatale

  - S.E. neonatale
  - S.E. in sindromi epilettiche neonatali
    . Encefalopatia infantile precoce
    . Encefalopatia mioclonica neonatale
    . Crisi familiari neonatali benigne
    . Crisi neonatali benigne

Revised classification of SE

(Shorvon 1994)

- **2) S.E. confinato alla prima e seconda infanzia**

  - Spasmi infantili

  - S.E. febbrile

  - S.E. nelle sindromi miocloniche dell'infanzia (SMEI, forme criptogeniche/sintomatiche, mioclono-astatica)

  - S.E. nelle sindromi parziali benigne dell'infanzia (BECTS, EOB)

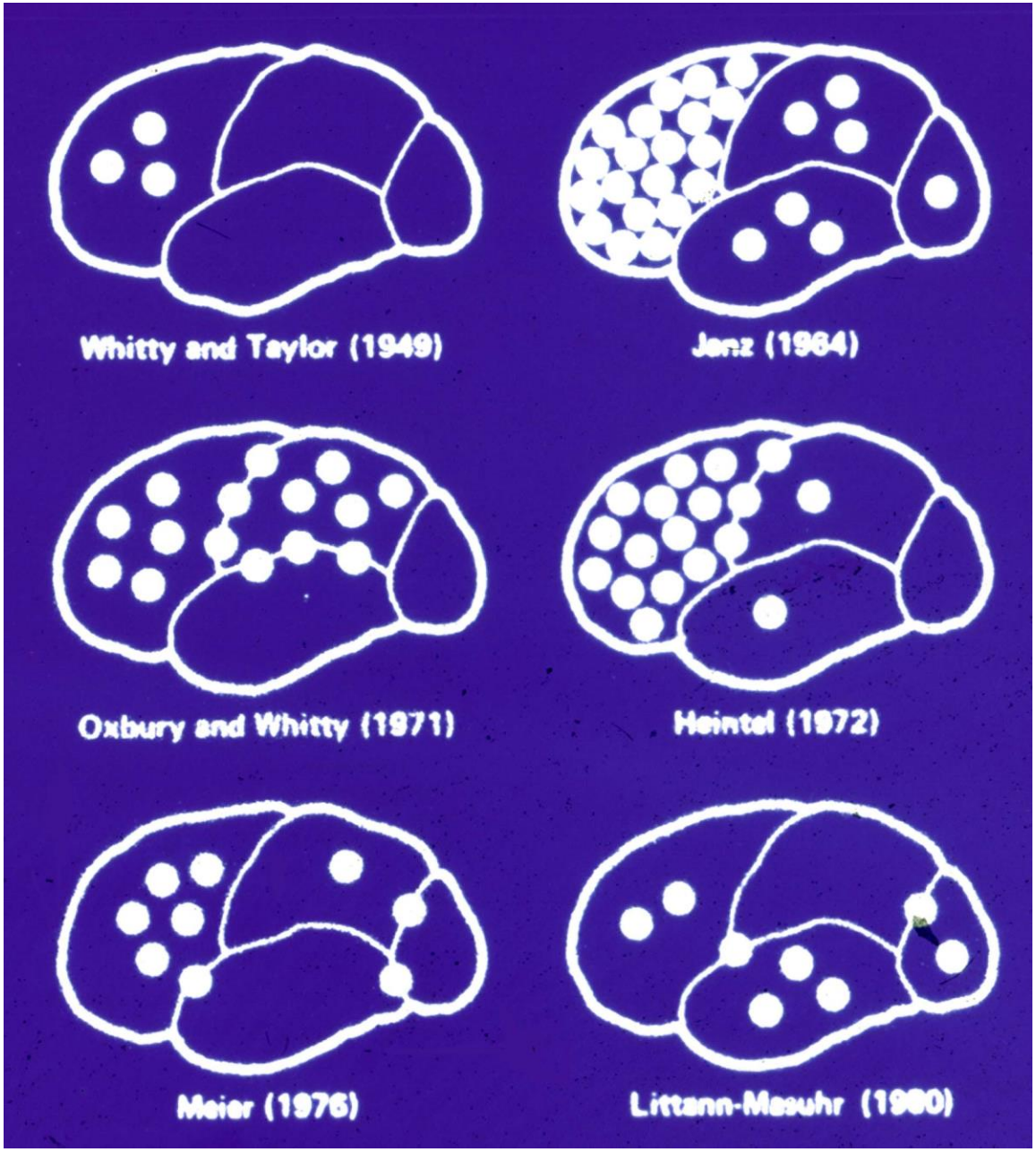
  - ESES/Landau-Kleffner

Table 3.8. *The causes of status epilepticus as the presenting symptom of epilepsy, or as an intercurrent event in established epilepsy*[a] *(in 554 patients from 5 case series)*

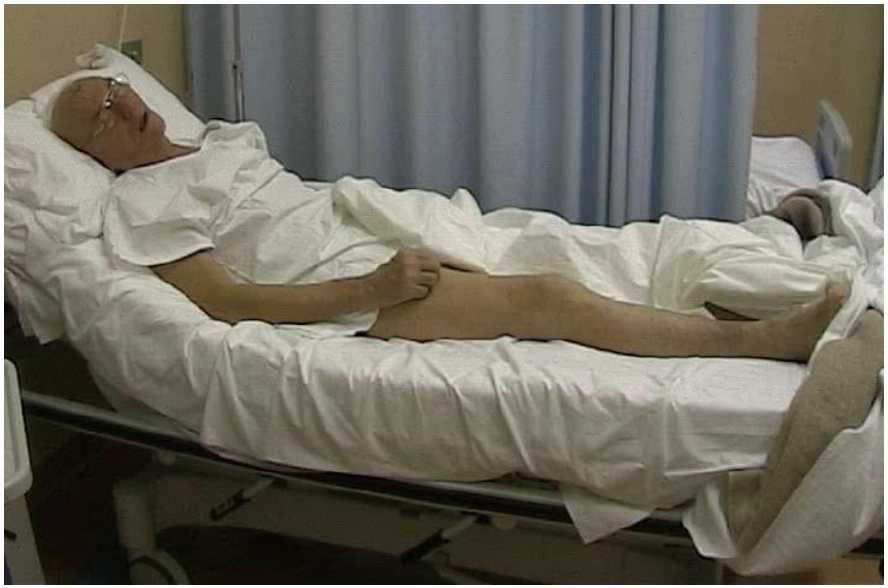
	Status as presenting symptom of epilepsy (%) (n = 327)	Status as an intercurrent event (%) (n = 227)
Cerebral trauma	12	17
Cerebral tumour	16	10
Cerebrovascular disease	20	19
Intracranial infection	15	6
Acute metabolic disturbance	12	5
Other acute event	14	3
No cause found	11	41

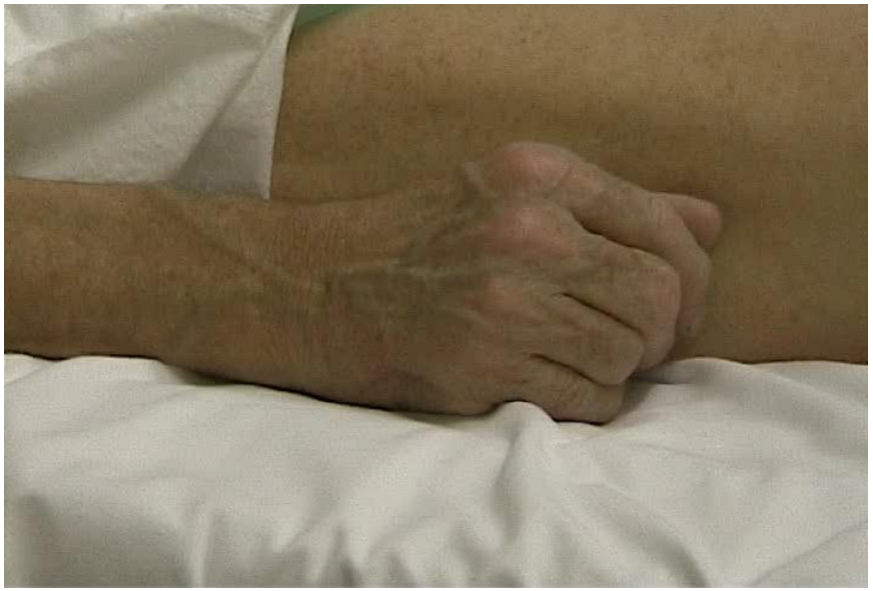
[a] Excluding precipitating causes.

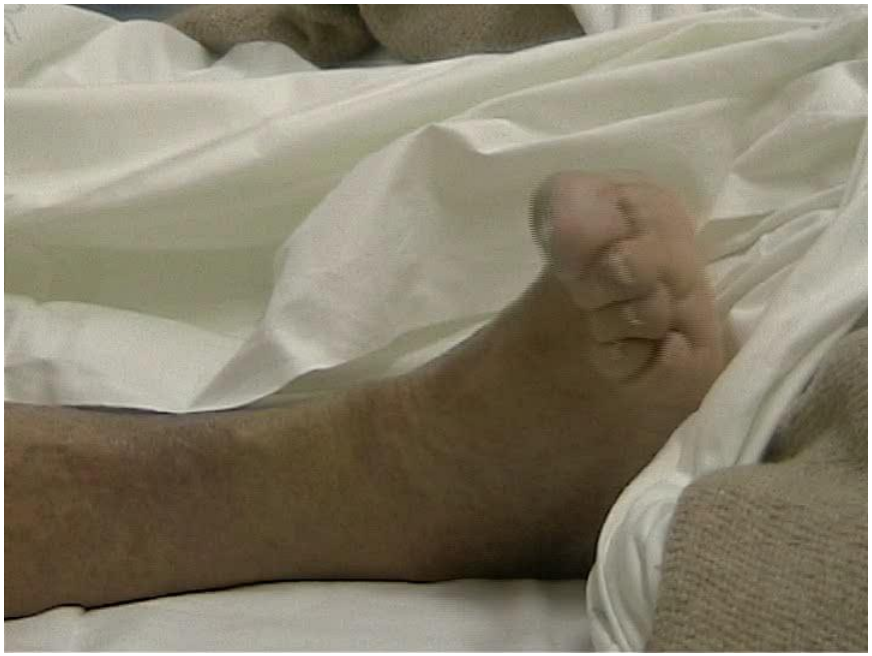
From Janz 1961; Oxbury & Whitty 1971*a*; Aminoff & Simon 1980; Goulon *et al.* 1985; Dunn 1988.

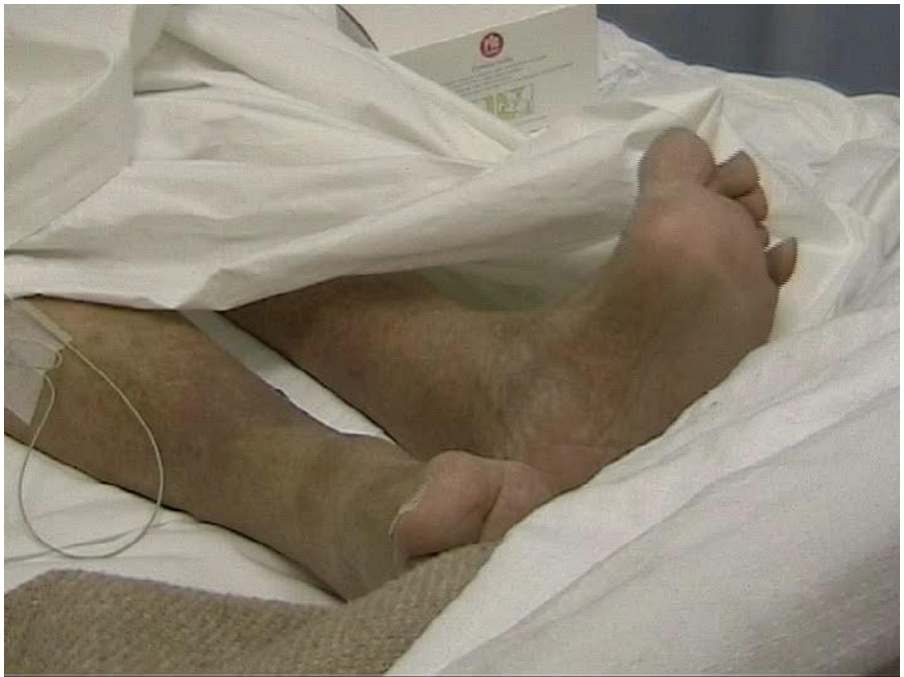

Whitty and Taylor (1949)
Jenz (1964)
Oxbury and Whitty (1971)
Heintel (1972)
Meier (1976)
Littann-Mauhr (1980)

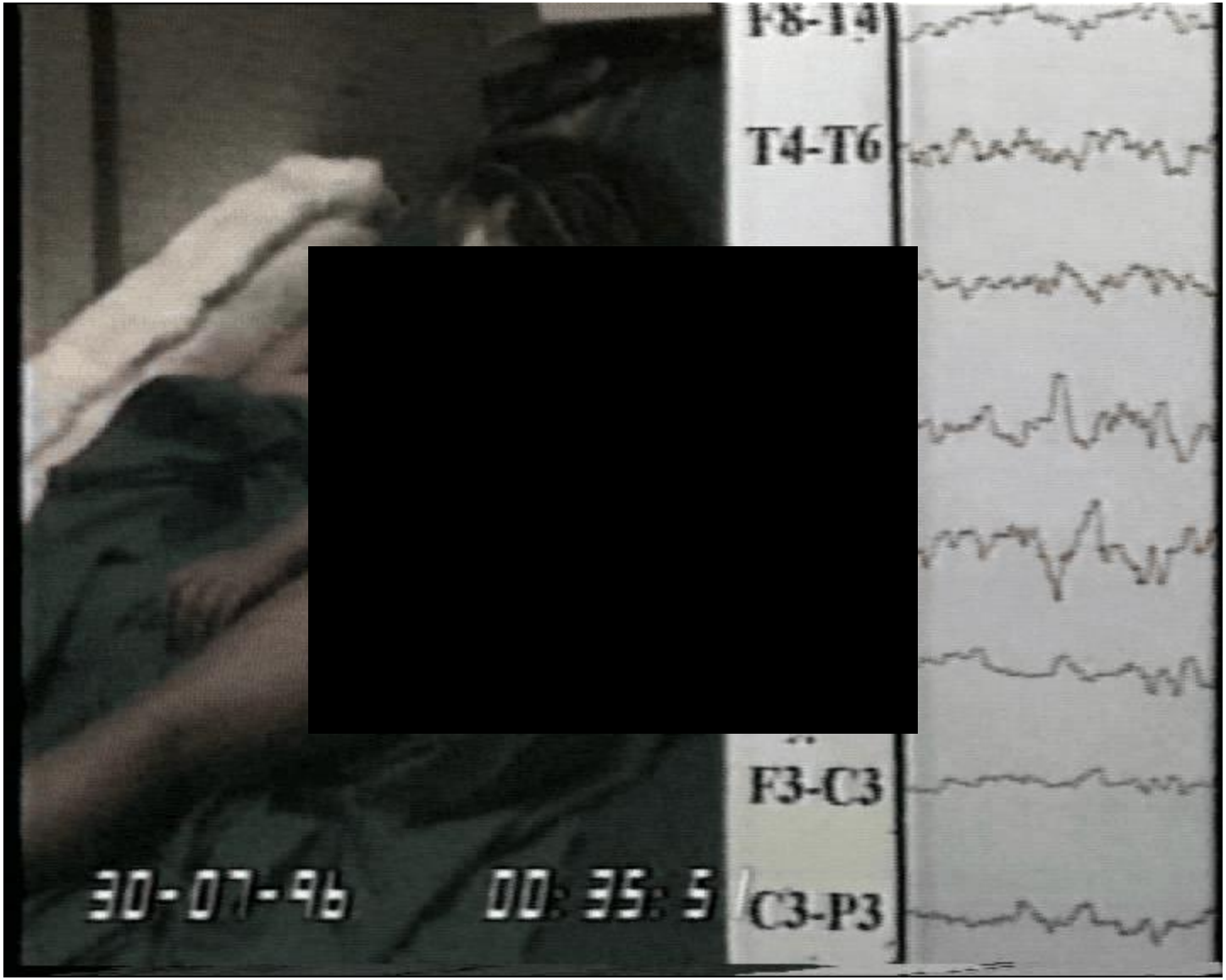
Pz con Parkinson il giorno dopo intervento di MCS con test di stimolazione corticale intraoperatoria per definizione del target

