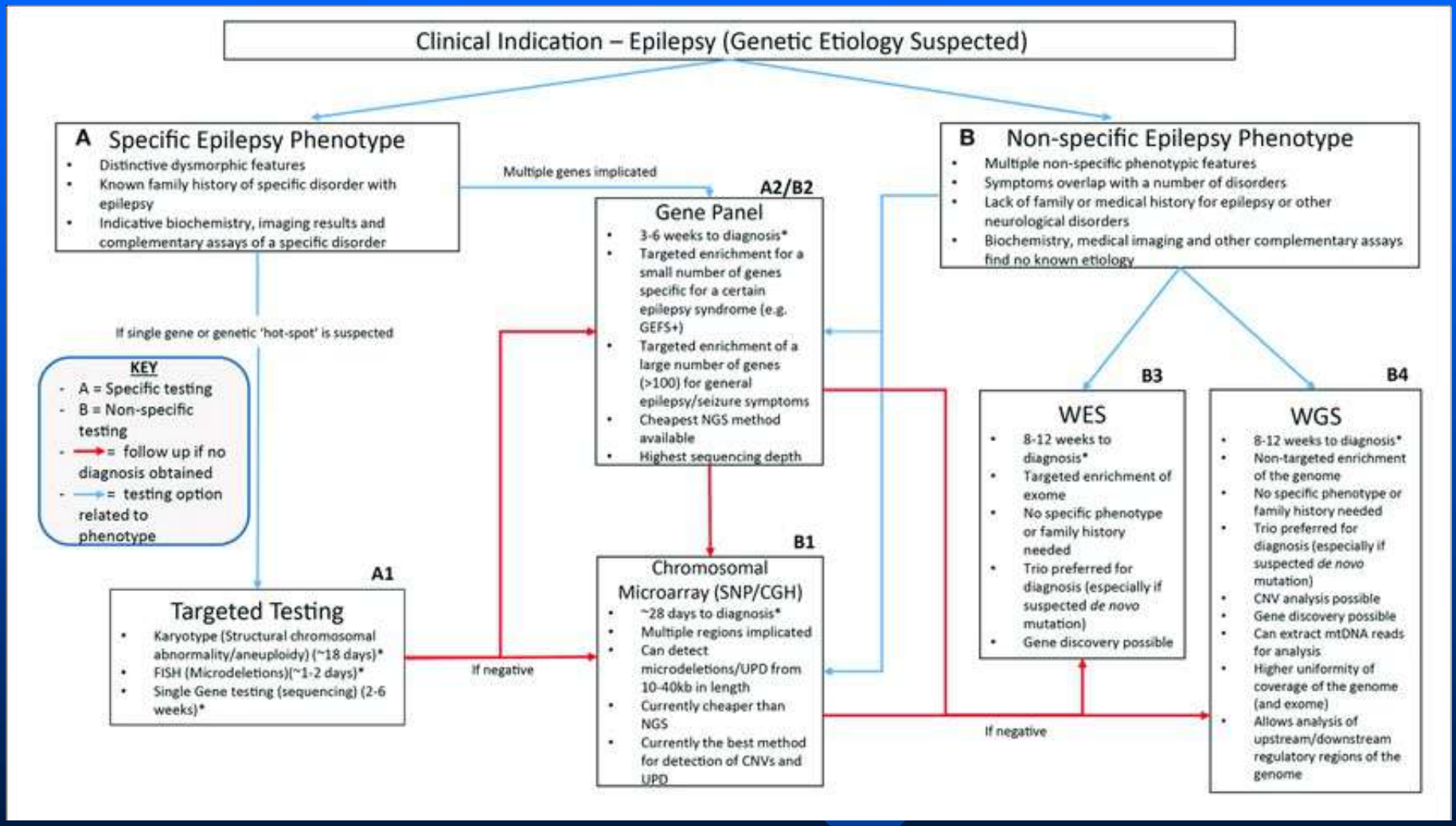
Le sindromi epilettiche da causa genetica a esordio in età evolutiva

Maurizio Elia

U.O.C di Neurologia e Neurofisiopatologia Clinica e Strumentale

IRCCS "Associazione Oasi Maria SS", Troina (EN)

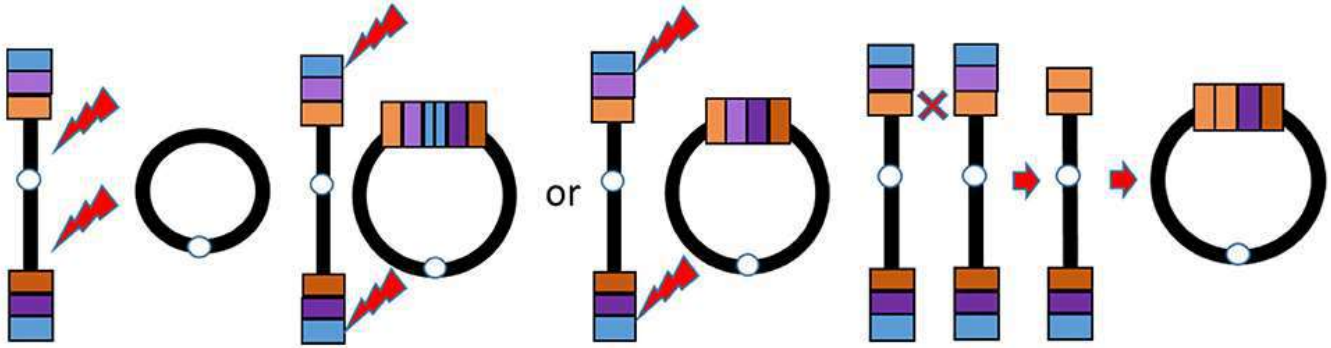
melia@oasi.en.it



(Xue et al., 2015)

Sindrome del cromosoma 20 ad anello

- Perlopiù sporadici
- Circa 200 casi riportati finora (Peron et al., 2020)
- Spesso mosaicismi
- >90% dei casi con crisi
- D.I. di grado variabile, assenza di segni dismorfici maggiori, rare anomalie cardiache o urogenitali;
- In alcuni casi evidenza di alterazioni a carico del lobo frontale: RM (3 casi, Takahashi et al., 1995; Inoue et al., 1997), SPECT (3 casi, Inoue et al., 1997)
- Ipoplasia del corpo calloso e del cervelletto (1 caso, de Mota Gomes et al., 2002)
- Uptake della[18F]fluoro-l-DOPA significativamente ridotta nei nn. della base (putamen e caudato) (Biraben et al., 2004)

Mechanism	Break and fusion	Telomere/subtelomere junction	inv dup del rearrangement
Predisposing event	Double-strand breaks (after exposure to ultraviolet radiation)	Critical shortening of telomere repeats [Surace et al. (9)]	U-type recombination. During meiosis I parental chromosomes may recombinate at microhomology regions. The result is a dicentric chromosome that undergoes asymmetric breakage with consequent formation of a monocentric linear rearranged chromosome with a terminal deletion and an inverted duplication
Description	An inefficient DSBs repair with fusion of two unstable chromosome ends or fusion of an unstable chromosome end with the opposite telomeric end	Junction of telomeric or subtelomeric sequences of the p and q arms of the same chromosome	Fusion of a broken rearranged chromosome end (originated as the consequence of an intra-chromosomal U-type recombination) and the opposite arm of the same chromosome
Genetic imbalances on the resulting RC	Loss of genetic material on the p and/or q arm whose extent depends on the distance between the break and the telomere	No loss of genetic material is present, with the exception of the common telomeric sequences that may be missing in some cases	Variable combination of losses and gains within the arm involved in the U-type recombination
Schematic representation			
Examples in literature	r(20): Conlin et al. (10) (pts 22, 24, 26, and 28) r(3), r(10), r(13), r(15), r(18), r(22): Guilherme et al. (11) (pts 1–5, 8–11, 13,14)	r(20): Giardino et al. (12) r(20): Conlin et al. (10) (pts 1–21) r(14) and r(22): Guilherme et al. (11) (pts 7, 12) r(17): Surace et al. (9)	r(20): Conlin et al. (10) (pts 26 and 27) r(13): Guilherme et al. (11) (pt 6) r(7) and r(13): Rossi et al. (13)

For each mechanism a schematic description is provided for the normal (left) linear chromosome and the derived RC (right). Red flash: break event; red cross: U-type exchange event; light blue boxes: common telomeric repeats; violet boxes: specific p/q arm subtelomeric sequences; brown boxes: inner arm specific sequences.