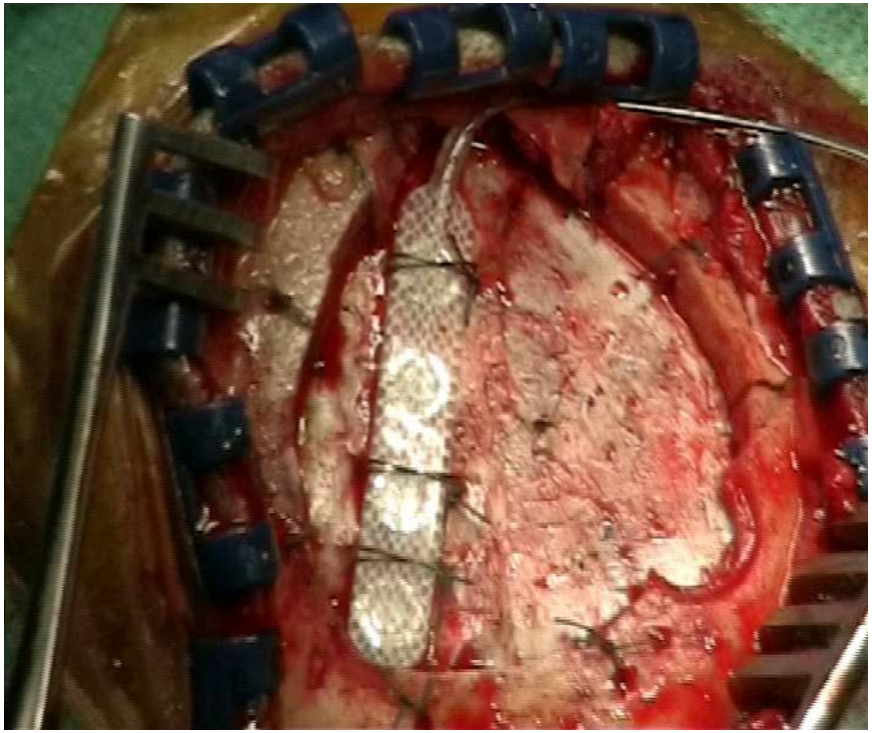


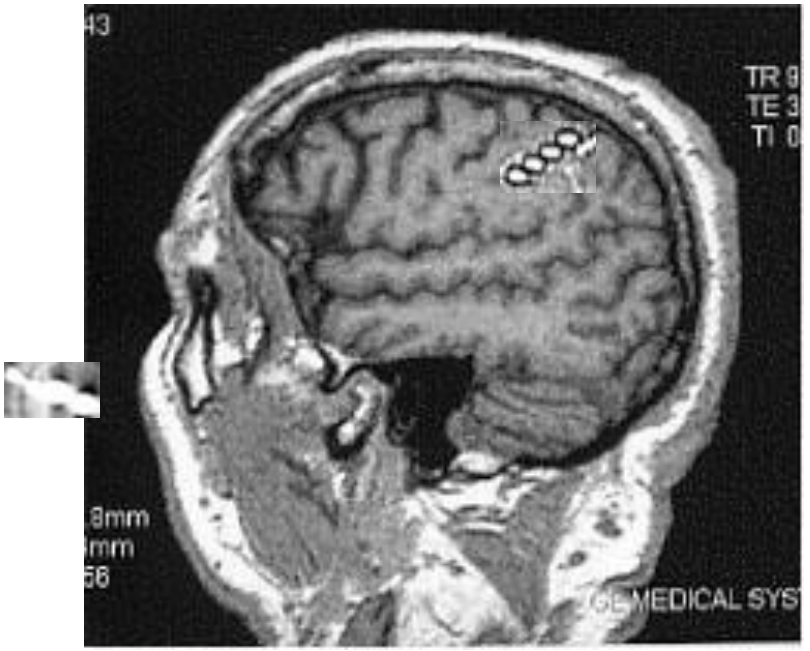


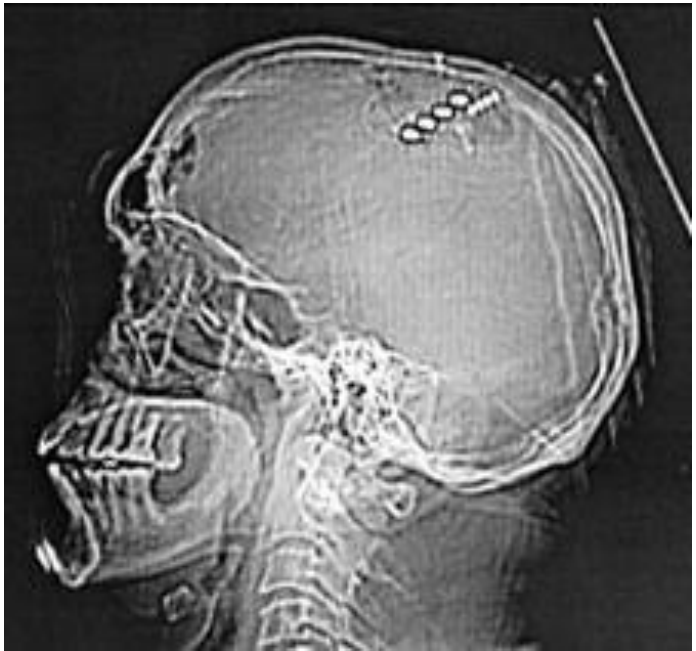





T4-T6
F3-C3
C3-P3
30-07-96
00:35:5




43
TR 9
TE 3
TI 0
8mm
mm
56
MEDICAL SYS



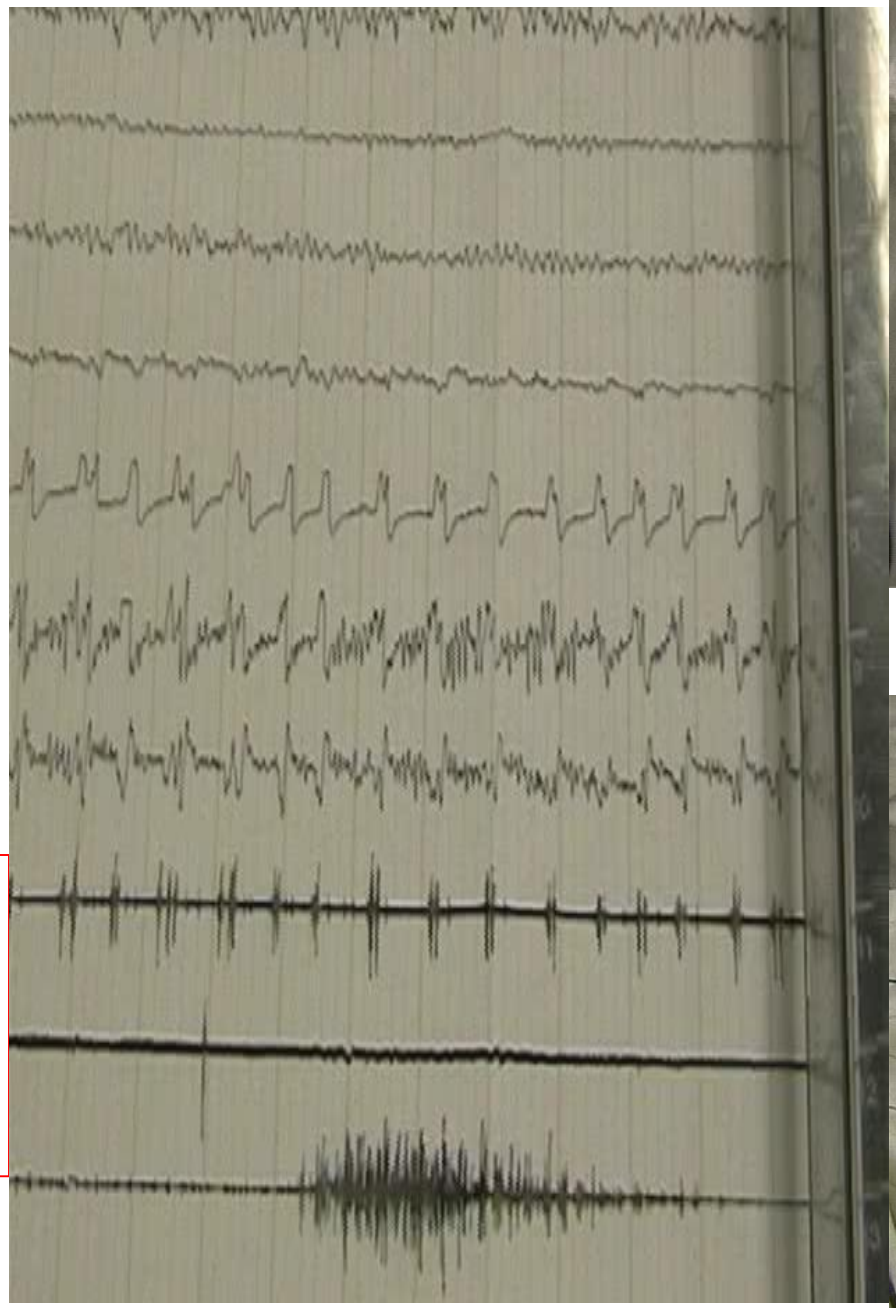
SCALPO

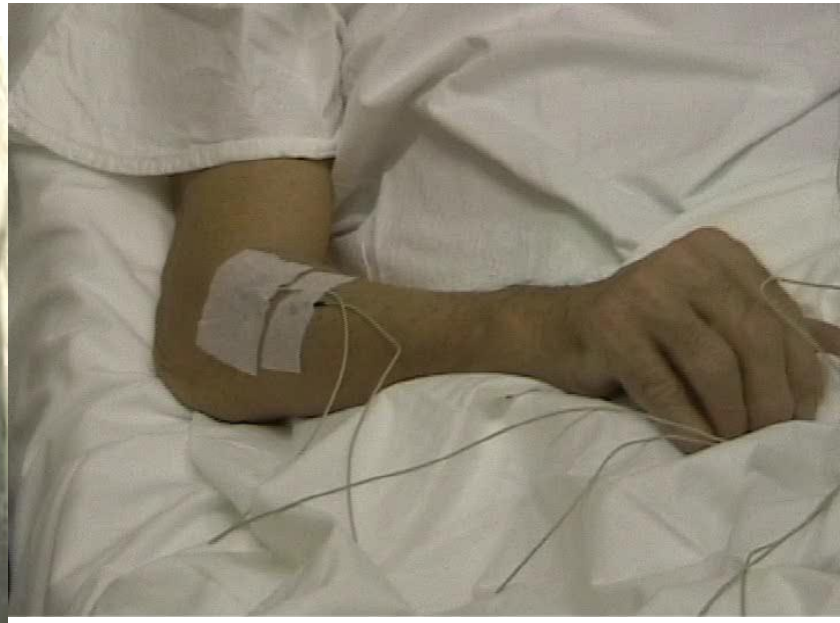
1
2
3
4

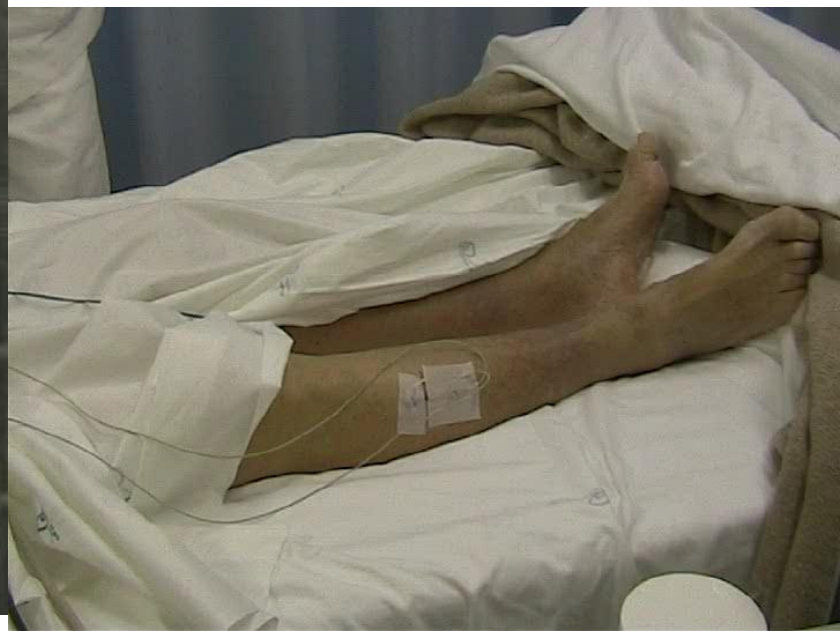
ECR dx

TA dx

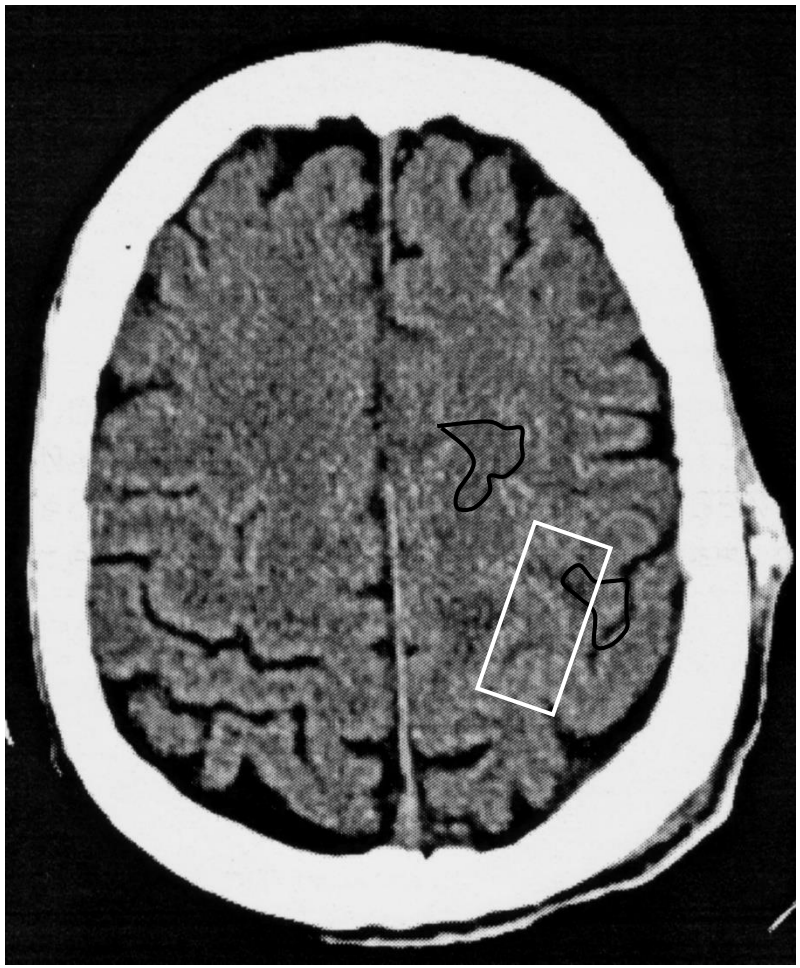
TA sn

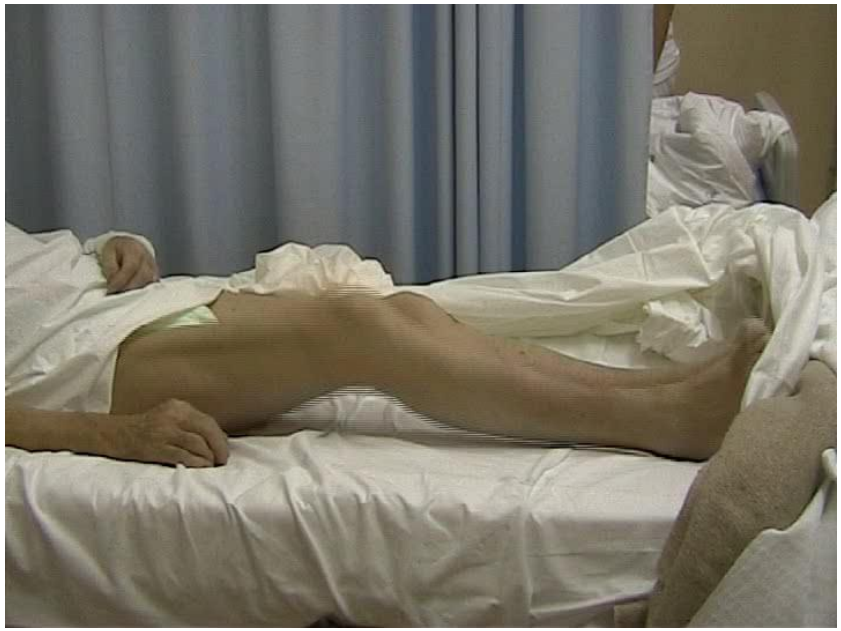






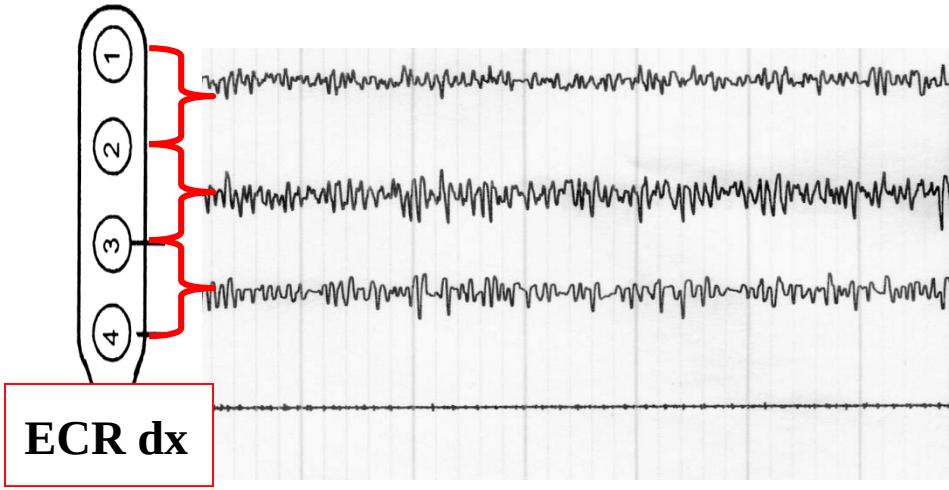
Non presenta deficit stenici

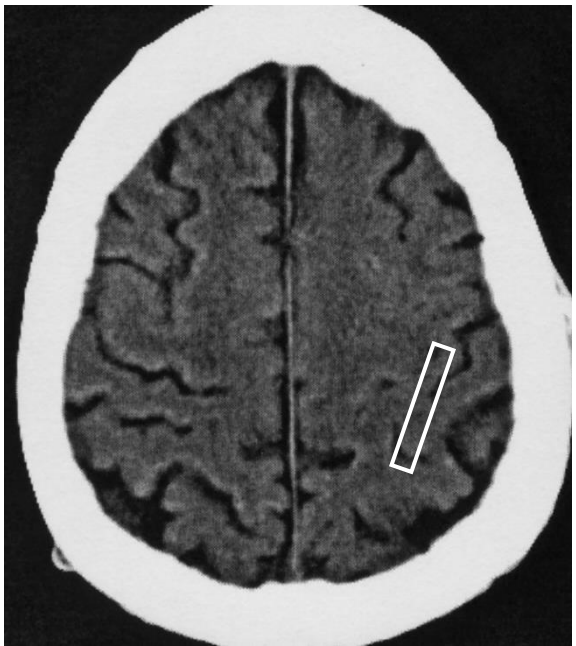




Evoluzione

- Scomparsa del fenomeno motorio: arto sup dopo 2 ore, arto inf dopo 24 ore
- Normalizzazione EEG al controllo del giorno seguente
- Copertura con dintoina per 3 gg
- Lieve deficit stenico emisoma dx per 5 gg
- Scomparsa area ipodensa alla TC dopo