(Peron et al., 2020)

r(20) pathophysiology

1) Deletion of candidate genes (CHRNA4, KCNQ2, DNAJC5) close to 20p and 20q telomeres
2) Epigenetic silencing of candidate genes near the telomeres
3) Deleterious effect of ring instability on cellular proliferation and function
4) Compensatory UPD

Sindrome del cromosoma 20 ad anello

- esordio delle crisi tra 1 mese e 21 anni di età
- stato di male non convulsivo (63%), crisi focali (31%), generalizzate tonico-cloniche (50%), assenze (25%), crisi notturne (9%) (Serrano-Castro et al., 2001)
- crisi scatenate da eventi emozionali (Roubertie et al., 1999) o da video-games (Takahashi et al., 1995)
- alla MEG, le crisi iniziano dalle regioni mesiali del lobo frontale (Tanaka et al., 2004)
- crisi generalmente intrattabili (VNS? Chawla et al., 2002)

r(20) seizures

1) **Nocturnal Seizures (Hyperkinetic or Hypermotor Seizures)** are characterized by waking up, staring, and mild tonic stiffening evolving into clonic movements of the face and of the extremities, followed by agitation and confusion (Augustijn et al., 2001; Elens et al., 2012; Radhakrishnan et al., 2012; Zambrelli et al., 2013)
2) **Subtle Nocturnal Seizures** are expressed as minimal motor activity, such as subtle stretching, turning, or rubbing movements (Augustijn et al., 2001)
3) **Seizures With Impaired Awareness** are characterized by unresponsiveness, staring and confusion, with or without oral or motor automatisms, frightened expression, and focal motor symptoms including head turning (Ville et al., 2006; Elens et al., 2012; Vignoli et al., 2016)

- Epilepsy in r(20) syndrome has an age dependent course. When epilepsy starts in childhood, very frequent nocturnal motor seizures or dyscognitive seizures associated with terrific hallucinations are the prominent manifestations, and often evolve into EE and NCSE; on the contrary, when epilepsy begins in adolescence the course is usually milder, with dyscognitive seizures and NCSE, but without cognitive decline

SM nel ring 20	SMNC
giornalmente o settimanalmente	sporadico
durata 10-50’ ritmo circadiano	durata > 60’
POL e P di alto voltaggio	PO atipiche
esordio SM = esordio crisi	SM dopo esordio crisi

Epilepsia, 39(9):942–951, 1998
Lippincott Williams & Wilkins, Philadelphia

Chromosome 20 Ring: A Chromosomal Disorder Associated with a Particular Electroclinical Pattern

Maria Paola Canevini, Vincenzo Sgro, *Orsetta Zuffardi, Raffaele Canger, ‡Romeo Carrozzo, §Elena Rossi, ‖David Ledbetter, †Fabio Minicucci, Aglaia Vignoli, Ada Piazzini, Loredana Guidolin, Amalia Saltarelli, and ¶Bernardo dalla Bernardina

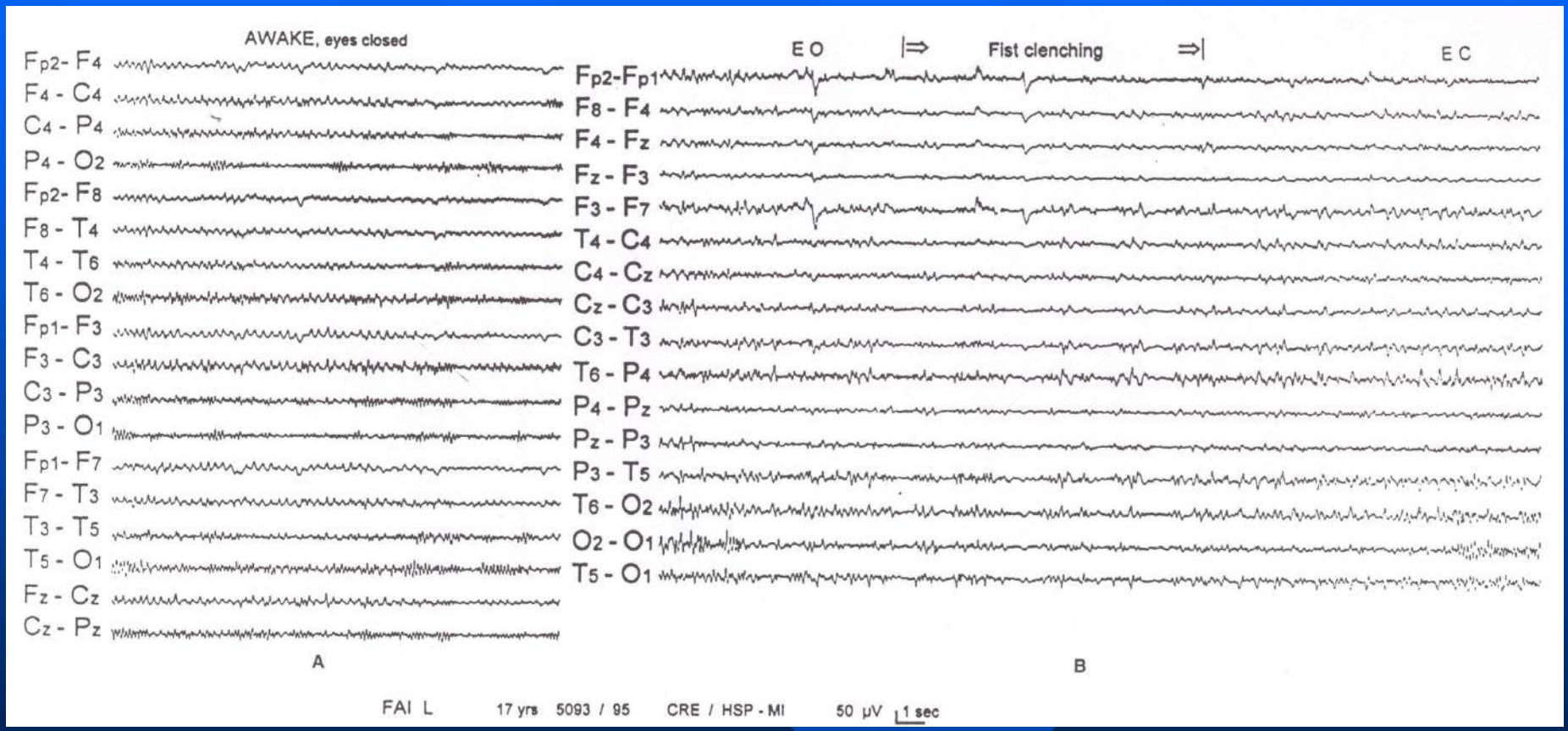
*Centro Regionale Epilessia, Ospedale San Paolo, "Università degli Studi," Milan; *Biologia Generale e Genetica Medica, "Università degli Studi," Pavia; †Neurofisiologia Clinica, Ospedale San Raffaele, Milan; ‡Servizio di Genetica Medica, Ospedale San Raffaele, Milan; §Laboratorio di Citogenetica, Ospedale San Raffaele, Milan; ‖Center for Medical Genetics, The University of Chicago, Chicago, Illinois, U.S.A.; and ¶Servizio di Neuropsichiatria Infantile, Policlinico Borgo Roma, "Università degli Studi," Verona, Italy*

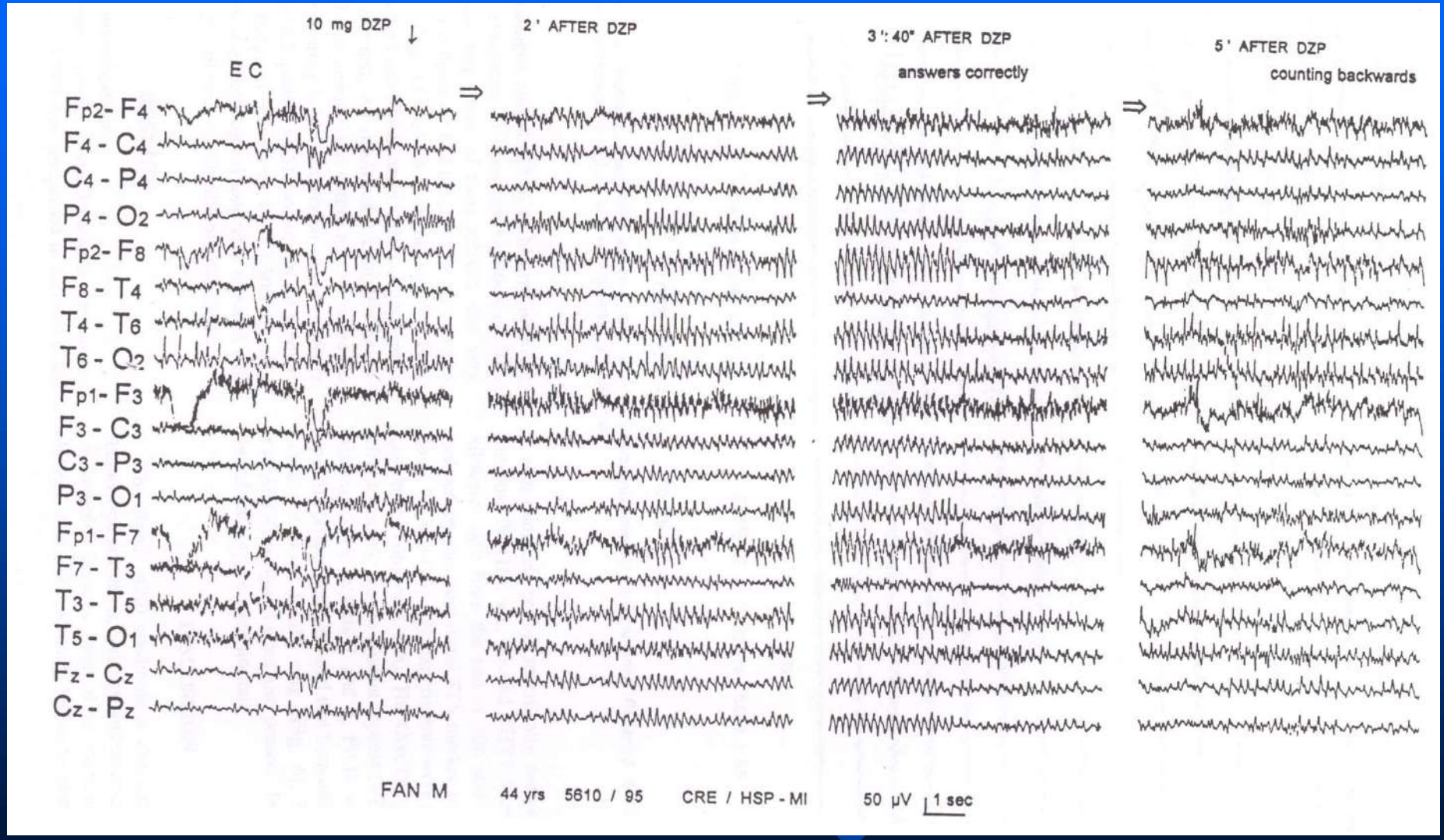
Summary: *Purpose:* The chromosome 20 ring [r(20)] is a rare chromosomal disorder without clear phenotypical markers. We describe the electroclinical pattern in a group of patients with r(20).

Methods: We observed 3 patients (a boy, patient 1; his mother, patient 2; and an unrelated man, patient 3), performing prolonged video-EEG and cytogenetic studies and fluorescent in situ hybridization (FISH) with chromosome-specific telomeric probes.

Results: All 3 patients had a very similar abnormal electroclinical pattern characterized by long bursts or trains of rhythmic theta waves, which were sharply contoured or had a notched appearance (with no detectable clinical correlate), and generalized spike waves (SW) associated with seizures of probable frontotemporal origin (SFT). In all 3 patients, the cytogenetic analysis of T lymphocytes showed mosaicism with a normal cell line and a second cell line with a chromosome 20, although the latter was little represented in patients 2 and 3. A few cells with a single chromosome 20 were also found. The same cytogenetic findings were confirmed in the lymphoblastoid cell line of patient 1 and in the fibroblasts of patient 3. FISH with chromosome-specific telomeric probes and TTAGGG sequences demonstrated the integrity of the ring chromosomes.

Conclusions: The clinical picture of these patients appears to be related to the instability of the r(20)-generating cells monosomic for chromosome 20 and is thus haploinsufficient for a gene. In these patients, the electroclinical pattern of theta waves (probably unrelated to epilepsy) and the SW and SFT, even with mild mental retardation (MR) or no MR and without dysmorphic features, suggest that the r(20) syndrome may be present. **Key Words:** Chromosome 20 ring syndrome—Molecular studies—Epilepsy—Electroencephalography—Adults.


AWAKE, eyes closed
Fp2- F4
F4 - C4
C4 - P4
P4 - O2
Fp2- F8
F8 - T4
T4 - T6
T6 - O2
Fp1- F3
F3 - C3
C3 - P3
P3 - O1
Fp1- F7
F7 - T3
T3 - T5
T5 - O1
Fz - Cz
Cz - Pz
A
E O
Fist clenching
E C
Fp2-Fp1
F8 - F4
F4 - Fz
Fz - F3
F3 - F7
T4 - C4
C4 - Cz
Cz - C3
C3 - T3
T6 - P4
P4 - Pz
Pz - P3
P3 - T5
T6 - O2
O2 - O1
T5 - O1
B
FAI L
17 yrs 5093 / 95
CRE / HSP - MI
50 µV
1 sec


10 mg DZP
2 ' AFTER DZP
3 ': 40" AFTER DZP
answers correctly
5 ' AFTER DZP
counting backwards
E C
Fp2- F4
F4 - C4
C4 - P4
P4 - O2
Fp2- F8
F8 - T4
T4 - T6
T6 - O2
Fp1- F3
F3 - C3
C3 - P3
P3 - O1
Fp1- F7
F7 - T3
T3 - T5
T5 - O1
Fz - Cz
Cz - Pz
FAN M
44 yrs
5610 / 95
CRE / HSP - MI
50 µV
1 sec

Epilepsia, 50(11):2420–2427, 2009
doi: 10.1111/j.1528-1167.2009.02176.x

FULL-LENGTH ORIGINAL RESEARCH

Ring chromosome 20 syndrome: A link between epilepsy onset and neuropsychological impairment in three children

*Aglaia Vignoli, *Mario Paola Canevini, †Francesca Darra, ‡Lorita La Selva, †Elena Fiorini, *Ada Piazzini, †Francesca Lazzarotto, §Claudio Zucca, and †Bernardo Dalla Bernardina

*Epilepsy Centre, San Paolo Hospital, University of Milan, Milan, Italy; †Child Neuropsychiatry Unit, University of Verona, Verona, Italy; ‡Pediatric Epilepsy Service, San Paolo Hospital, Bari, Italy; and §"La Nostra Famiglia" Institute–Bosisio Parini, Lecco, Italy

SUMMARY

Purpose: Ring chromosome 20 [r(20)] syndrome is a well-defined chromosomal disorder characterized by epilepsy, mild-to-moderate mental retardation, and lack of recognizable dysmorphic features. Epilepsy is often the most important clinical manifestation of the syndrome, even if its appearance is not constantly precocious. Seizures are frequently drug resistant.

Methods: We describe three children with [r(20)] syndrome in whom the onset of epilepsy (age at onset range: 4 years and 6 months to 9 years and 4 months) determined a kind of epileptic status (age at onset range: 6 years and 10 months to 9 years and 8 months) with dramatic neuropsychological deterioration. This epileptic status lasted for several months because of refractoriness to most antiepileptic drugs (AEDs), but it was treated successfully with a combination of valproate and lamotrigine in two children.

Results: As soon as seizures stopped, the children showed prompt recovery with partial restoration of the neuropsychological impairment.

Conclusion: This clinical picture can be described as abrupt epileptic encephalopathy.

KEY WORDS: Ring 20 syndrome, Epilepsy, Childhood, Epileptic encephalopathy.