CASE REPORT : History

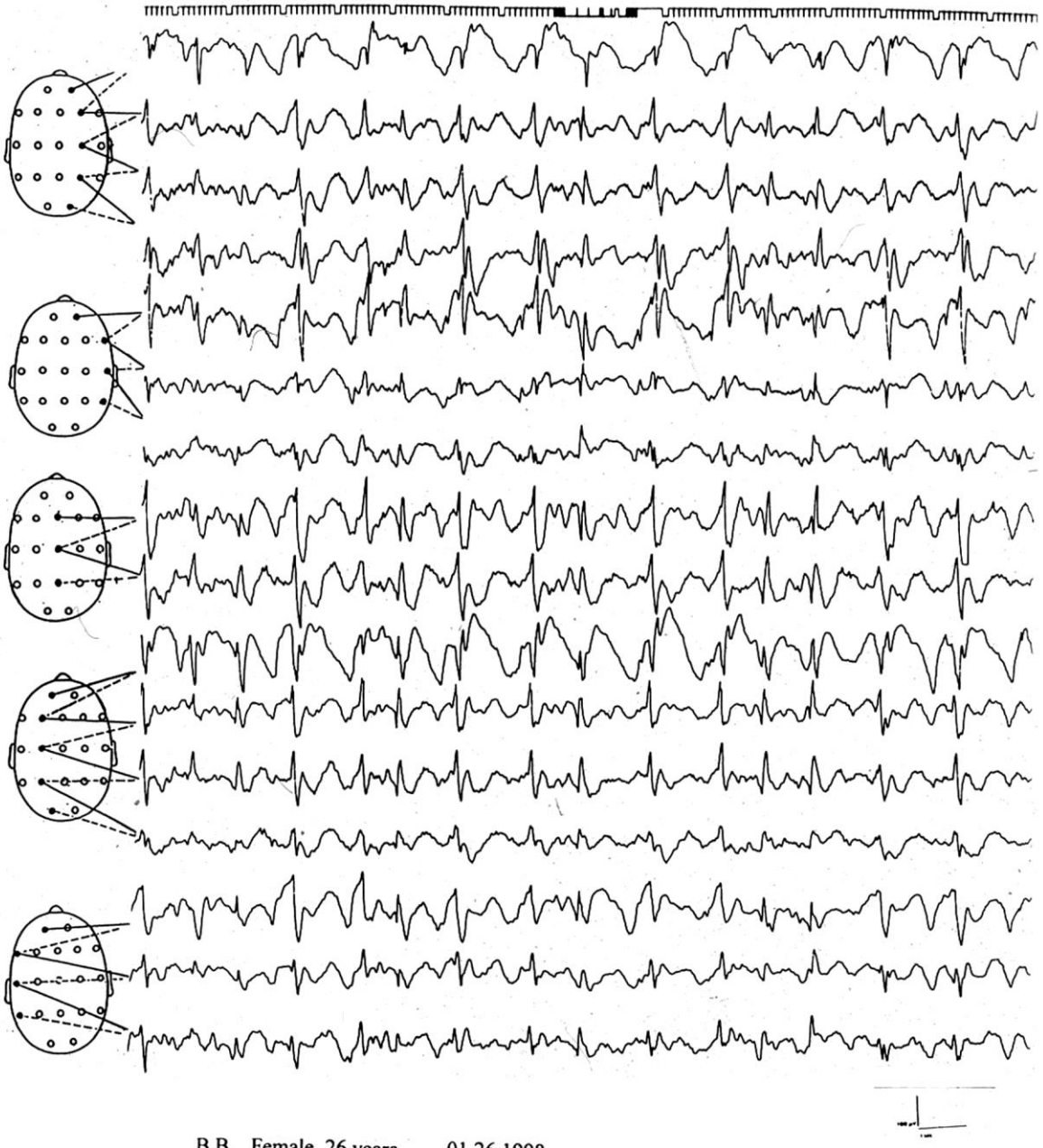
➔ Female, aged 26

➔ Aged 10: onset of rare tonic-clonic seizures, sometimes preceded by head deviation to the right

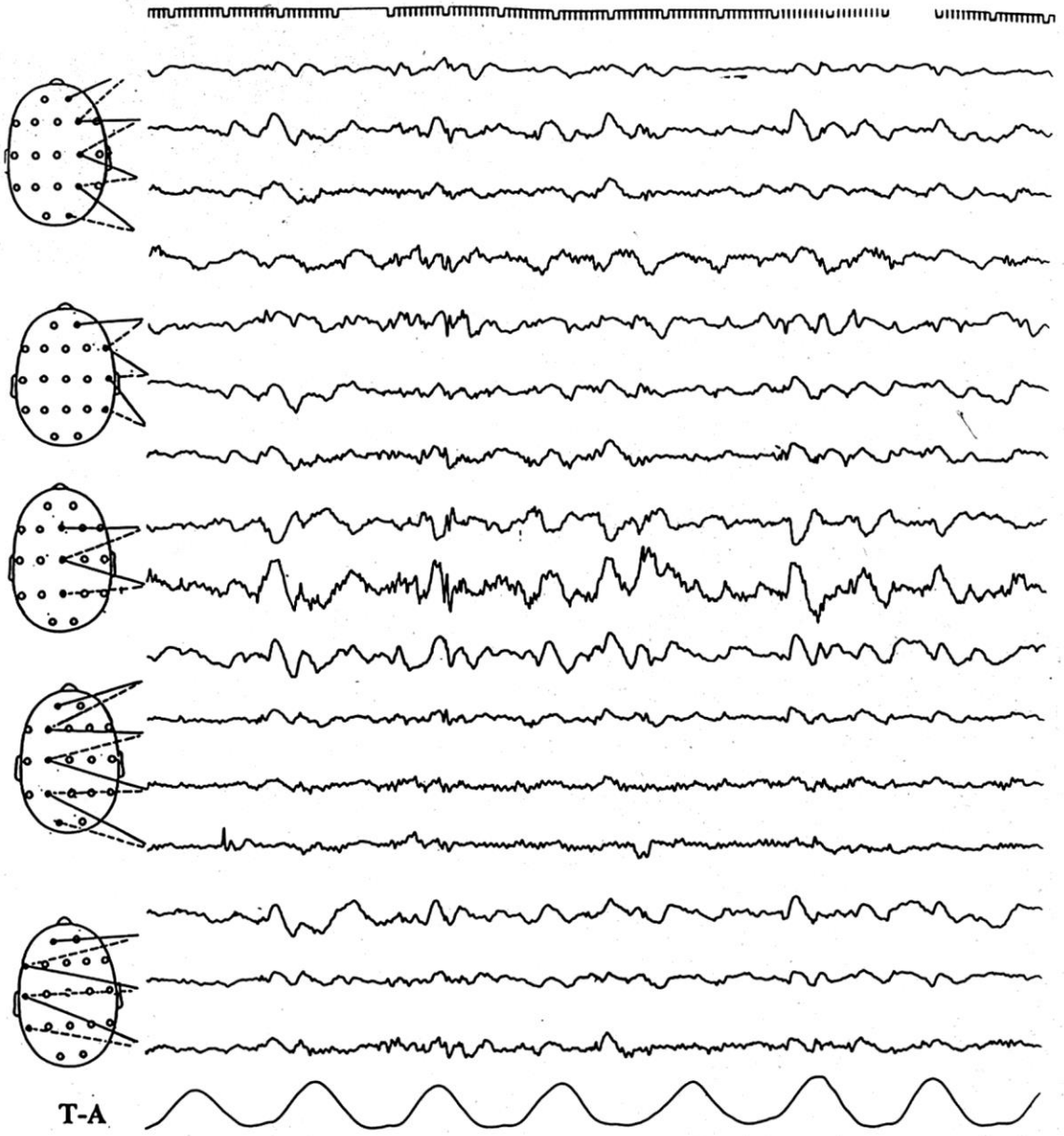
➔ Age 13 : onset of complex partial seizures (abdominal sensation, staring, gestual automatisms) refractory to AEDs

➔ Age 25: onset of weekly episodes, lasting 30-60', characterized by "sleep" and gradual recovery of consciousness. The patient was usually found lying on the ground, motionless, with the eyes closed and unresponsive.

➔ Therapy:VGB and LTG.



B.B. Female 26 years 01.26.1998



10' after 10 mg diazepam i.v.

B.B. Female 26 years 10.09.1997

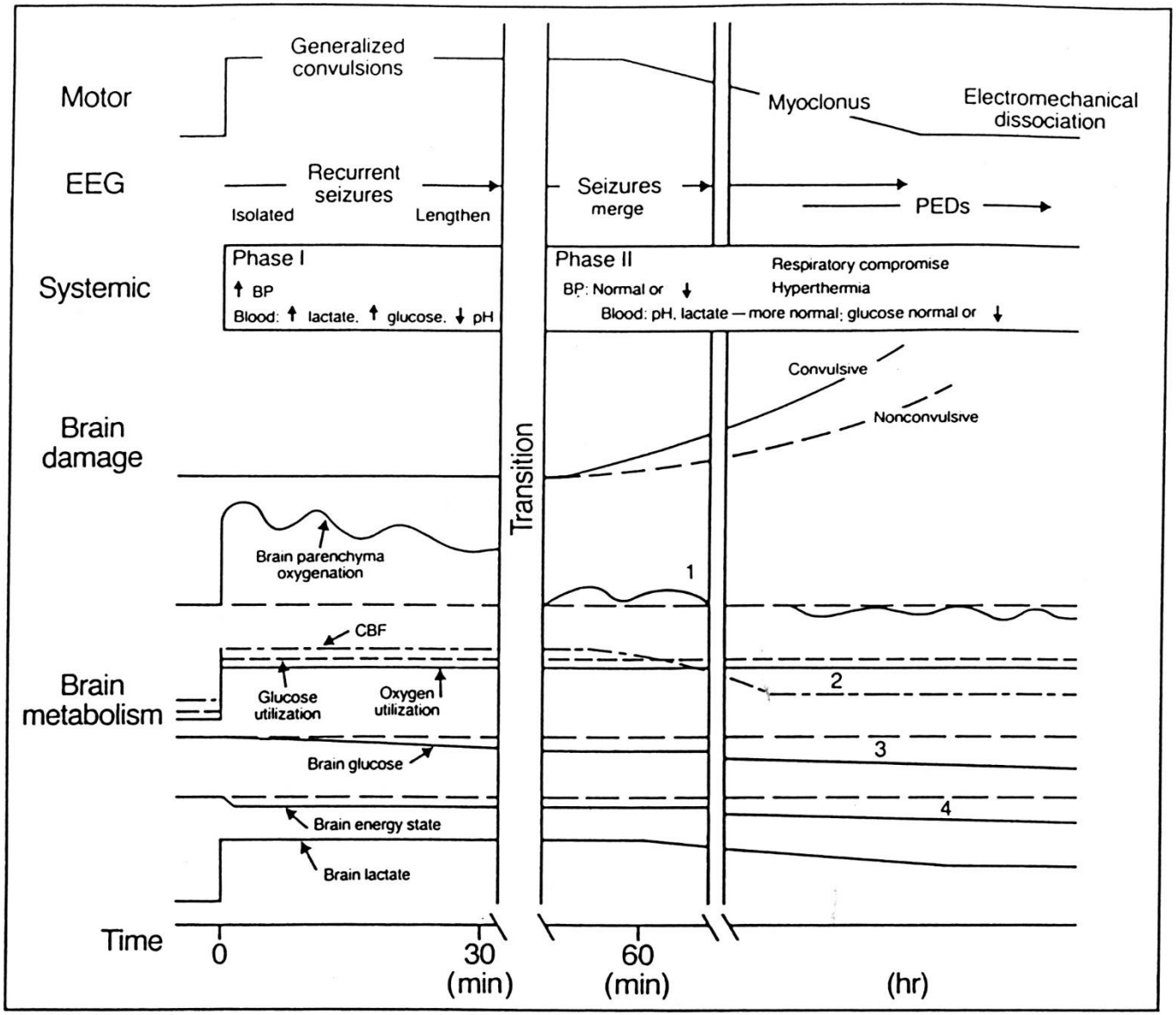
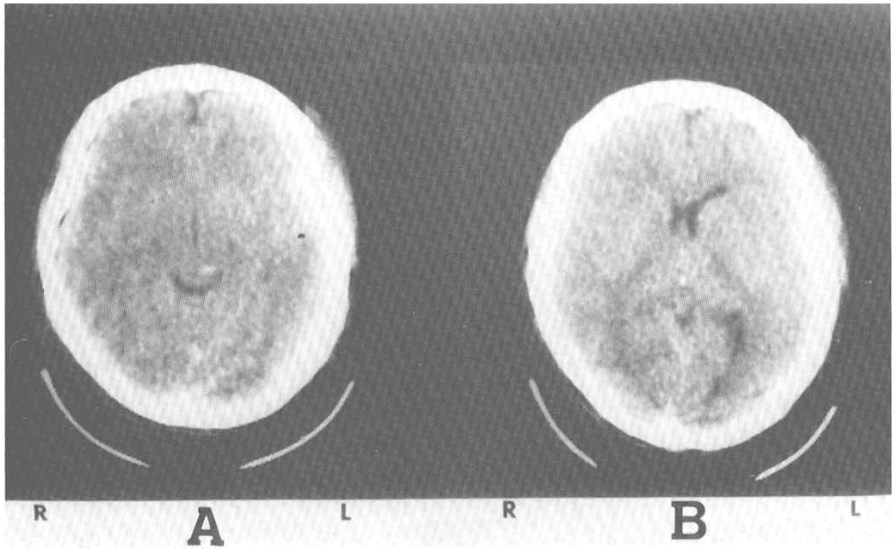
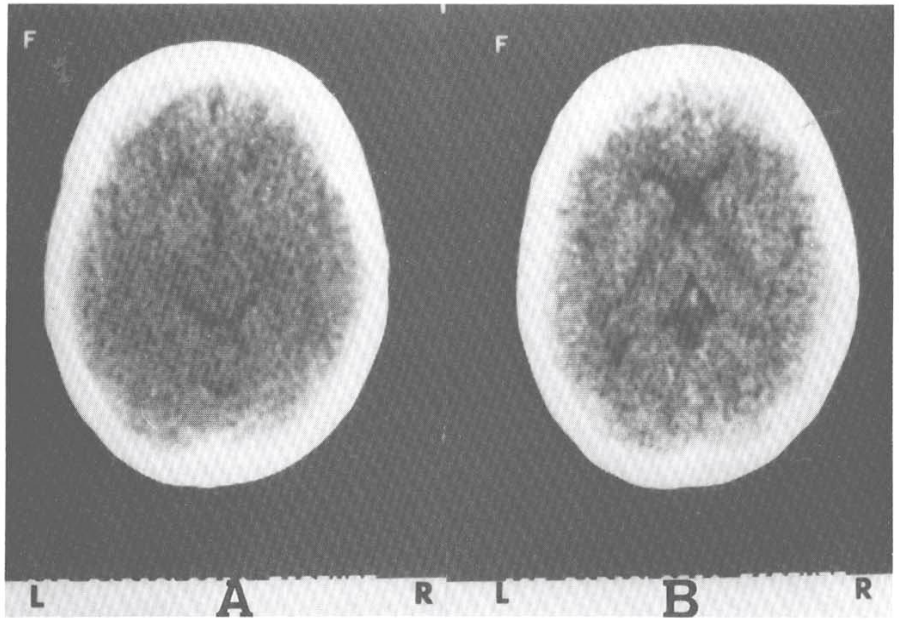


Figure 1. Summary of systemic alterations and brain metabolism in SE. Various events are aligned with respect to a time line. Note discontinuities in the time line and the designation of a critical transition period after 30 minutes of SE. In the 4 lower traces depicting metabolic responses in the brain, information from several sources was combined. Included are (1) findings of a loss of "reactivity" of brain oxygen tension later in SE,[36] (2) a mismatch between the sustained increase in oxygen and glucose utilization and a fall in cerebral blood flow as postulated by Siesjo and associates,[22] (3) a depletion of brain glucose and glycogen (not labeled), and (4) a decline in the brain energy state.[22]