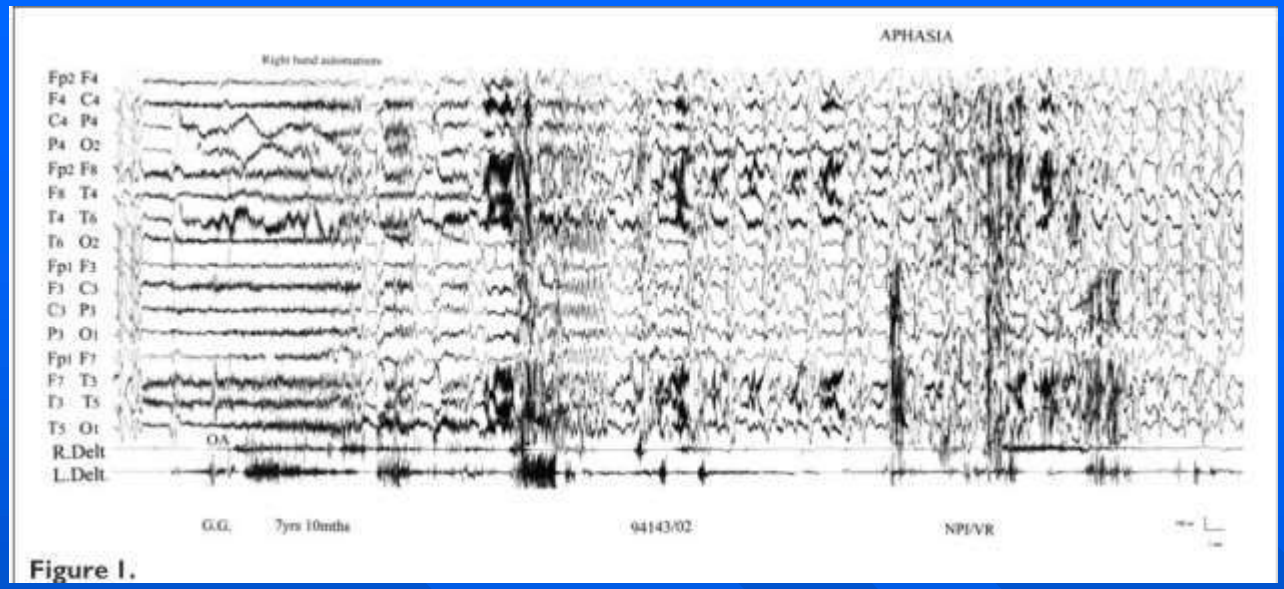
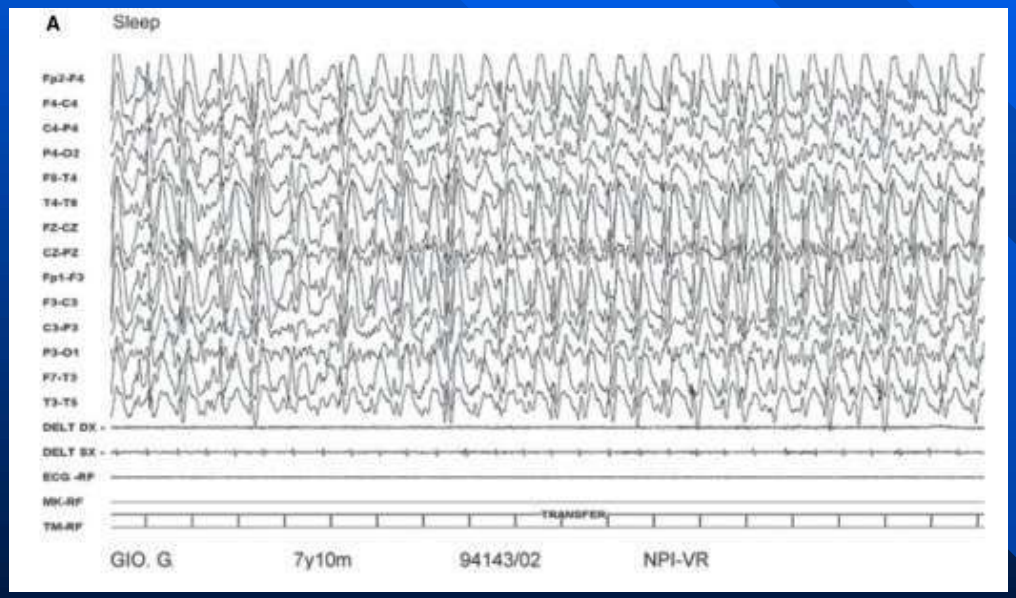
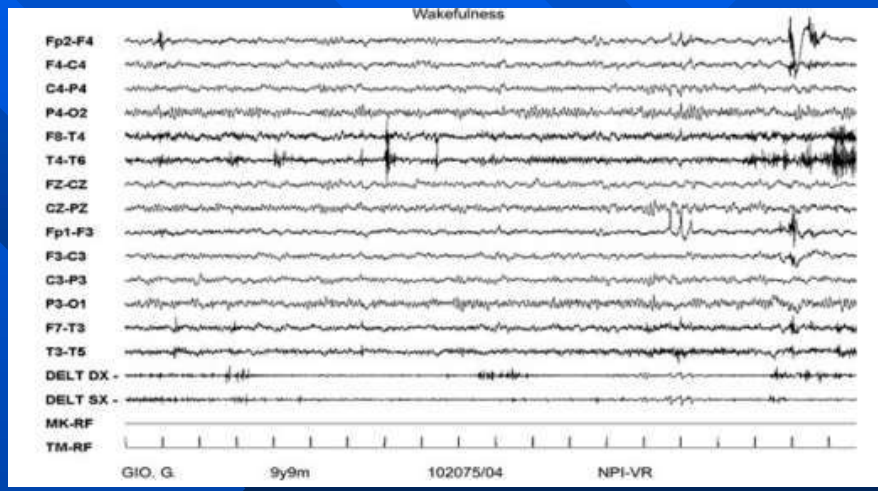

APHASIA
Right hand automatisms
Fp2 F4
F4 C4
C4 P4
P4 O2
Fp2 F8
F8 T4
T4 T6
T6 O2
Fp1 F3
F3 C3
C3 P3
P3 O1
Fp1 F7
F7 T3
T3 T5
T5 O1
R.Delt
L.Delt
O.A
G.G. 7yrs 10mths 94143/02 NPI/VR

Figure 1.


A
Sleep
Fp2-F4
F4-C4
C4-P4
P4-O2
F8-T4
T4-T6
FZ-CZ
CZ-PZ
Fp1-F3
F3-C3
C3-P3
P3-O1
F7-T3
T3-T5
DELT DX -
DELT SX -
ECG -RF
MK-RF
TM-RF
TRANSFER
GIO. G 7y10m 94143/02 NPI-VR


Wakefulness
Fp2-F4
F4-C4
C4-P4
P4-O2
F8-T4
T4-T6
FZ-CZ
CZ-PZ
Fp1-F3
F3-C3
C3-P3
P3-O1
F7-T3
T3-T5
DELT DX -
DELT SX -
MK-RF
TM-RF
GIO. G. 9y9m 102075/04 NPI-VR