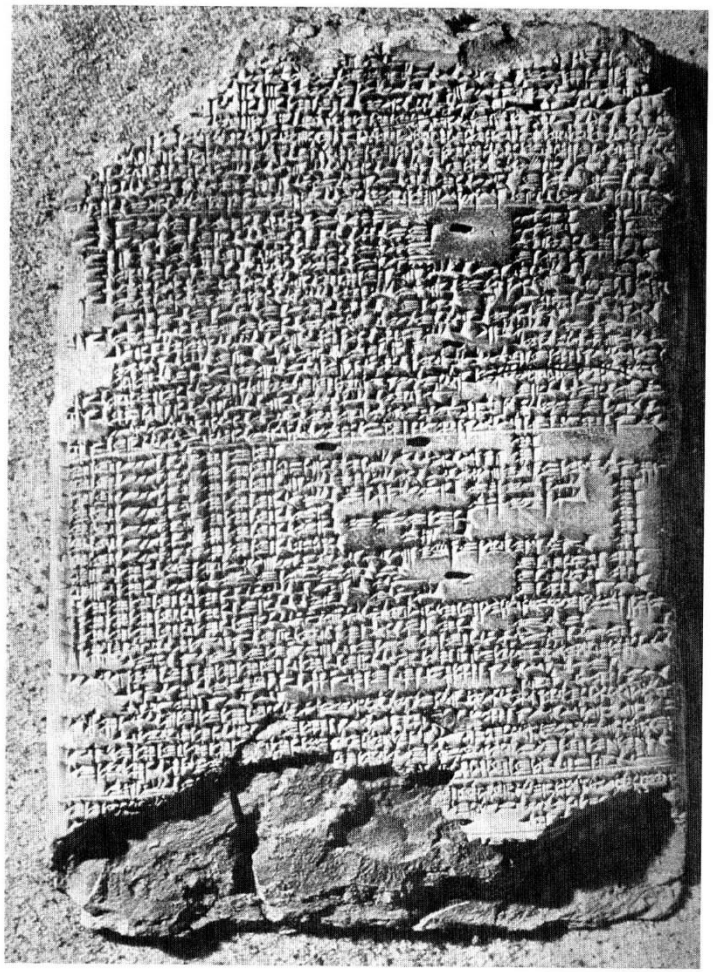


Michelucci et al 1985

Prima descrizione di uno stato di male convulsivo (1° M B.C.)

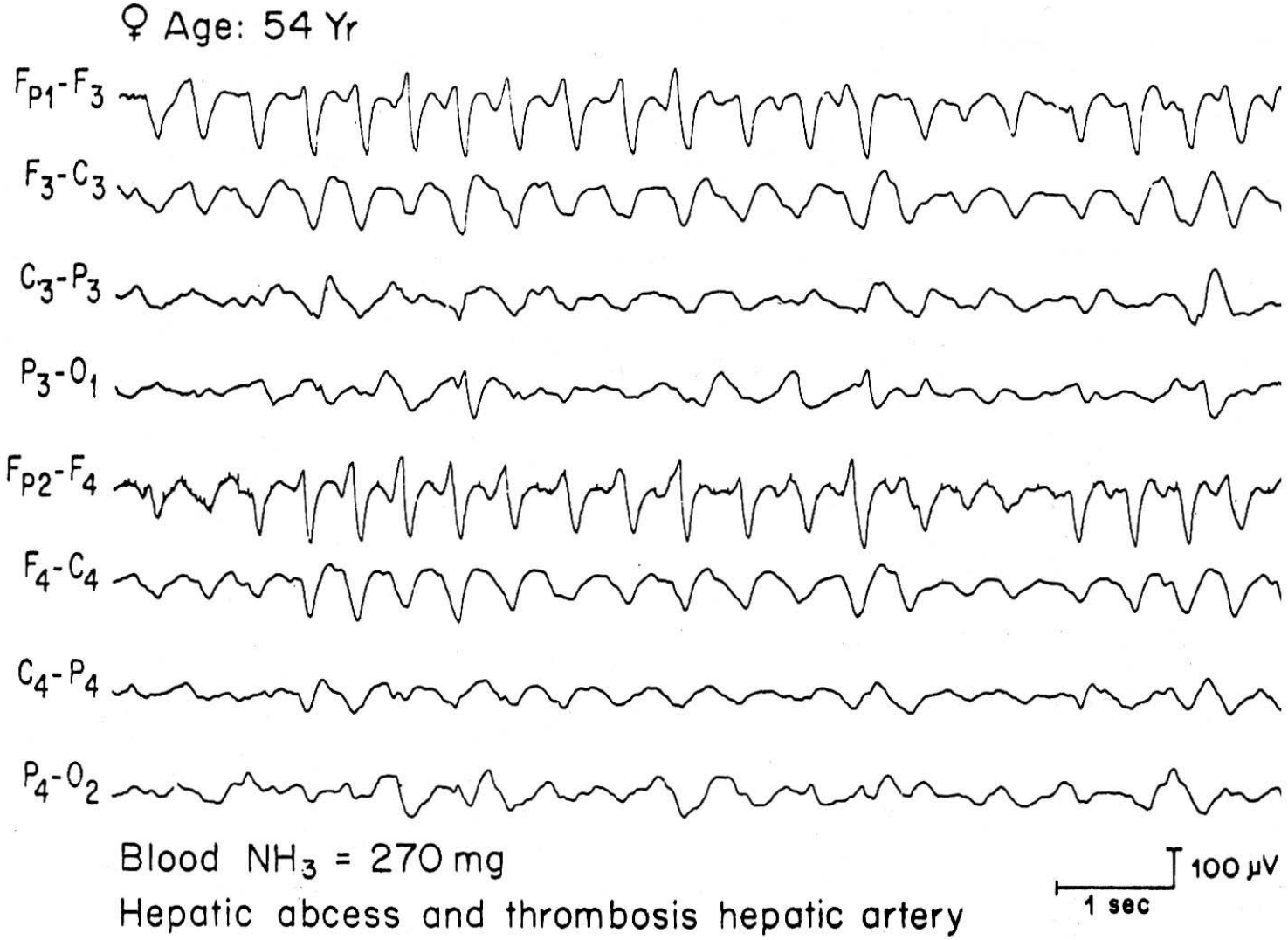
If the possessing demon possesses him many times…and his hands and feet are cold, he is much darkened, keeps opening and closing his mouth…it may go on for some time, but he will die

…..Translation and analysis of a cuneiform text forming part of a babylonian treatise on epilepsy….

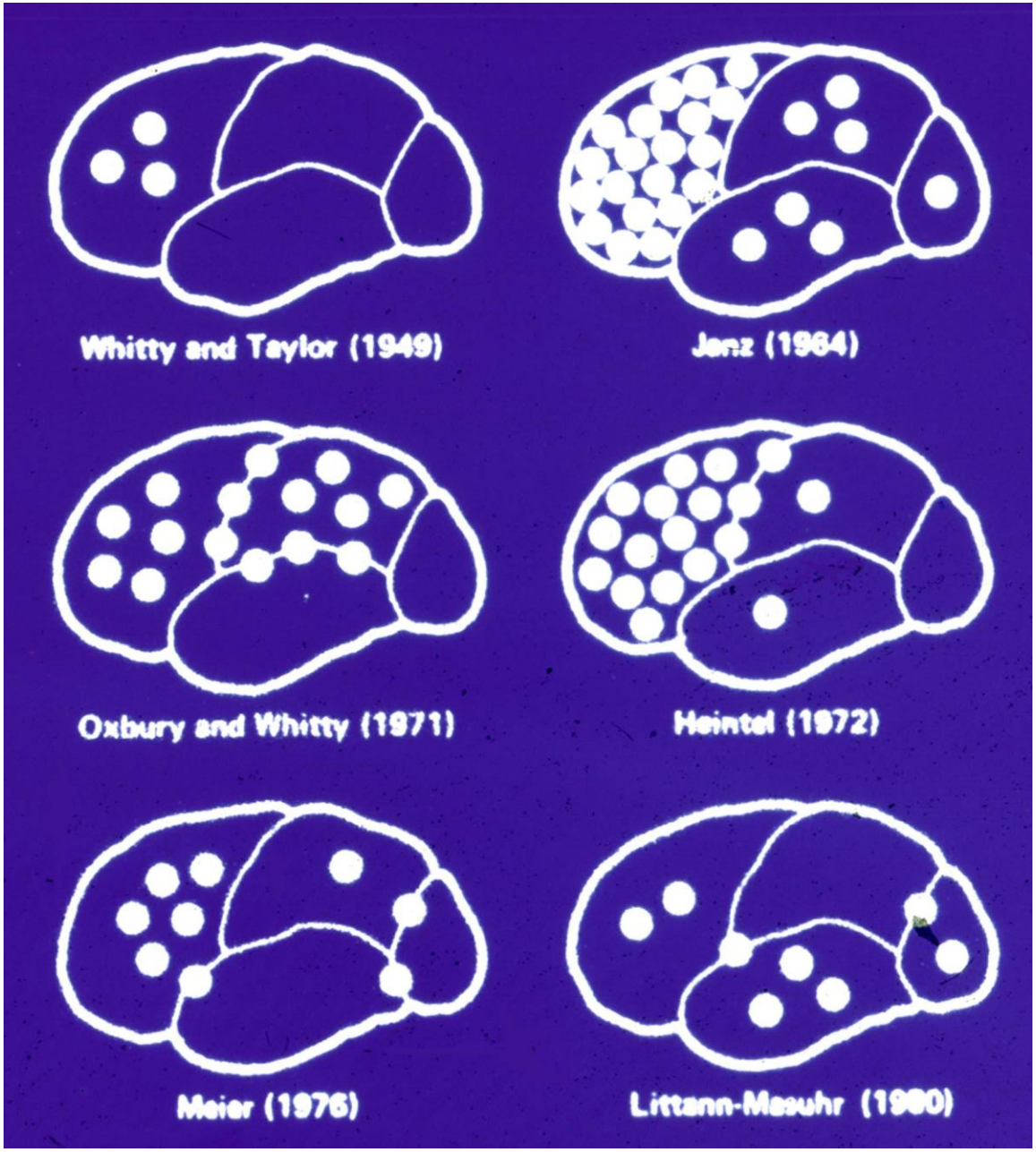


Definizioni di Stato Epilettico

- Lo Stato epilettico è una condizione caratterizzata da crisi epilettiche che sono di durata sufficientemente lunga o si ripetono ad intervalli di tempo così brevi da creare una condizione stabile e duratura (Marseille Colloquium, 1962)
- Lo Stato Epilettico è una condizione in cui l'attività epilettica persiste per 30 min o più, causando un ampio spettro di sintomi clinici e manifestando una grande variabilità delle sue basi fisiopatologiche, anatomiche ed eziologiche (Shorvon, 1994)
- ***Perché aspettare 30 min prima di iniziare la terapia?*** Iniziare se una crisi persiste per più di 10 min (EFA 1993)….per più di 5 min (Lowenstein



Uomo di 54 aa: stato confusionale/soporoso
Punte trifasiche anteriori → insuf. epatica


Whitty and Taylor (1949)
Jenz (1964)
Oxbury and Whitty (1971)
Heintel (1972)
Meier (1976)
Littann-Mauhr (1980)

Ruolo del monitoraggio EEG nello Stato di male

- Riconoscimento dello status
- Classificazione dello status

} **++ SM non convulsivo**

- Guida per la terapia
- Guida per il rianimatore

} **++ SM convulsivo**

Diagnosi di stato di male: *ruolo dell'EEG*

- Spesso indispensabile per la diagnosi ma talora non dirimente, in particolare per lo SE non convulsivo….
- Condizioni che simulano lo stato di male pseudo-status, turbe metaboliche, etc.
- Forme borderline di status "subtle clinical signs", turbe comportamentali prolungate con EEG ++
- EEG: può dare indicazioni anche sull'eziologia
- E' importante (ma non diagnostico in senso assoluto) *testare la reattività dell'attività elettrica e delle manifestazioni cliniche alle BDZ e.v.*

SE NON CONVULSIVO A SEMEIOLOGIA CONFUSIONALE

- **Generalizzato**
  - **stato di assenza tipico**
  - **stato di assenza atipico**

- **Focale**
  - **stato parziale complesso (temporale, frontale)**

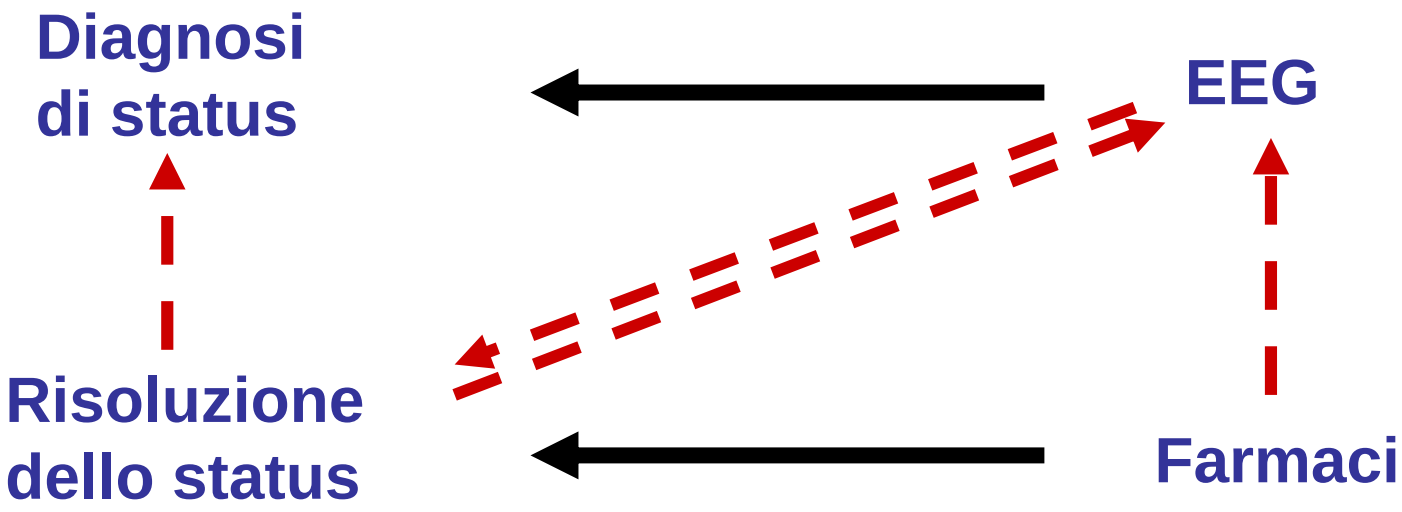
- **Stato di assenza “de novo” ad esordio tardivo**

Epilettologo e trattamento dello stato di male

Obiettivi

- ✓ **Prima di iniziare la terapia** ⇒ effettuare la diagnosi di status!
- ✓ **Al momento di iniziare la terapia** ⇒ scegliere il trattamento più appropriato in relazione alla forma di status e al contesto eziologico nel più breve tempo possibile
- ✓ **Durante la terapia** ⇒ monitorarne l'efficacia e decidere quando ricorrere al **rianimatore**
- ✓ **Dopo la risoluzione dello status** ⇒ prevenire la ricorrenza di crisi

Ruolo dell'EEG e della terapia farmacologica nella diagnosi e nella risoluzione dello stato di male non convulsivo



Classificazione dello stato di male

(in base all'urgenza terapeutica)

- **Stato di male convulsivo**

  - S.E. tonico-clonico generalizzato

  - S.E. focale motorio ("epilepsia partialis continua")

- **Stato di male non convulsivo**

  - stato di assenza ("absence status")

  - focale con alterazione della coscienza

  - stato focale sensoriale

  - stato di male non convulsivo nei pz in coma

SM "de novo" o in corso di epilessie croniche?

A comparison of lorazepam, diazepam, and placebo for the treatment of out of hospital status epilepticus

TABLE 2. STATUS EPILEPTICUS AT THE TIME OF ARRIVAL AT THE EMERGENCY DEPARTMENT.*

VARIABLE	LORAZEPAM GROUP (N=66)	DIAZEPAM GROUP (N=68)	PLACEBO GROUP (N=71)
		no. of patients (%)	
Status epilepticus terminated	39 (59.1)	29 (42.6)	15 (21.1)
Ongoing status epilepticus	27 (40.9)	39 (57.4)	56 (78.9)
	LORAZEPAM VS. PLACEBO	LORAZEPAM VS. DIAZEPAM	DIAZEPAM VS. PLACEBO
Odds ratio (simultaneous 95 percent CI) for termination of status epilepticus			
Unadjusted	5.4 (2.3–13.2)	1.9 (0.9–4.3)	2.8 (1.2–6.7)
Adjusted†	4.8 (1.9–13.0)	1.9 (0.8–4.4)	2.3 (1.0–5.9)

*CI denotes confidence interval.

†Each odds ratio was adjusted for race or ethnic group, the intervals from the onset of status epilepticus to study treatment and from study treatment to arrival at the emergency department, and cause of status epilepticus within each prognostic group.

Alldredge et al N Engl J Med 2001

Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

Robert Silbergleit, M.D., Valerie Durkalski, Ph.D., Daniel Lowenstein, M.D., Robin Conwit, M.D., Arthur Pancioli, M.D., Yuko Palesch, Ph.D., and William Barsan, M.D., for the NETT Investigators*

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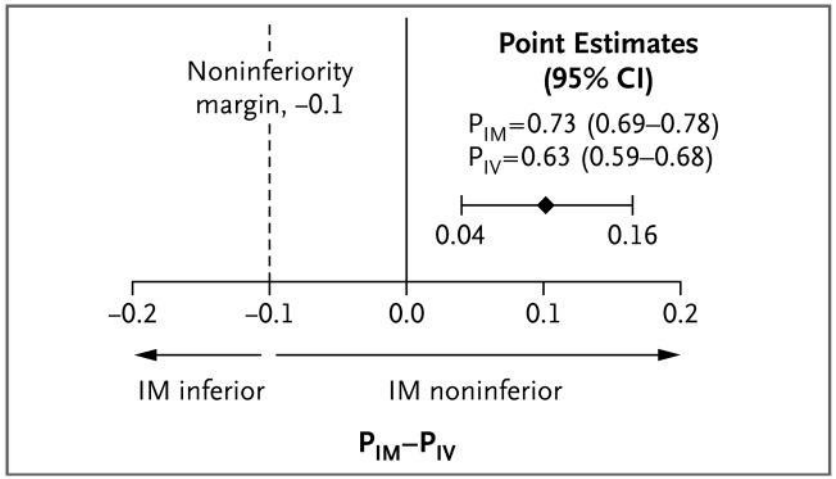
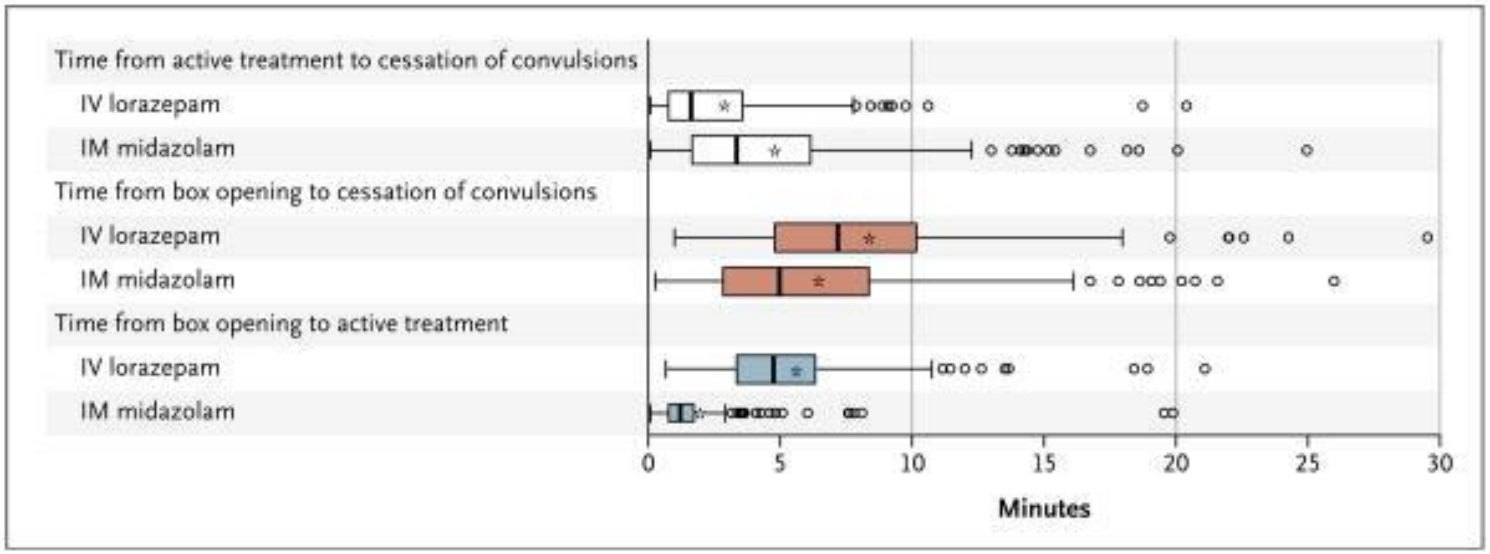
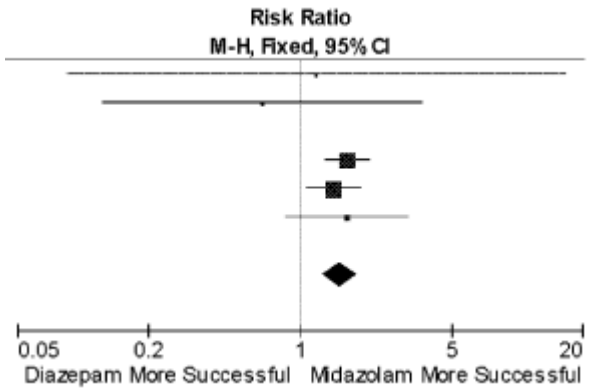


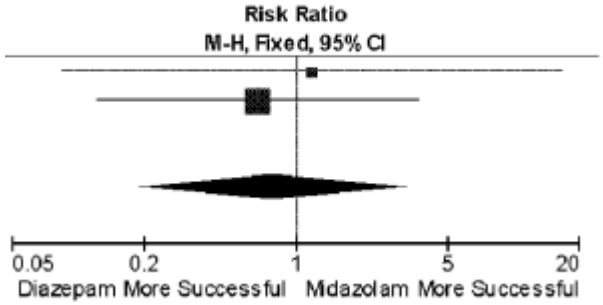
for subjects in status epilepticus, intramuscular midazolam is at least as safe and effective as intravenous lorazepam for prehospital seizure cessation



Midazolam Versus Diazepam for the Treatment of Status Epilepticus in Children and Young Adults: A Meta-analysis

Jason McMullan, MD, Comilla Sasson, MD, Arthur Pancioli, MD, and Robert Silbergleit, MD





For seizure cessation:

midazoalm by any route was superior to diazepam by any route

non-IV midazolam was as effective as IV diazepam

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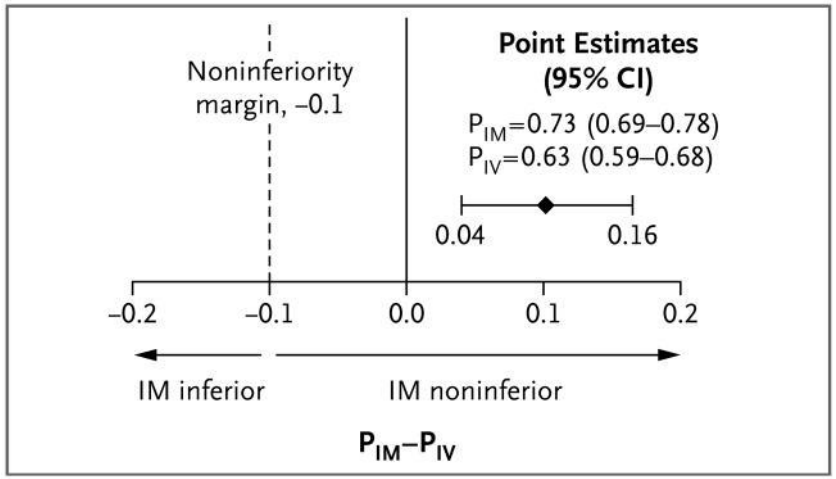

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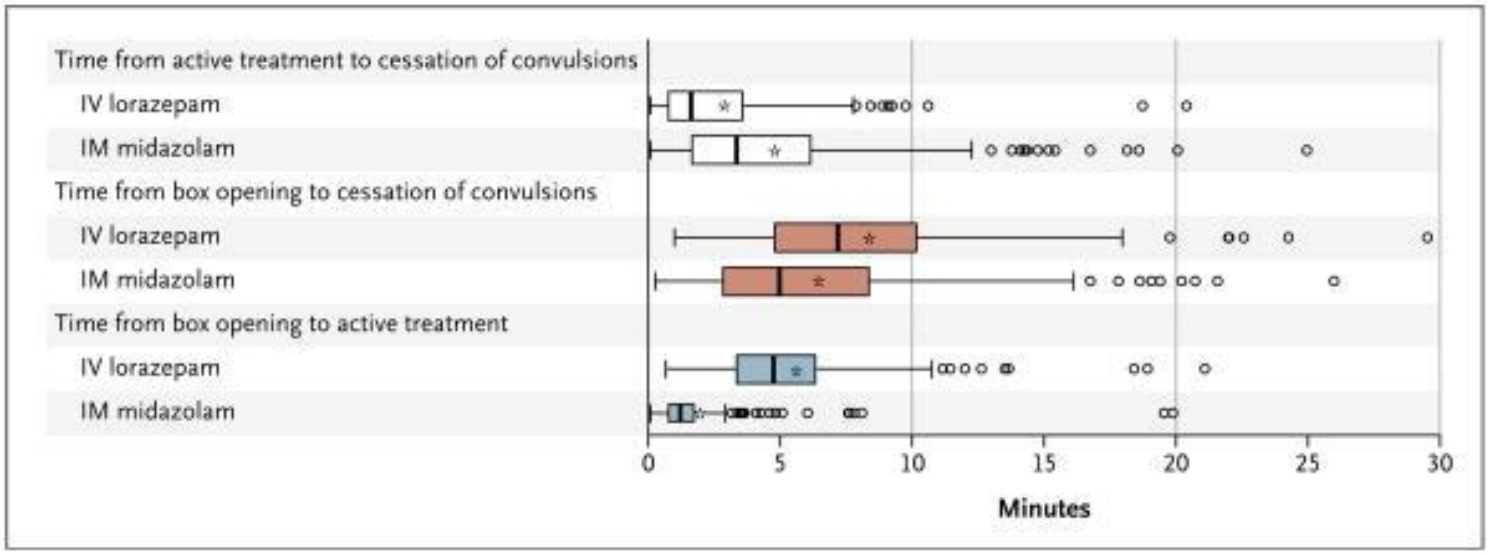
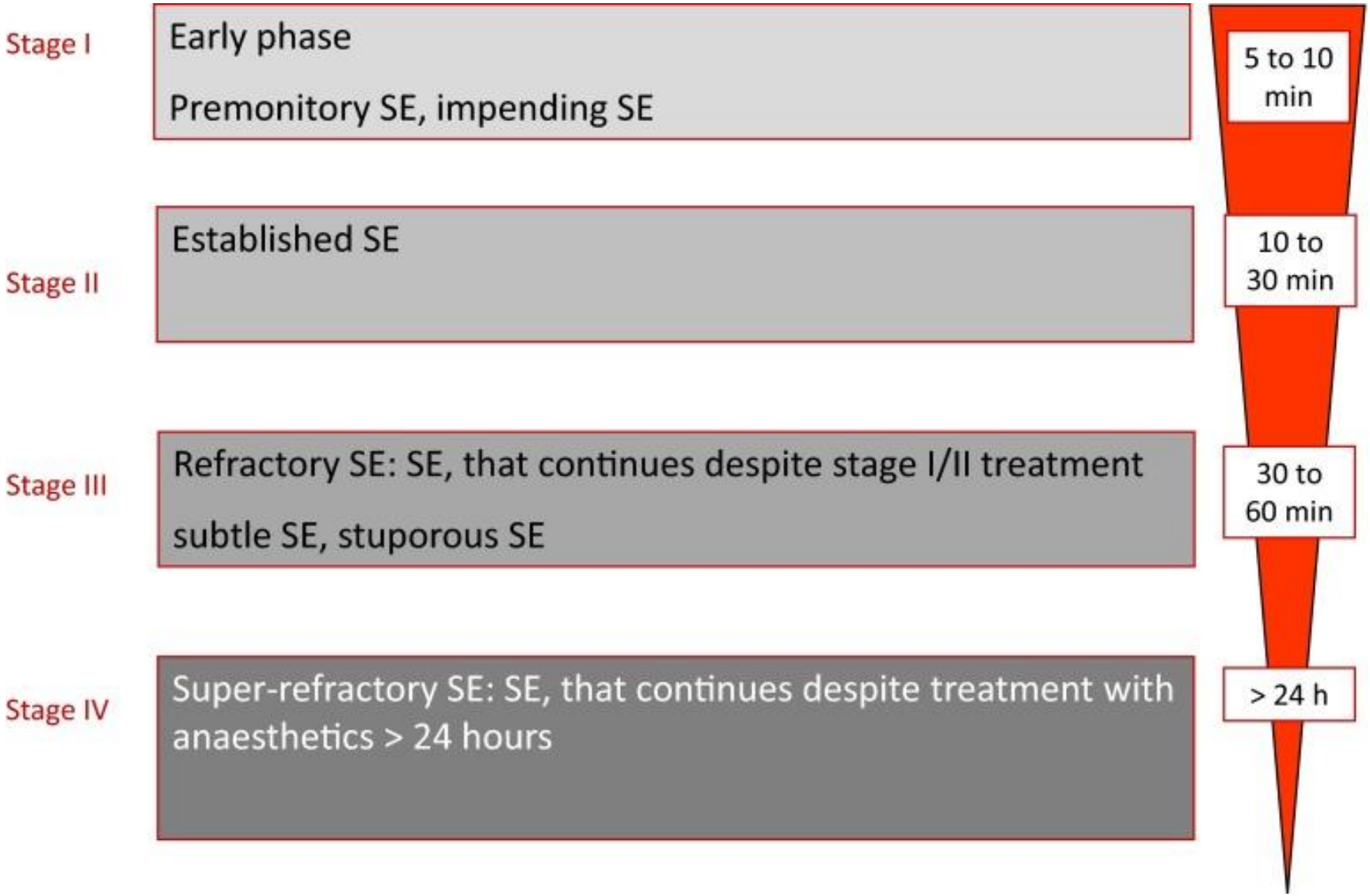
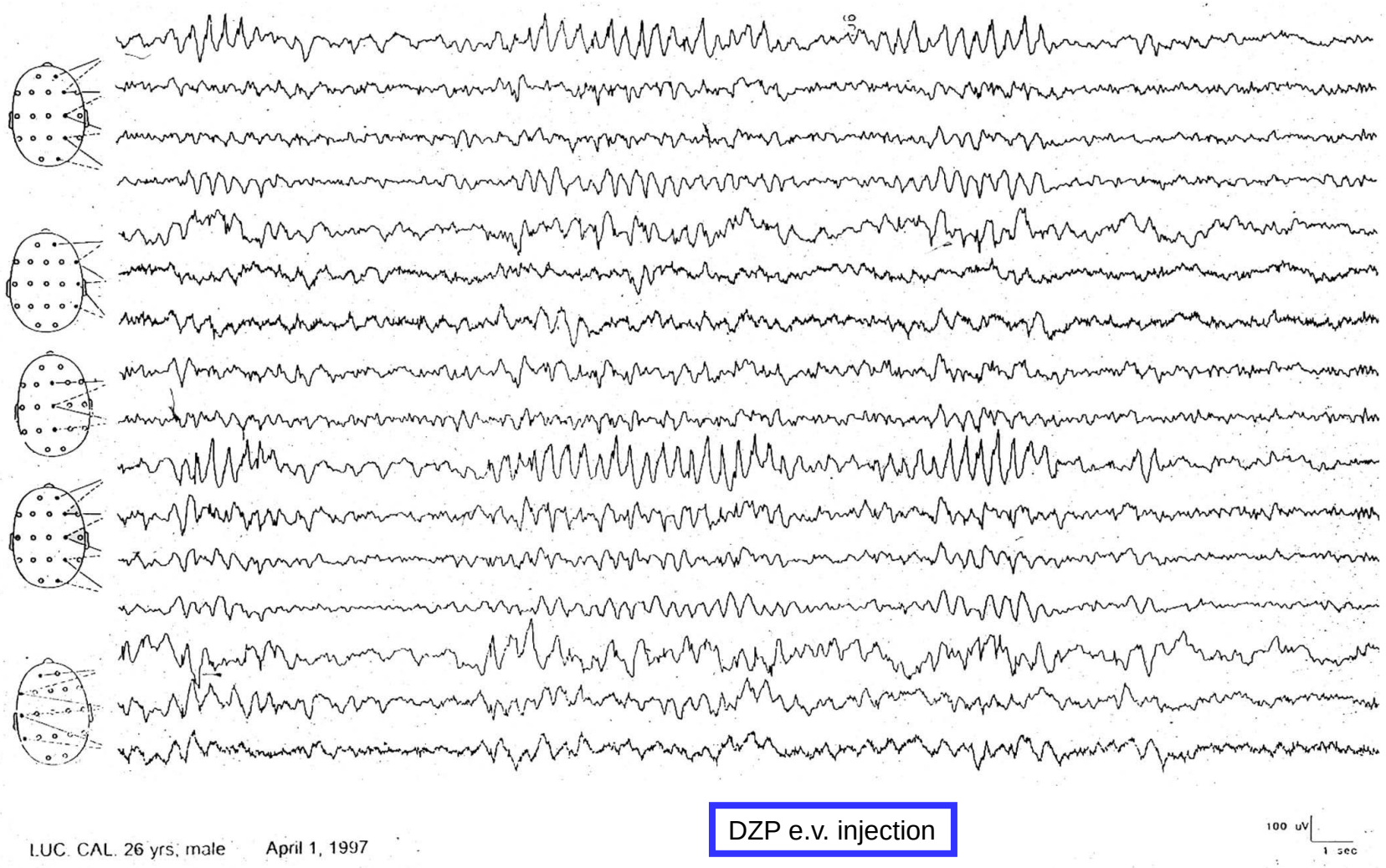