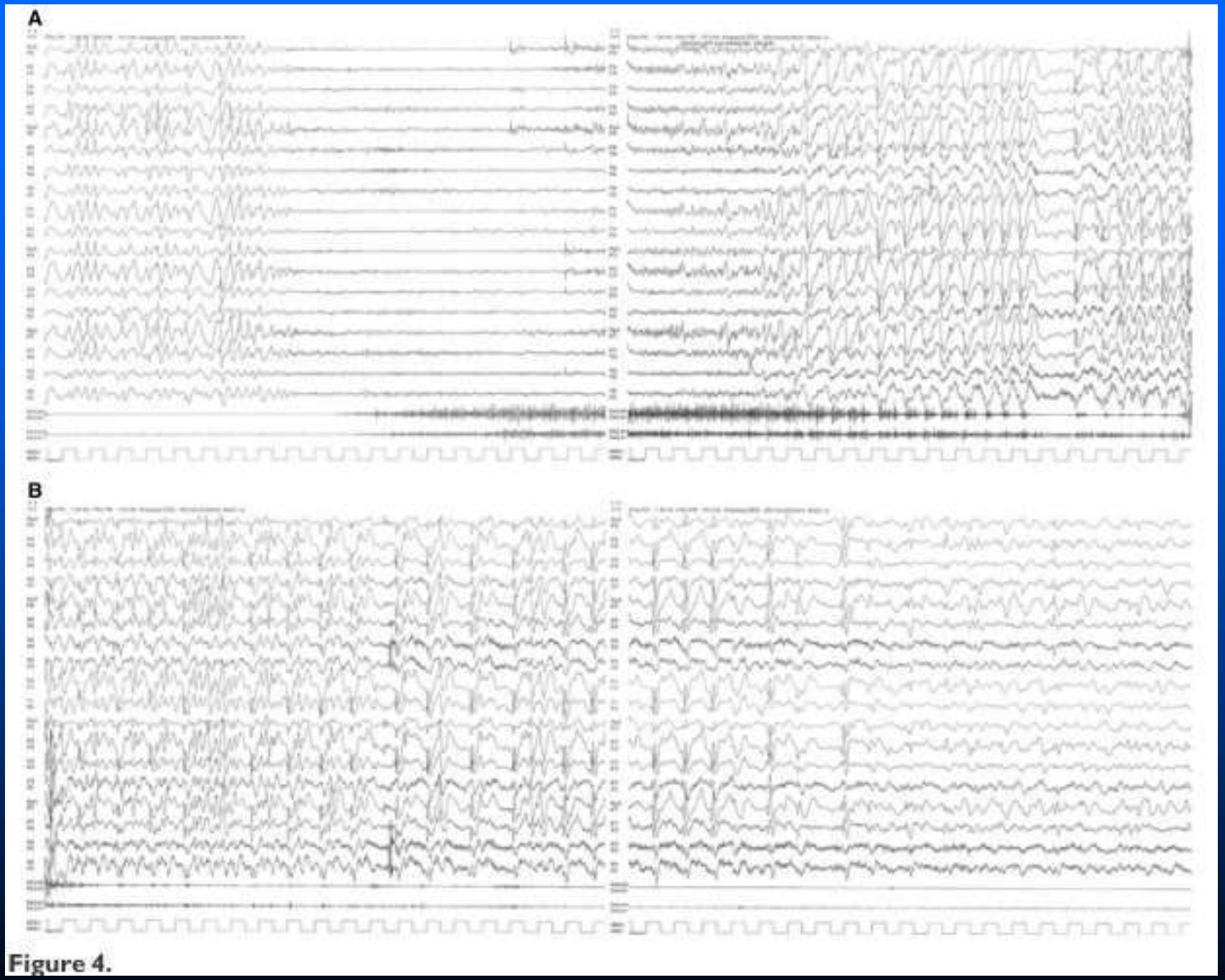


Figure 4.

Epilepsy & Behavior 45 (2015) 155–163

Contents lists available at ScienceDirect

Epilepsy & Behavior

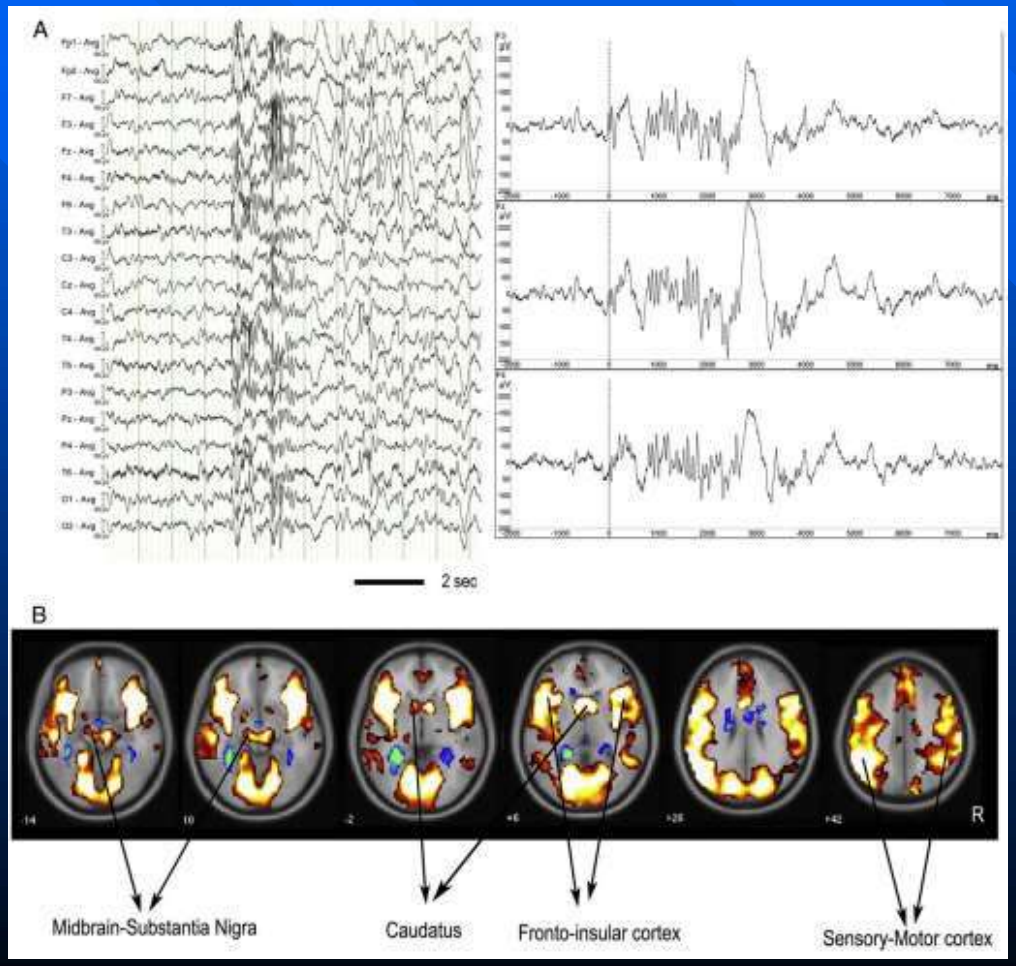
journal homepage: www.elsevier.com/locate/yebeh

Review

Emerging neuroimaging contribution to the diagnosis and management of the ring chromosome 20 syndrome

Anna Elisabetta Vaudano [a,b], Andrea Ruggieri [a], Aglaia Vignoli [c], Maria Paola Canevini [c], Stefano Meletti [a,b,*]

[a] Department of Biomedical, Metabolic, and Neural Science, University of Modena and Reggio Emilia, Modena, Italy
[b] N.O.C.S.A.E. Hospital, ASL Modena, Italy
[c] Department of Health Sciences, Epilepsy Centre, San Paolo Hospital, University of Milan, Italy