Clinical course of convulsive SE

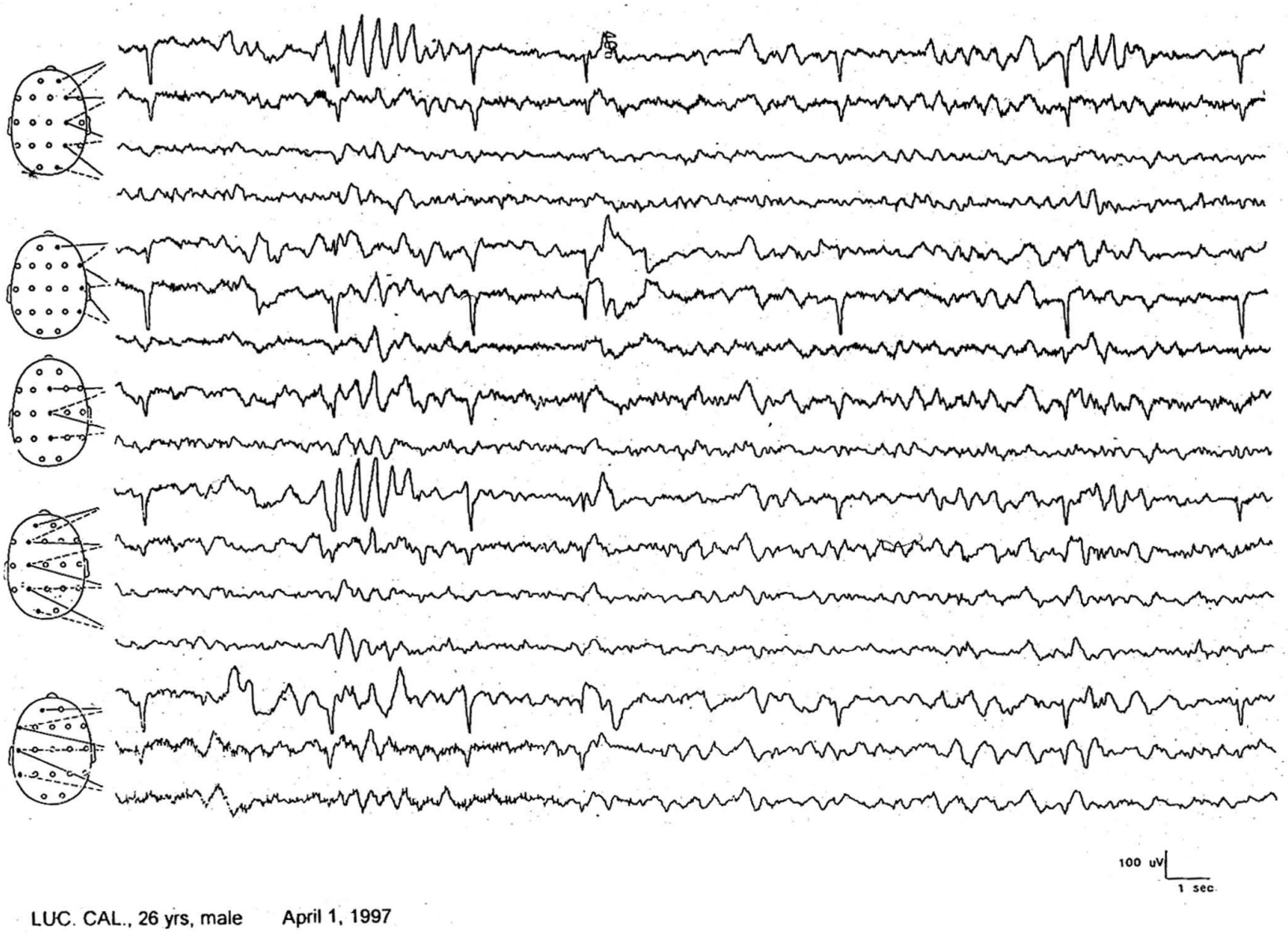


Trattamento prima dell'arrivo in PS

- **Obiettivo**: Interrompere il prima possibile crisi seriali/prolungate/stati di male
- ***Familiari*** (se epilessia già nota) → diazepam rettale, lorazepam sublinguale, clobazam orale, midazolam buccale o nasale (5-10 mg 0,3 mg/kg)
- ***Personale sanitario*** (ambulanza) → lorazepam 4 mg e.v. (0.1 mg/kg) o diazepam 10 mg e.v. (0.3 mg/kg). Midazolam nasale, e.v. o i.m. 5-10 mg (0,1-0,3 mg/kg).
- Aspetti organizzativi specifici



Uomo di 26 aa, affetto da epilessia occcipitale.
TC commotivo fortuito → piccola lesione contusiva frontale →
non recupera, appare confuso. Perché? → NCSE? → diazepam e.v.



→ **DZP risolve lo stato di "confusione" e modifica l'EEG**

→ **l'effetto del DZP è al tempo stesso la prova della origine epilettica del quadro**

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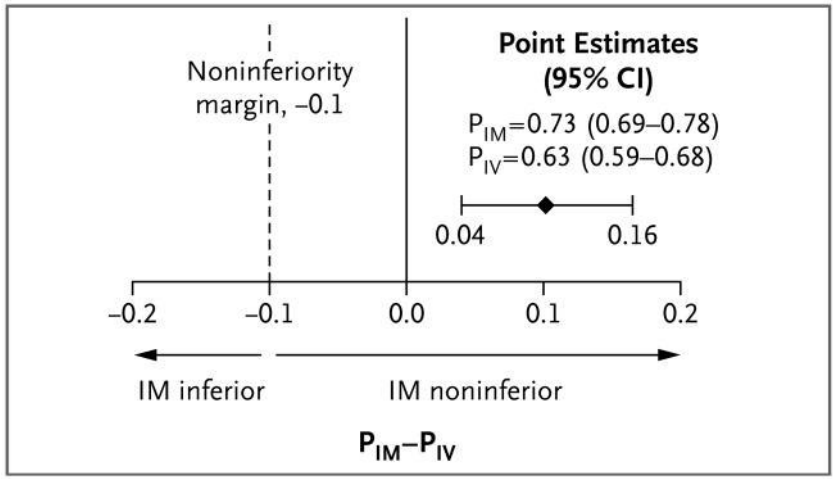

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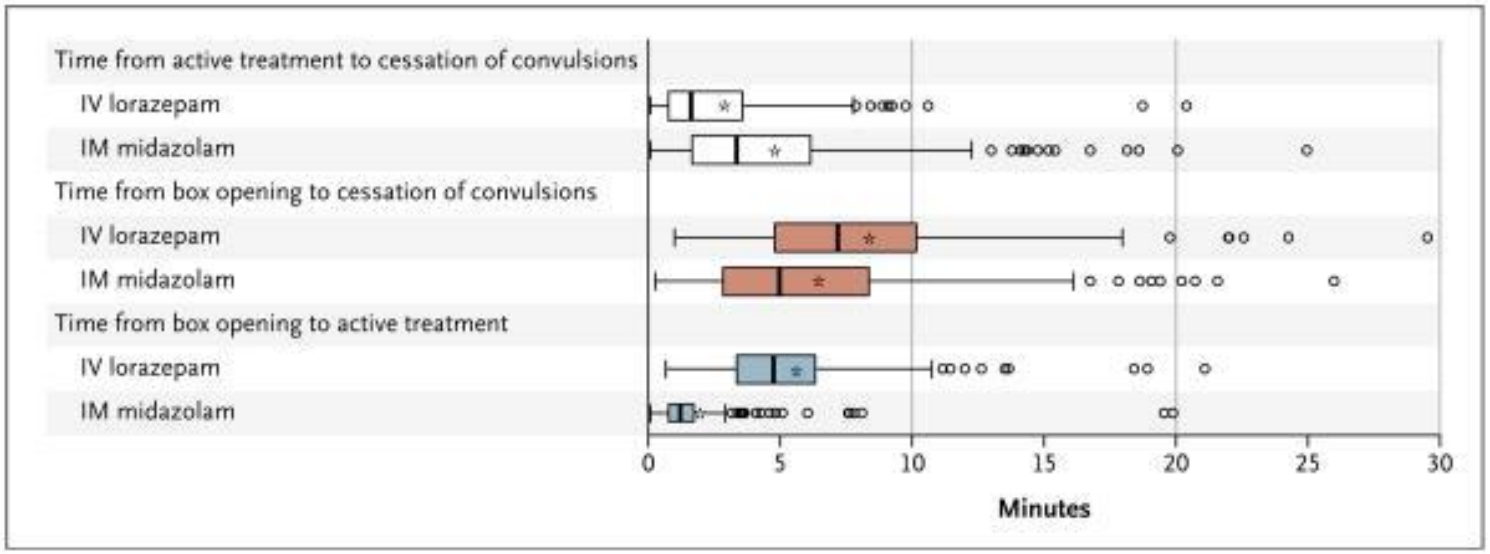

Timing Is Everything: Where Status Epilepticus Treatment Fails

Chloe E. Hill, MD,[1,2] Alomi O. Parikh, BA,[1] Colin Ellis, MD,[1]
Jennifer S. Myers, MD,[2,3] and Brian Litt, MD[1,4]

ANN NEUROL 2017;82:155–165

Status epilepticus is an emergency; however, prompt treatment of patients with status epilepticus is challenging. Clinical trials, such as the ESETT (Established Status Epilepticus Treatment Trial), compare effectiveness of antiepileptic medications, and rigorous examination of effectiveness of care delivery is similarly warranted. We reviewed the medical literature on observed deviations from guidelines, clinical significance, and initiatives to improve timely treatment. We found pervasive, substantial gaps between recommended and "real-world" practice with regard to timing, dosing, and sequence of antiepileptic therapy. Applying quality improvement methodology at the institutional level can increase adherence to guidelines and may improve patient outcomes.

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	tions
	elop more effective, user-friendly methods for family and caregivers dminister rescue medication
Journey to hospital is often prolonged	Outfit paramedics with the capability to deliver second-line therapy or early polytherapy
Unreliable administration and dosage of benzodiazepines as the first-line agent	Simplify and clarify recommended first-line dosing Create an explicit single, continuous protocol bridging prehospital to in-hospital treatment
Delays in diagnosis of status epilepticus	Improve the education of emergency personnel and family members Advance technologies for EEG diagnosis in the field and/or immediately upon arrival to the ED
Unclear relationship between treatment nonadherence and patient outcome	Establish and employ standard quality indicators of treatment adherence (timing, dose, sequence) Adopt consistent clinical outcomes, covariate considerations, and definitions of status epilepticus
Difficult to retrospectively assess seizure duration and clinical decision making	Collect patient data in real-time through technology innovation
Limited and laborious data collection	Innovate data abstraction and visualization tools Encourage reporting as performance measures
Health system and institution-specific factors impact protocol adherence	Apply quality improvement methodology to explore the local context and then implement responsive, targeted countermeasures

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Long-term Monitoring in Epilepsy (EEG Suppl. No. 37)
Editors: J. Gotman, J. R. Ives and P. Gloor

Status Epilepticus

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** Neurological Clinic, University of Bologna School of Medicine, 40123 Bologna, and ** 2nd Neurological Institute, University of Florence School of Medicine, 50100 Florence (Italy)*

Advances in Neurology, Vol. 34: Status Epilepticus, edited by A.V. Delgado-Escueta, C.G. Wasterlain, D.M. Treiman, and R.J. Porter. Raven Press, New York © 1983.

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Benzodiazepines: Efficacy in Status Epilepticus

C. A. Tassinari, O. Daniele, R. Michelucci, M. Bureau, C. Dravet, and J. Roger

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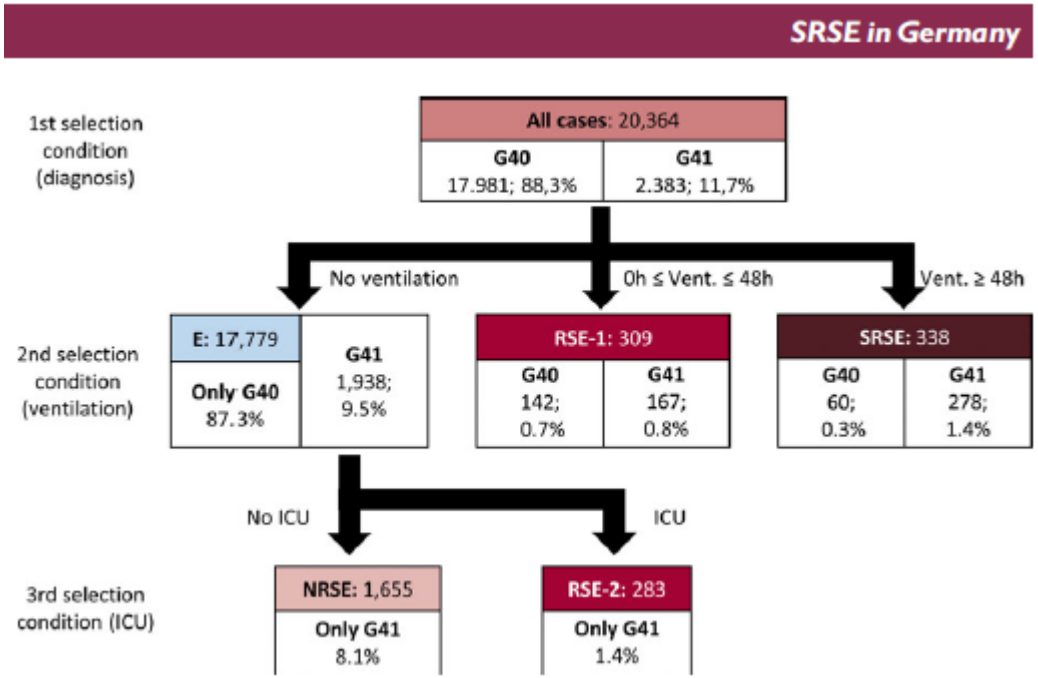
Costs, length of stay, and mortality of super-refractory status epilepticus: A population-based study from Germany

*†Adam Strzelczyk, ‡Sonja Ansorge, ‡Jana Hapfelmeier, §Vijayveer Bonthapally, ¶M. Haim Erder, and *†Felix Rosenow

Epilepsia, 58(9):1533–1541, 2017
doi: 10.1111/epi.13837



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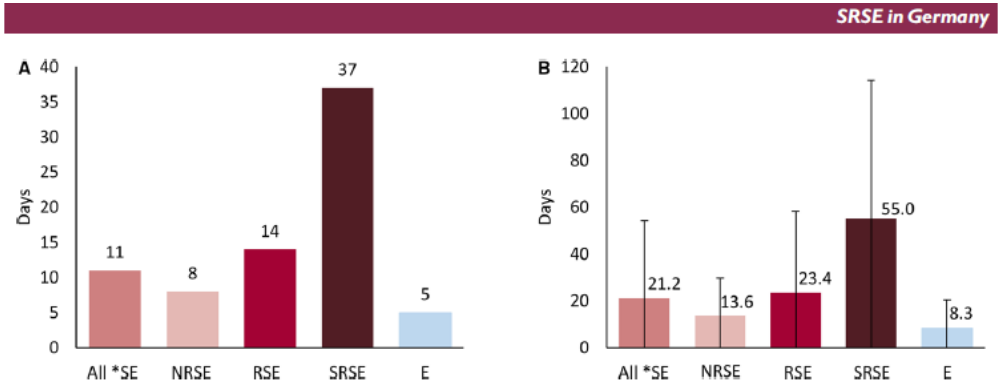

Figure 2.
Length of stay for status epilepticus (SE) patients. (**A**) Median length of stay per admission for All SE, NRSE, nonrefractory SE; RSE, refractory SE; SRSE, super-refractory SE; and epilepsy (E) cases. (**B**) Mean length of stay per admission for All SE, NRSE, RSE, SRSE, and E cases.

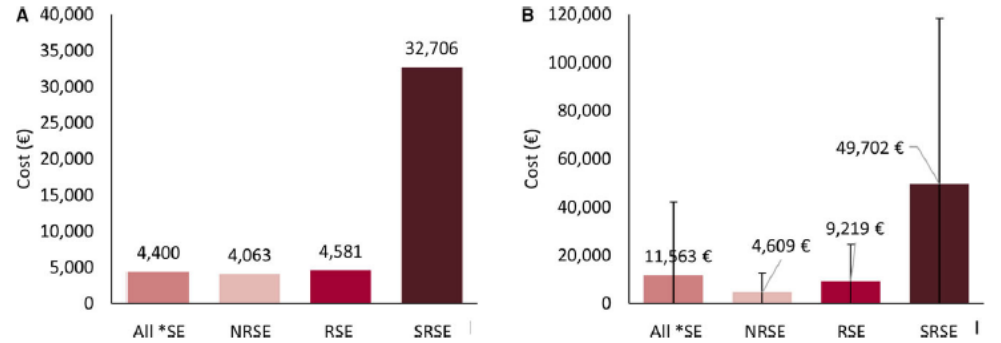

Figure 3.
Cost of status epilepticus (SE) patients. (**A**) Median inpatient costs per admission for All SE, NRSE, nonrefractory SE; RSE, refractory SE; and SRSE, super-refractory SE cases. (**B**) Mean inpatient costs per admission for All SE, NRSE, RSE, and SRSE cases.

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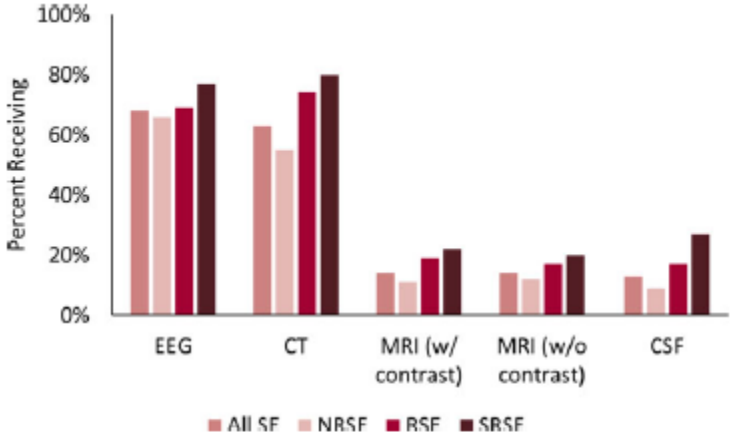


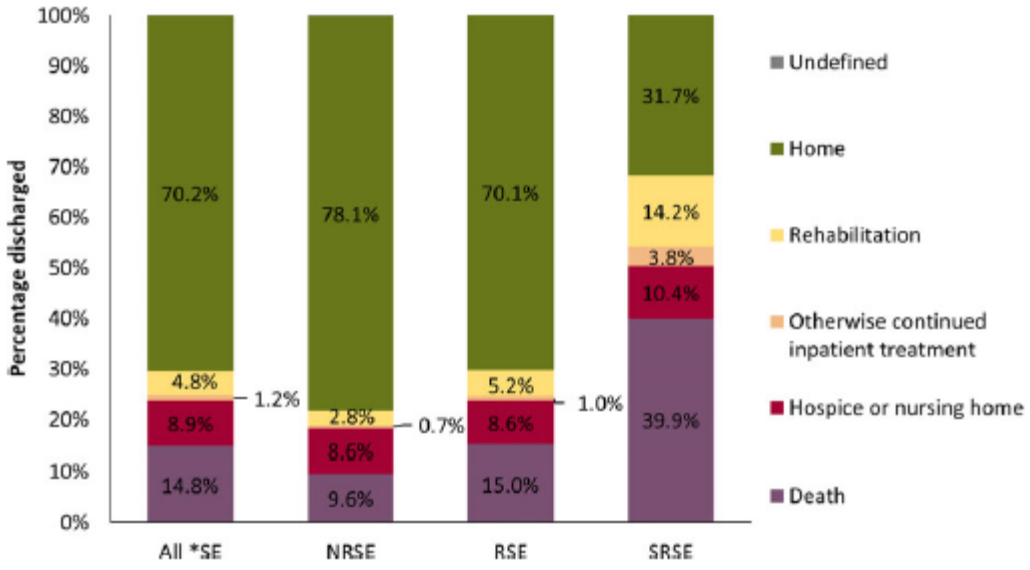
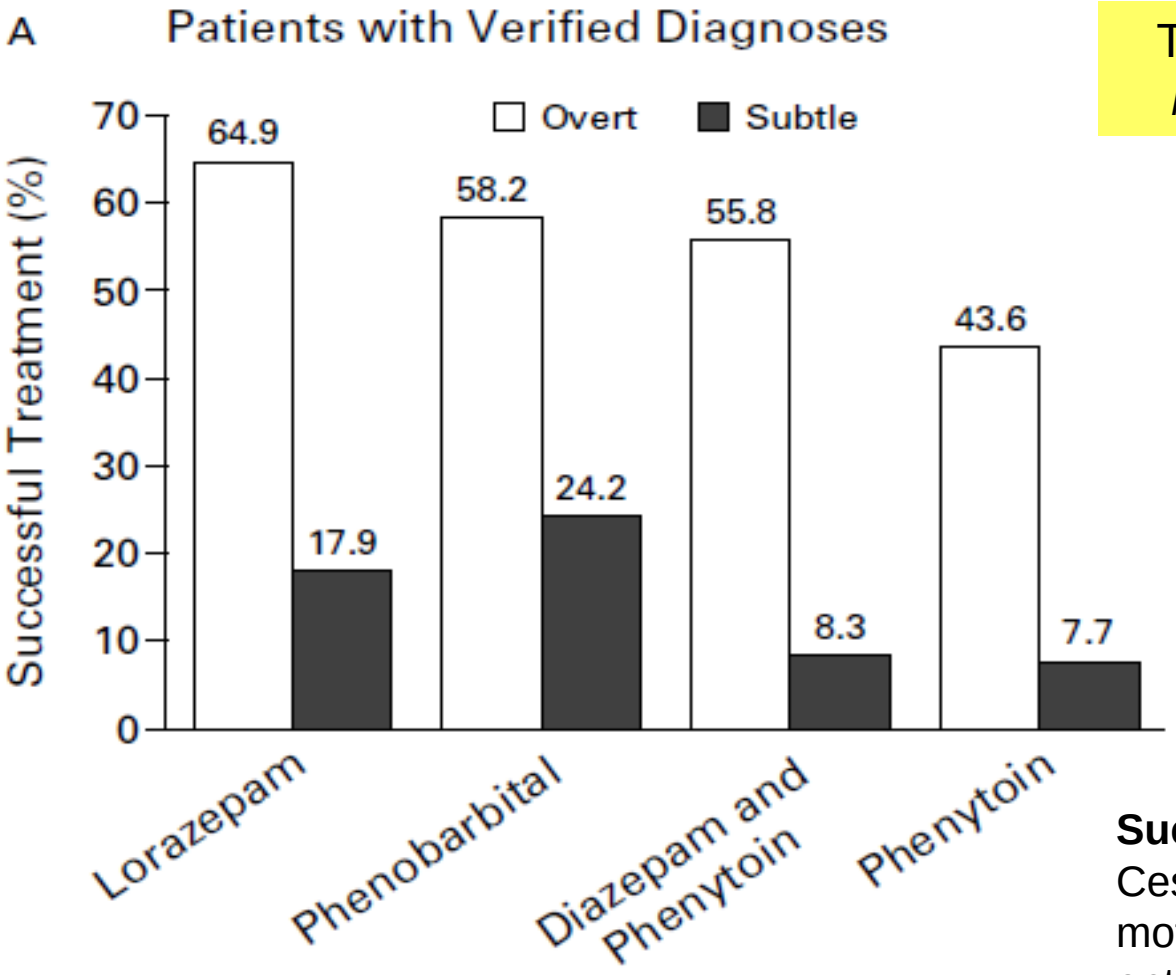


Figure 4.

Common procedures: electroencephalogram (EEG), computed tomography (CT), magnetic resonance imaging (MRI) with (w/) or without (w/o) contrast, and cerebrospinal fluid (CSF) examinations of status epilepticus (SE) patients. NRSE, nonrefractory SE; RSE, refractory SE; SRSE, super-refractory SE.

Treiman et al
N Engl J Med 1998



No. of Patients				
Overt	97	91	95	101
Subtle	39	33	36	26

LZP	PB	DZP +PHT	PHT
0.10±0.01 mg/kg	14.96±2.53 mg/kg	0.15±0.02 15.08±4.84 mg/kg	16.2 ±3.21 mg/kg

Successful treatment =
Cessazione manifestazioni motorie e EEGragiche entro 20 m dalla infusione senza ricorrenza durante i 40 m successivi

Fenitoina

- Farmaco più utilizzato, in genere in successione al bolo di BZD
- Trials comparativi vs VPA
- Farmaco «familiare», con «buona reputazione», di facile utilizzo
- Uso e.v.15-18 mg/kg in bolo (vel. max. 50 mg/min)

Non è sedativo ma può causare ipotensione (28-50%) e aritmie (2%)

Flebite nella sede dell'inoculo

Review

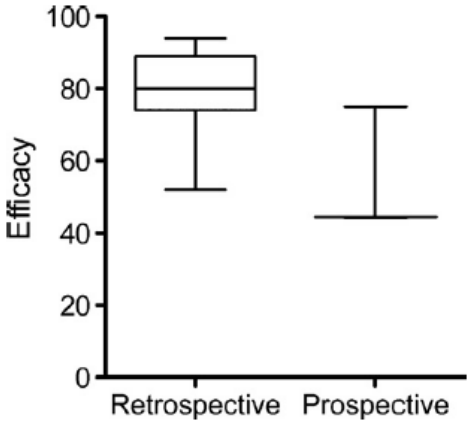
Levetiracetam as alternative stage two antiepileptic drug in status epilepticus: A systematic review

Johan Zelano *, Eva Kumlien

Seizure 21 (2012) 233–236

- Inclusi 10 studi
  (7 retrospettici, 3 prospettici di cui 1 randomizzato vs LRZ)
- 324 pz, in maggioranza con stato “focale”
- dose: 250-2500 mg
- successo compreso fra 60 e 94% (studi retrospettici)
  e 44-75% (studi prospettici)
- sedazione: 12,5-40%

Assenza di depressione respiratoria
Raramente agitazione, trombocitopenia



Efficacy and Safety of Intravenous Valproate for Status Epilepticus: A Systematic Review

E Trinka • et al CNS Drugs 2015

Patients: 860

Response rate: 70.9 % (601 out of 848 patients; 95 % confidence interval [CI] 67.8–73.9)

Dose: 15 to 45 mg/kg in bolus (6 mg/kg/ min) followed by 1–3 mg/kg/h infusion.

Side effects: low incidence (<10 %): dizziness, thrombocytopenia, and mild hypotension, which was independent of infusion rates, and a good cardiovascular and respiratory tolerability even in high doses and fast infusion rates up to 30 mg/kg at 10 mg/kg/min.

Valproate in generalized convulsive status epilepticus: a systematic review

Brigo F, Storti M, Del Felice A, Fiaschi A, Bongiovanni LG

A systematic review of randomized controlled trials on the theraputic effect of intravenous sodium valproate in status epilepticus.

Liu X, Wu Y, Chen Z, Ma M, Su L

Int J Neurosci 2012 122:277-83.

Selezionati solo RCT di comparazione VPA vs PHT, VPA vs DZ

Nessuna differenza di efficacia di VPA vs PHT e vs DZ, migliore tollerabilità di VPA vs PHT

Epilepsia, 54(3):393–404, 2013
doi: 10.1111/epi.12058

CRITICAL REVIEW AND INVITED COMMENTARY

Lacosamide as a new treatment option in status epilepticus

Julia Höfler and Eugen Trinka

- 19 studi (9 casistiche retrospettiche, 10 case report singoli)
- 136 episodi di status refrattario (50% non convulsivo, 31% stato focale motorio, 19% convulsivo)
- bolus e.v. con lacosamide (200-400 mg in 3-5 min)
- successo complessivo nel 56% (76/136) (++ SMNC)

EA nel 25%: lieve sedazione (25 casi), ipotensione (4 pz), reazioni cutanee (2 casi), BAV 3° grado e asistolia critica (1 caso)

Lyttle et al. Trials (2017) 18:283
DOI 10.1186/s13063-017-2010-8

Trials

STUDY PROTOCOL Open Access

Emergency treatment with levetiracetam or phenytoin in status epilepticus in children—the EcLiPSE study: study protocol for a randomised controlled trial

Mark D. Lyttle[1,2], Carrol Gamble[3], Shrouk Messahel[4], Helen Hickey[5], Anand Iyer[4], Kerry Woolfall[6], Amy Humphreys[5], Naomi E. A. Bacon[3], Louise Roper[6], Franz E. Babl[7,8,9], Stuart R. Dalziel[10,11], Mary Ryan[4], Richard E. Appleton[4*] and supported by Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI)

Dalziel et al. BMC Pediatrics (2017) 17:152
DOI 10.1186/s12887-017-0887-8

BMC Pediatrics

STUDY PROTOCOL Open Access

A multicentre randomised controlled trial of levetiracetam versus phenytoin for convulsive status epilepticus in children (protocol): Convulsive Status Epilepticus Paediatric Trial (ConSEPT) - a PREDICT study

Stuart R. Dalziel[1,7*], Jeremy Furyk[3,4], Megan Bonisch[1], Ed Oakley[5,6,7], Meredith Borland[8], Jocelyn Neutze[9], Susan Donath[6], Cynthia Sharpe[1], Simon Harvey[5], Andrew Davidson[5], Simon Craig[10], Natalie Phillips[11], Shane George[12,13,14], Arjun Rao[15], Nicholas Cheng[16], Michael Zhang[17], Kam Sinn[18], Amit Kochar[19], Christine Brabyn[20], Franz E. Babl[5,6,7] and On Behalf of the PREDICT research network[21]

ANNALS of Clinical and Translational Neurology Open Access

BRIEF COMMUNICATION

First-in-man allopregnanolone use in super-refractory status epilepticus

Henrikas Vaitkevicius[1,2], Aatif M. Husain[3], Eric S. Rosenthal[2,4], Jonathan Rosand[2,4], Wendell Bobb[3], Kiran Reddy[5], Michael A. Rogawski[6] & Andrew J. Cole[2,4]

Kellinghaus et al. BMC Neurology (2015) 15:230
DOI 10.1186/s12883-015-0486-y

BMC Neurology

STUDY PROTOCOL Open Access

Making SENSE - Sustained Effort Network for treatment of Status Epilepticus as a multicenter prospective registry

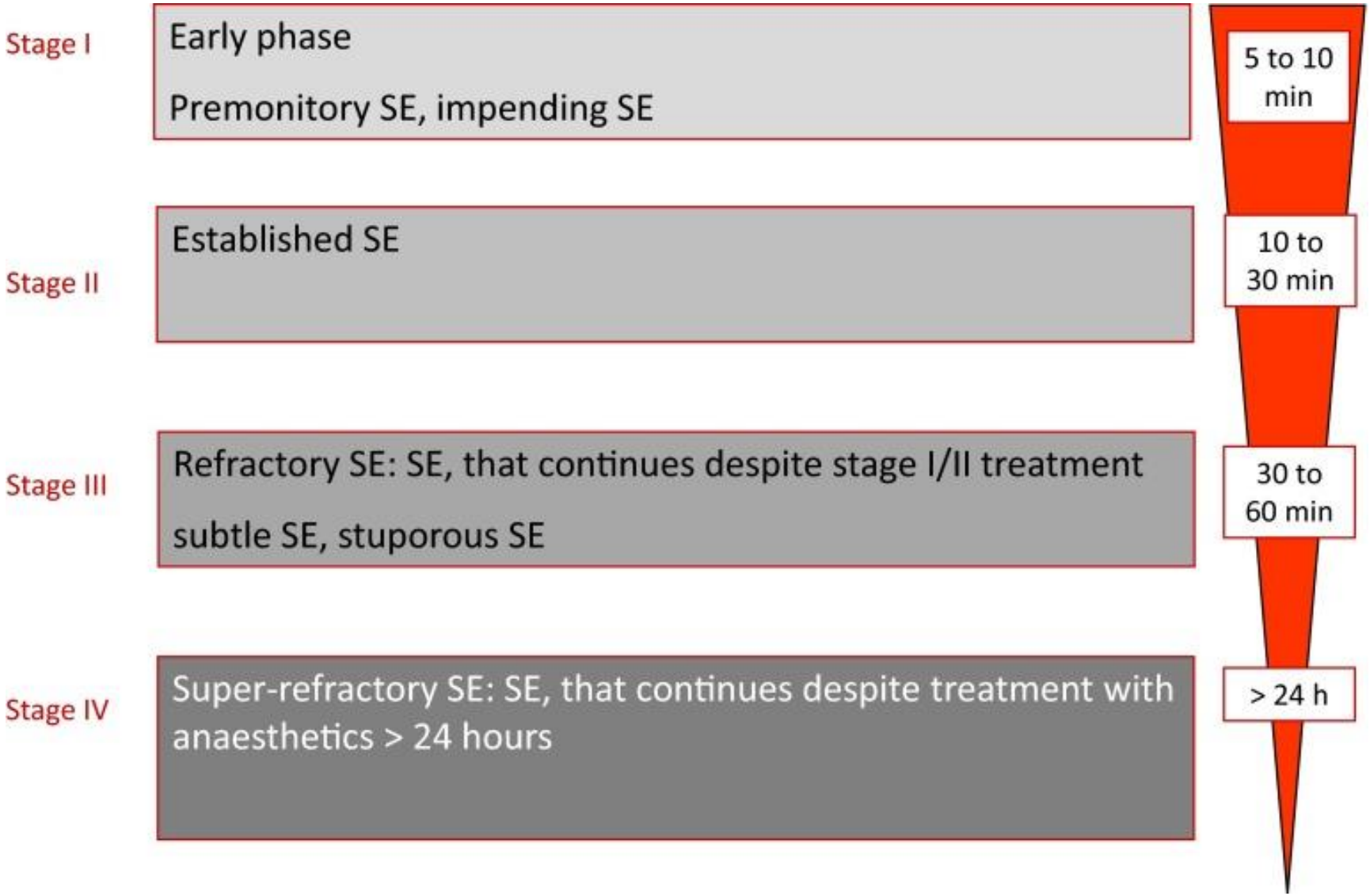
Christoph Kellinghaus[1*], Nicolas Lang[2], Andrea O. Rossetti[3], Stephan Rüegg[4], Christian Tilz[5], Eugen Trinka[6,10], Iris Unterberger[7], Zeljko Uzelac[8] and Felix Rosenow[9]

Preliminary results of the global audit of treatment of refractory status epilepticus.