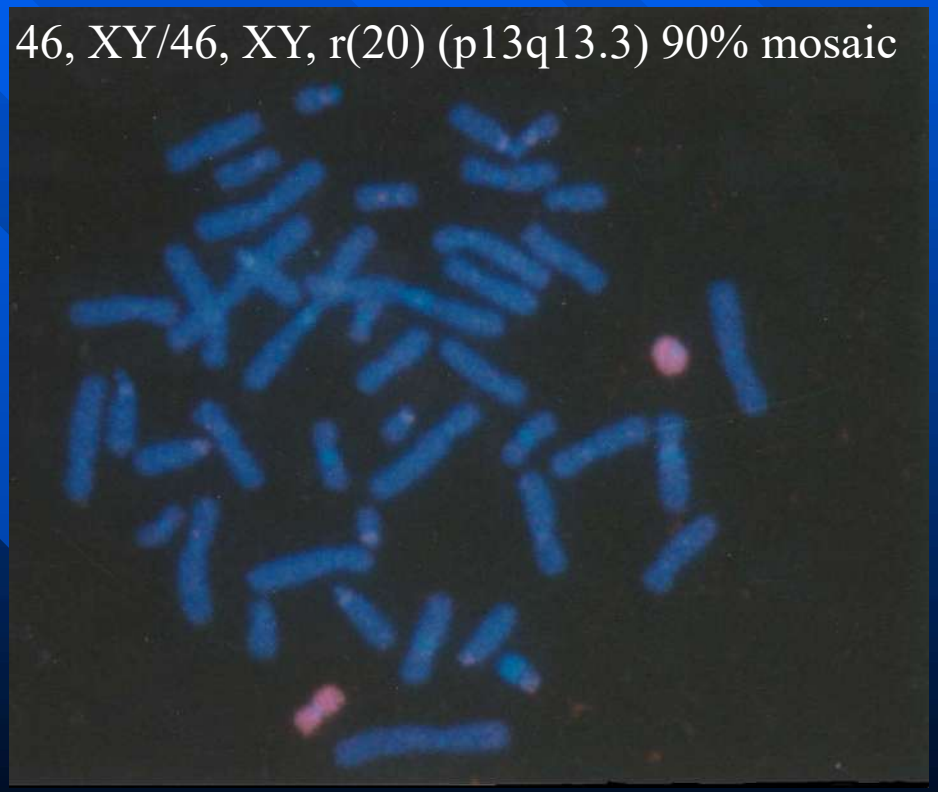


CASE 16

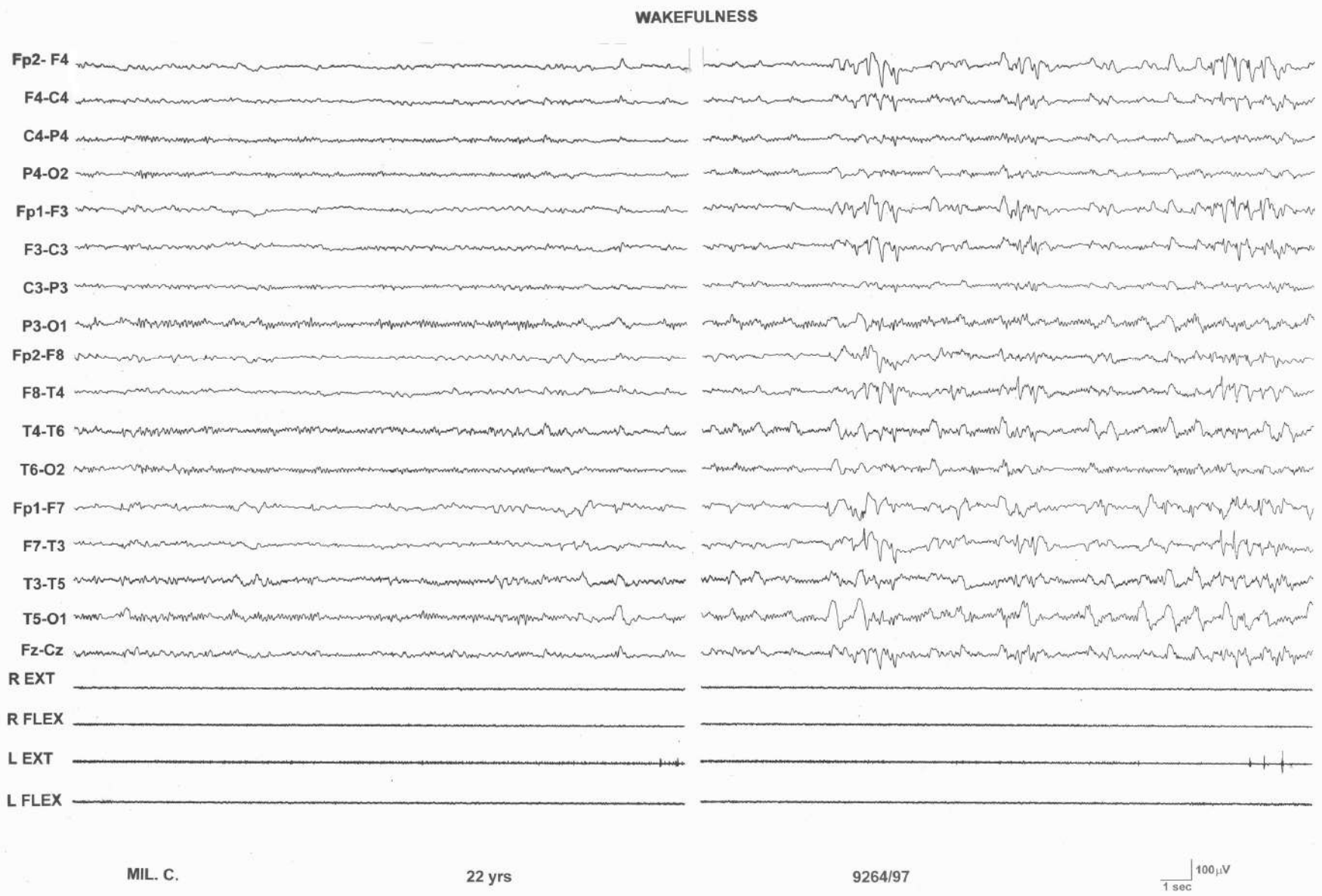
2009

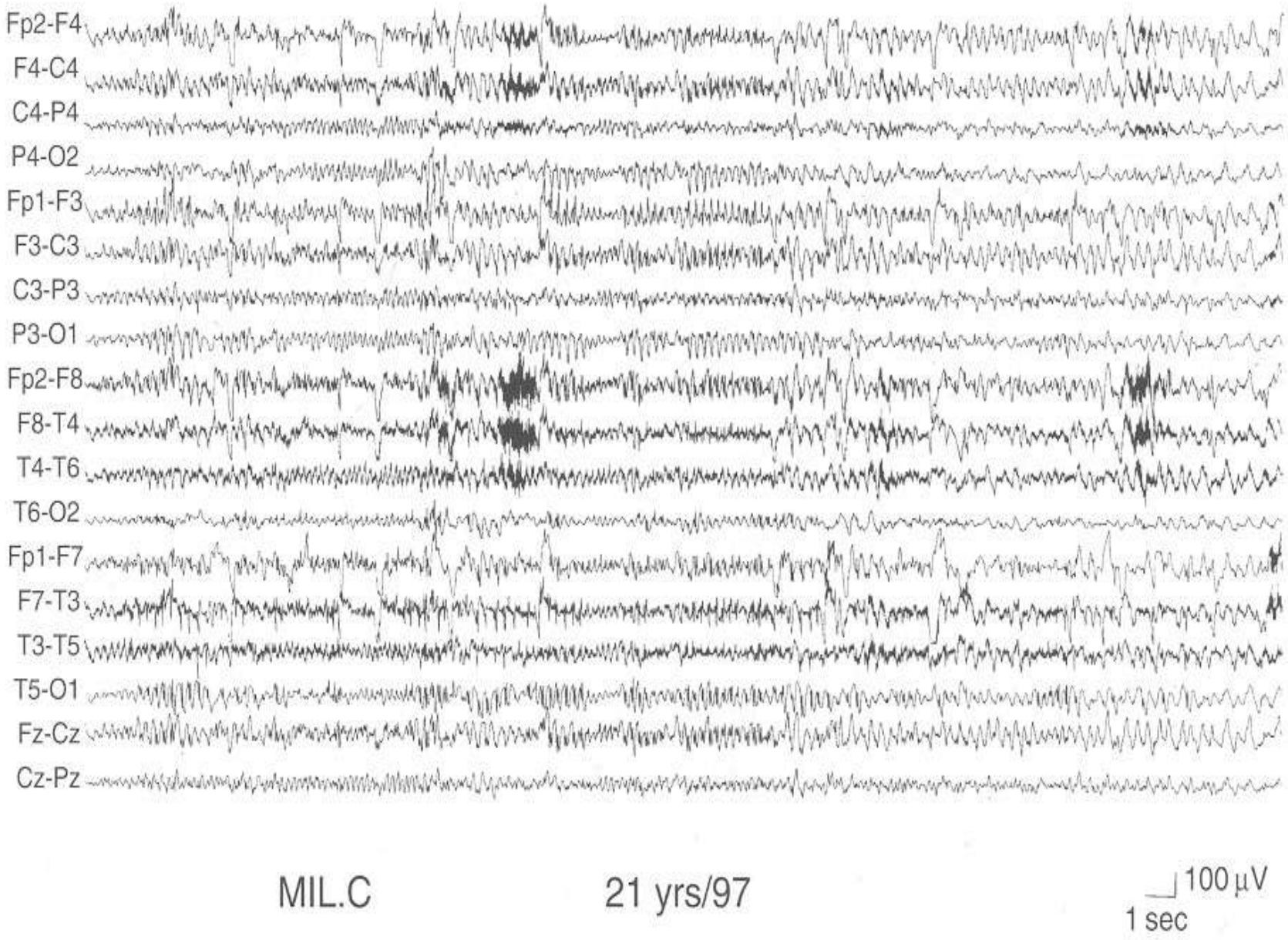
Non-convulsive Status Epilepticus and Frontal Lobe Seizures in a Patient with a Chromosome Abnormality