Ferlisi M[1], Hocker S[2], Grade M[3], Trinka E[4], Shorvon S[5]; International Steering Committee of the StEp Audit.

Epilepsy Behav. 2015 Aug;49:318-24

Clinical course of convulsive SE



trattamento di prima linea al PS
Stadio dello SE iniziale

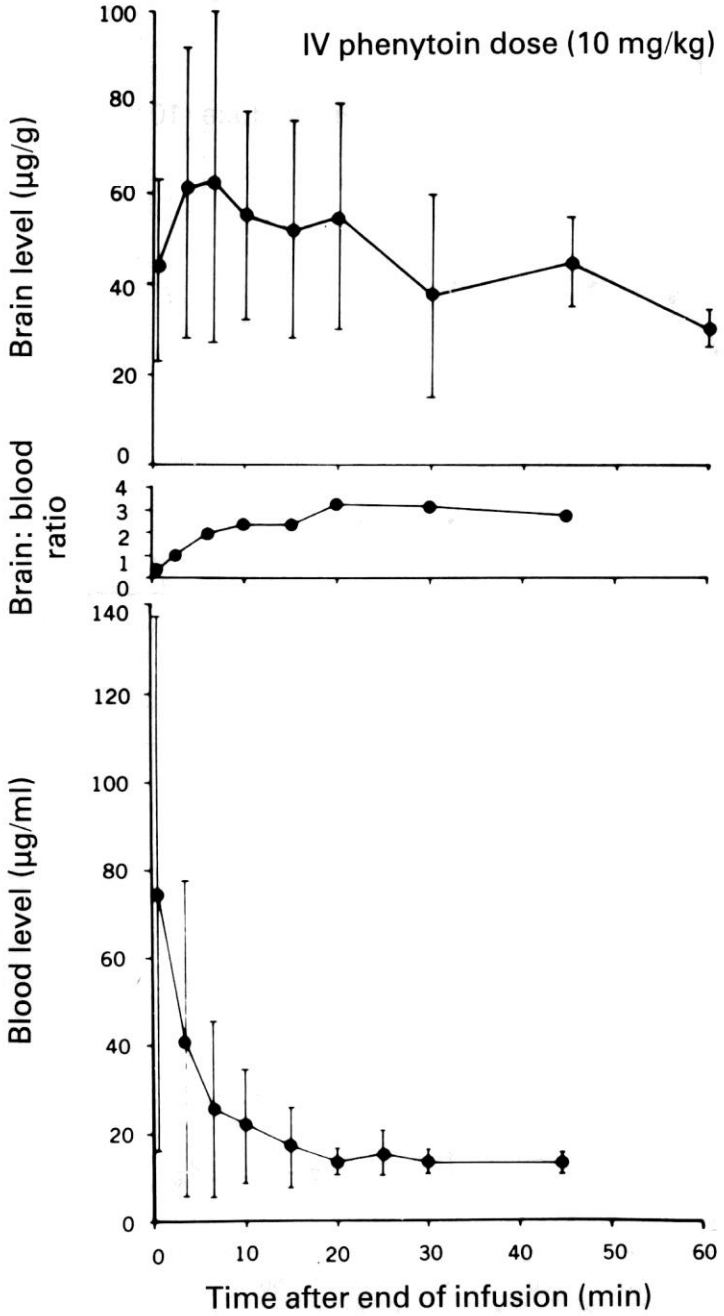
- Misure generali (funzione cardio-respiratoria, O_2 etc)
- 50 ml di soluzione di Glucosio al 50% (in presenza di ipoglicemia) + 250 mg di tiamina i.m. (stati di denutrizione, alcoolismo)
- **Lorazepam** e.v. 4 mg (0.1 mg/kg età ped.) in bolo (vel. max. 2 mg/min) (possibile ripetere dopo 10 min)

  oppure

  Diazepam e.v. 10-20 mg (0.25-0.5 mg/kg età ped.) in bolo (vel. max. 2-5 mg/min)
- Pari efficacia e rapidità d'azione, ma il **lorazepam ha una maggiore durata d'azione** (Leppik 1983, Andermann 1992)

- Uso sempre più comune di **Midazolam** i.m. 5-10 mg o e.v. 0.1-0.3 mg/kg

(*c*)


IV phenytoin dose (10 mg/kg)
Brain level (µg/g)
100
80
60
40
20
0
Brain: blood ratio
4
3
2
1
0
Blood level (µg/ml)
140
120
100
80
60
40
20
0
0
10
20
30
40
50
60
Time after end of infusion (min)

Timing Is Everything: Where Status Epilepticus Treatment Fails

Chloe E. Hill, MD,[1,2] Alomi O. Parikh, BA,[1] Colin Ellis, MD,[1]
Jennifer S. Myers, MD,[2,3] and Brian Litt, MD[1,4]

ANN NEUROL 2017;82:155–165

TABLE 5. Proposed Future Directions

Problem	Solutions
Minority of patients receive treatment before arrival in the hospital	Develop more effective, user-friendly methods for family and caregivers to administer rescue medication
Journey to hospital is often prolonged	Outfit paramedics with the capability to deliver second-line therapy or early polytherapy
Unreliable administration and dosage of benzodiazepines as the first-line agent	Simplify and clarify recommended first-line dosing Create an explicit single, continuous protocol bridging prehospital to in-hospital treatment
Delays in diagnosis of status epilepticus	Improve the education of emergency personnel and family members Advance technologies for EEG diagnosis in the field and/or immediately upon arrival to the ED
Unclear relationship between treatment nonadherence and patient outcome	Establish and employ standard quality indicators of treatment adherence (timing, dose, sequence) Adopt consistent clinical outcomes, covariate considerations, and definitions of status epilepticus
Difficult to retrospectively assess seizure duration and clinical decision making	Collect patient data in real-time through technology innovation
Limited and laborious data collection	Innovate data abstraction and visualization tools Encourage reporting as performance measures
Health system and institution-specific factors impact protocol adherence	Apply quality improvement methodology to explore the local context and then implement responsive, targeted countermeasures

Timing Is Everything: Where Status Epilepticus Treatment Fails

Chloe E. Hill, MD,[1,2] Alomi O. Parikh, BA,[1] Colin Ellis, MD,[1]
Jennifer S. Myers, MD,[2,3] and Brian Litt, MD[1,4]

Status epilepticus is an emergency; however, prompt treatment of patients with status epilepticus is challenging. Clinical trials, such as the ESETT (Established Status Epilepticus Treatment Trial), compare effectiveness of antiepileptic medications, and rigorous examination of effectiveness of care delivery is similarly warranted. We reviewed the medical literature on observed deviations from guidelines, clinical significance, and initiatives to improve timely treatment. We found pervasive, substantial gaps between recommended and "real-world" practice with regard to timing, dosing, and sequence of antiepileptic therapy. Applying quality improvement methodology at the institutional level can increase adherence to guidelines and may improve patient outcomes.

ANN NEUROL 2017;82:155–165

Timing Is Everything: Where Status Epilepticus Treatment Fails

Chloe E. Hill, MD,[1,2] Alomi O. Parikh, BA,[1] Colin Ellis, MD,[1]
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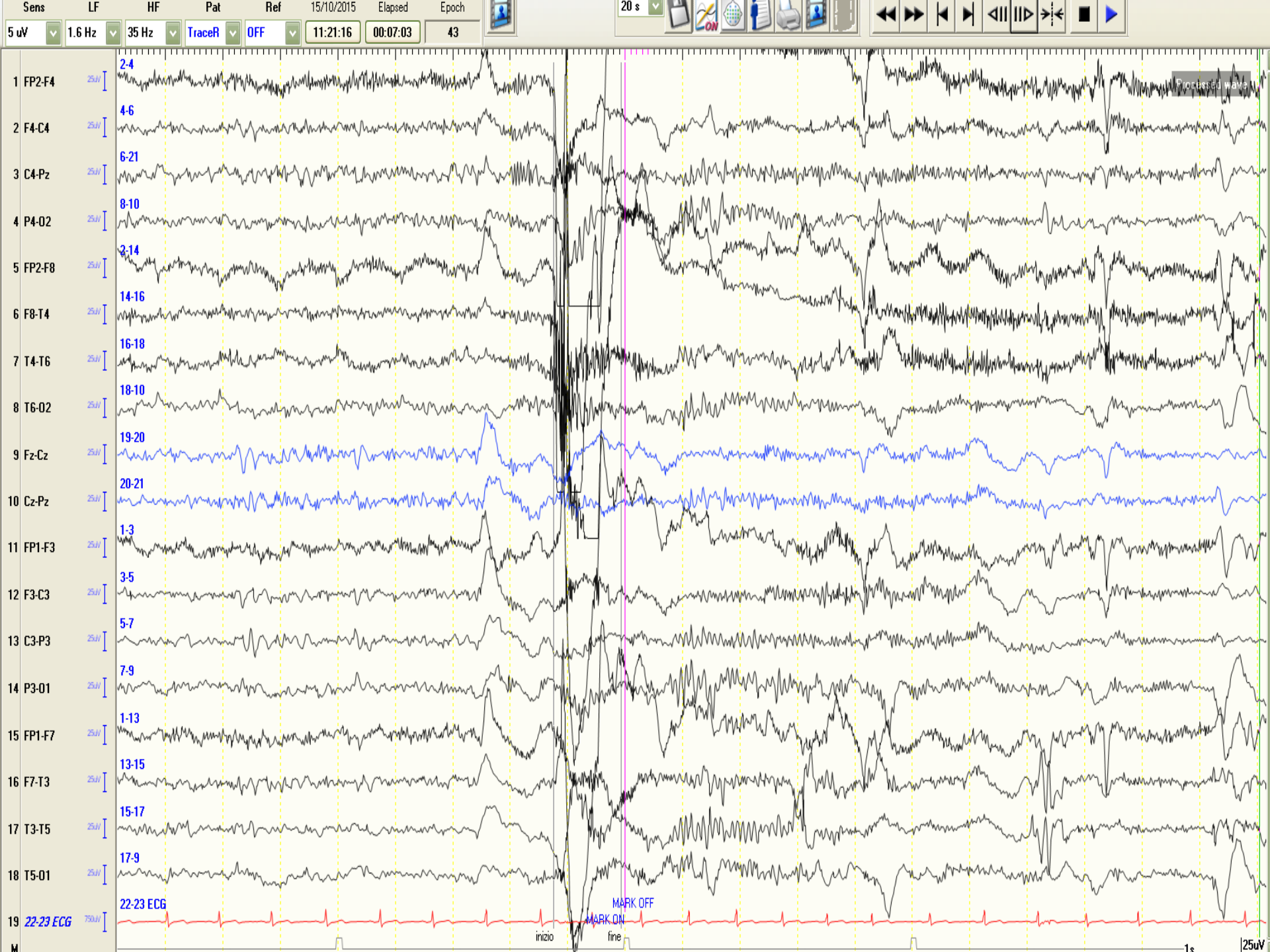
ANN NEUROL 2017;82:155–165

TABLE 1. Time-Related Deviations From Protocol

Citation	Patient Population	Method	Presentation of Included Patients	Delay to First-Line Therapy	Delay to Second-Line Therapy	Delay to Third-Line Therapy
Pellock et al. (2004)[29]	889 adults and children with SE at multiple hospitals in the US	Prospective database	Sz ≥30 min	>30 min for 58% (520/889) of pts; >60 min for 29% (256/889) of pts		
Eriksson et al. (2005)[31]	157 children with convulsive sz in the ED or pediatric ICU at an academic hospital in Finland	Retrospective review	Convulsive sz ≥5 min	>30 min for 17% (26/157) of pts		
Lewena et al. (2009)[23]	542 episodes in 467 children with convulsive sz in the ED of eight hospitals in Australia and New Zealand	Retrospective review	Motor sz activity >10 min		Median 24 min from hospital presentation (IQR, 15–36 min)	Median 45 min from hospital presentation (IQR, 25–68 min)
Hillman et al. (2013)[21]	109 consecutive visits in 100 adults with SE in the ED at an academic hospital in Finland	Retrospective review	Sz ≥30 min or recurring szs without return to baseline in between	Median 70 min for out-of-hospital treatment		
Kämppi et al. (2013)[33]	82 adults with SE in the ED at an academic hospital in Finland	Retrospective review	Continuous sz ≥30 min, recurrent szs without return of consciousness, or >4 szs within 60 min	Median 35 min (range 0 min–77 h 5 min)	Median 3 h (range 30 min –77 h 5 min)	Median 2 h 55 min (range 0 min –81 h 45 min)
Rantsch et al. (2013)[30]	167 episodes in 118 adults with SE seen by neurology at an academic hospital in Germany	Retrospective review	Continuous sz ≥5 min or ≥2 discrete szs with incomplete return to baseline in between	>30 min for 61% (99/162) of pts		
Rossetti et al. (2013)[36]	263 episodes in 225 adults with SE at an academic center in Switzerland	Prospective data set	Continuous sz >5 min or repeated szs without return to baseline in between	>60 min for 62% (139/225) of pts		
Seinfeld et al. (2014)[22]	179 children with febrile (convulsive) SE at five academic hospitals in the US	Prospective observation	Sz ≥30 min or a series of szs without full recovery in between lasting ≥30 min	Median 30 min (IQR, 35; range 1–175 min)		
Ferlisi et al. (2015)[35]	488 children and adults with refractory SE in an ICU, multinational	Online registry dataset	Refractory SE with initiation of anesthetic agent in the ICU	>60 min for 62% (282/453) of pts		>60 min for 84% (393/466) of pts
Kämppi et al. (2015)[34]	70 adults with generalized convulsive SE in the ED at an academic hospital in Finland	Retrospective review	≥1 convulsive sz within (a) continuous sz ≥30 min, (b) recurrent szs without return of consciousness, or (c) >4 szs within 60 min irrespective of return of consciousness	Median 30 min (range 0 min–8 h 5 min)	Median 2 h 40 min (range 30 min –61 hours 54 min)	Median 2 h 38 min (range 0 min –66 h 20 min)
Sánchez Fernández et al. (2015)[27]	81 children with refractory convulsive SE at nine tertiary pediatric hospitals in the US	Prospective observation	Focal or generalized convulsive szs at onset with (a) failure of ≥2 AEDs, or (b) initiation of continuous AED infusion	Median 30 min (IQR 6–70 min)	Median 69 min (IQR 40–120 min)	Median 180 min (IQR 120–645 min)
Cheng et al. (2016)[32]	151 adults treated for SE at an academic hospital in the US	Retrospective review	≥5 min of (a) continuous clinical and/or electrographical sz activity, or (b) recurrent szs without recovery in between	>30 min for 64% (97/151) of pts		

SE = status epilepticus; US = United States; sz = seizure; min = minute(s); pts = patients; ED = emergency department; ICU = intensive care unit; IQR = interquartile range; h = hour(s); EEG = electroencephalogram; AED = antiepileptic drug.


Sens
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Epoch
5 uV
1.6 Hz
35 Hz
TraceR
OFF
11:21:16
00:07:03
43
20 s
1 FP2-F4
2 F4-C4
3 C4-Pz
4 P4-O2
5 FP2-F8
6 F8-T4
7 T4-T6
8 T6-O2
9 Fz-Cz
10 Cz-Pz
11 FP1-F3
12 F3-C3
13 C3-P3
14 P3-O1
15 FP1-F7
16 F7-T3
17 T3-T5
18 T5-O1
19 22-23 ECG
2-4
4-6
6-21
8-10
2-14
14-16
16-18
18-10
19-20
20-21
1-3
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5-7
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22-23 ECG
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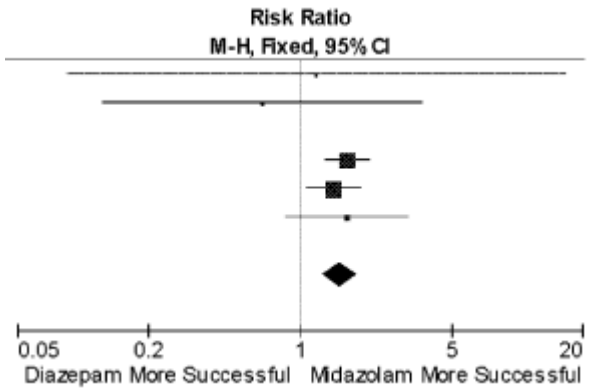
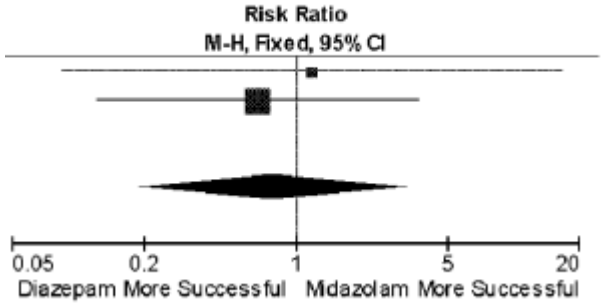
Midazolam Versus Diazepam for the Treatment of Status Epilepticus in Children and Young Adults: A Meta-analysis

Jason McMullan, MD, Comilla Sasson, MD, Arthur Pancioli, MD, and Robert Silbergleit, MD





For seizure cessation:

midazoalm by any route was superior to diazepam by any route

non-IV midazolam was as effective as IV diazepam