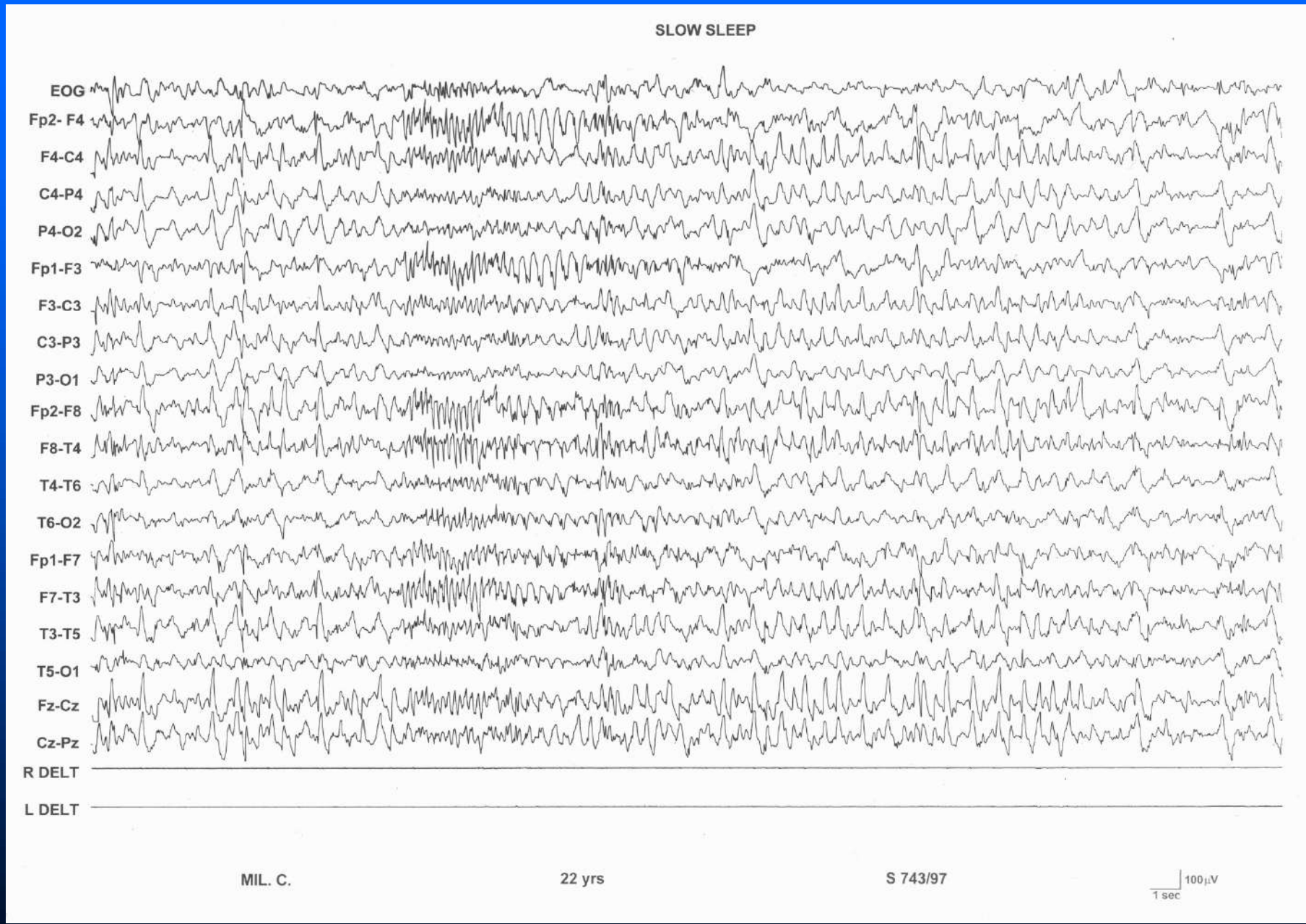
46, XY/46, XY, r(20) (p13q13.3) 90% mosaic

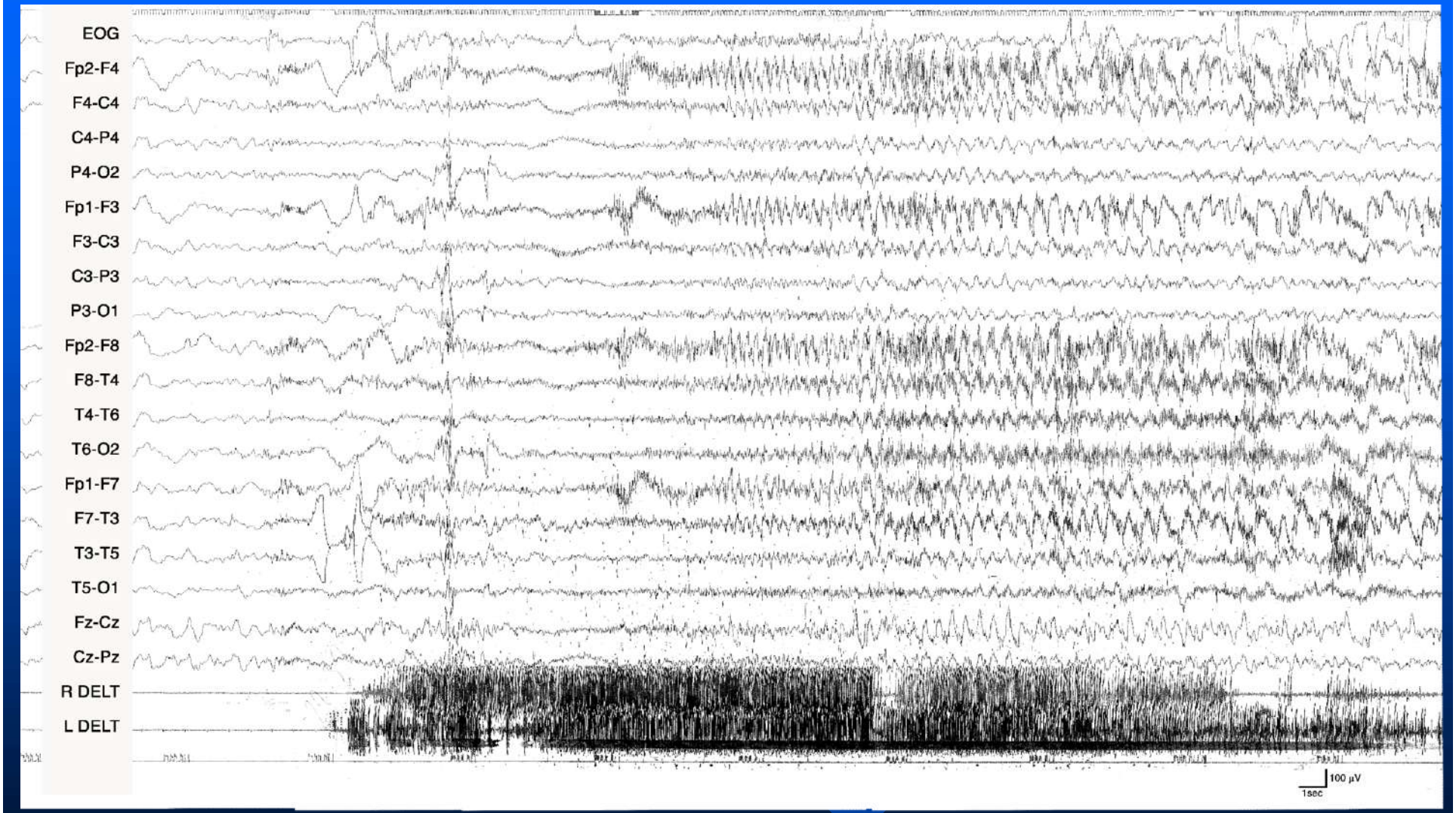


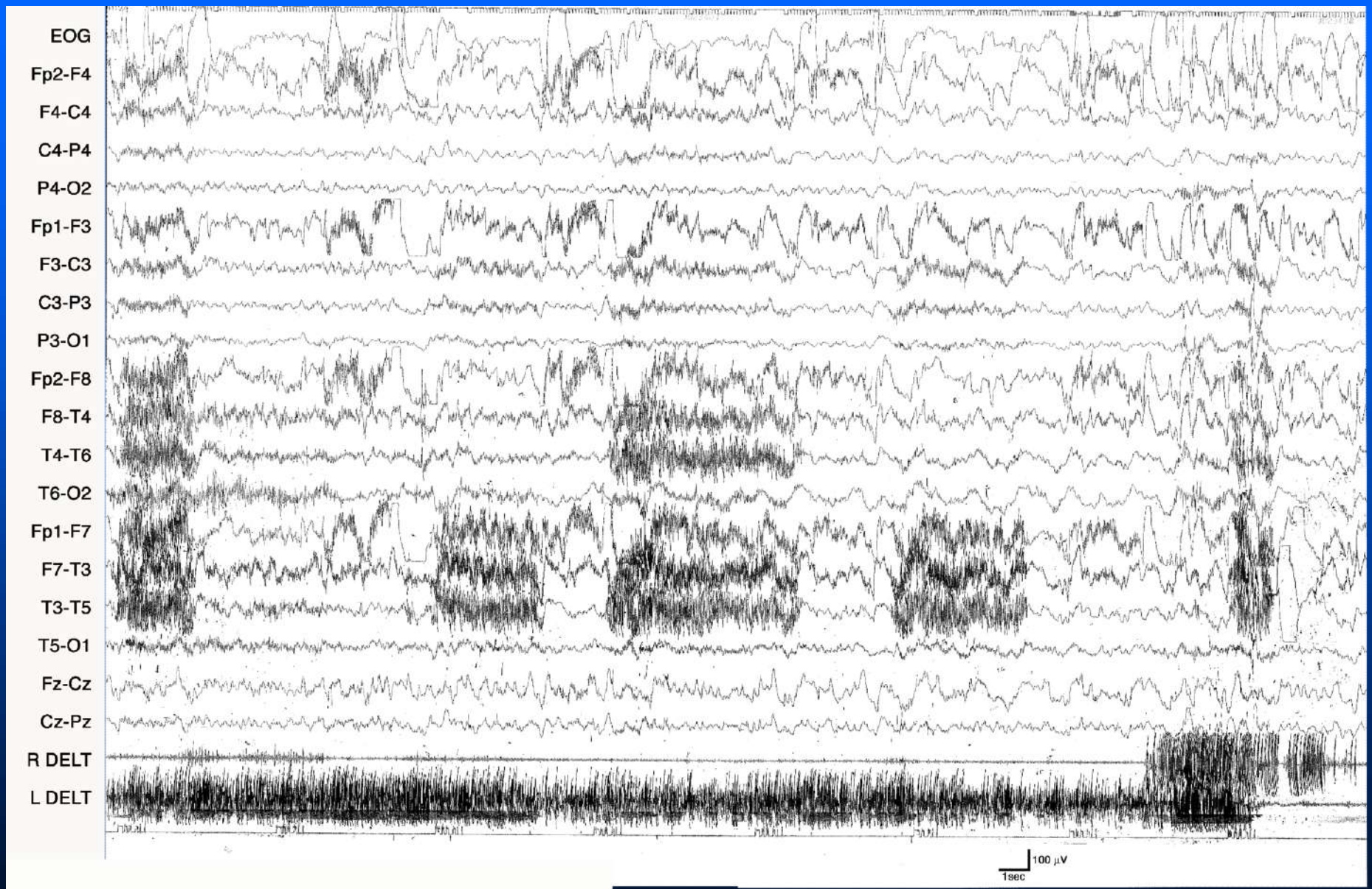
- A 27-year-old man
- Mild intellectual disability
- No neurological signs, normal brain MRI
- His mother suffered from epilepsy and took AEDs during pregnancy
- First seizure at 3 years of age: myoclonic jerks of the upper limbs
- The seizures increased in frequency until they occurred many times a day during infancy; over time the seizures changed and began to include impaired consciousness, pallor, abdominal pain, the expression of fear, mydriasis, motor automatisms, and complex visual hallucinations; they often had a long duration and occurred in clusters
- Other seizures were characterized by a staring gaze, diffuse hypertonia, and clonic jerks of the upper limbs
- Polytherapy with PB, CBZ, VPA, PHT, LTG had little effect
- Behavioral disturbances with frequent and sudden outbursts of rage
- Daily episodes of non-convulsive status epilepticus occurred, with clouding of consciousness, unresponsiveness to stimuli, crying or expression of terror, gestures, and verbal automatisms
- He was also having several focal seizures at night that were characteristic of frontal lobe onset

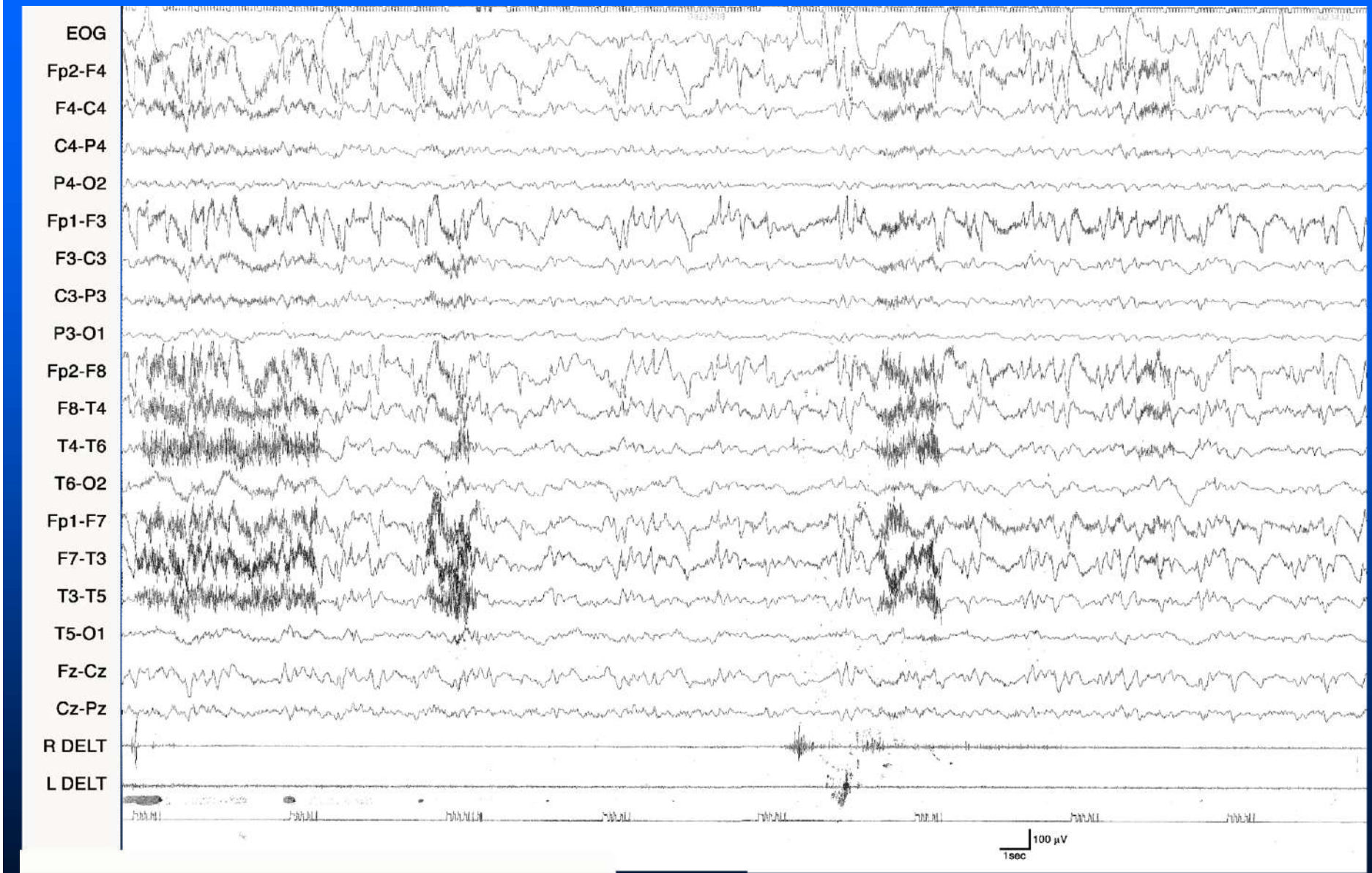

WAKEFULNESS
Fp2- F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fz-Cz
R EXT
R FLEX
L EXT
L FLEX
MIL. C.
22 yrs
9264/97
100 µV
1 sec

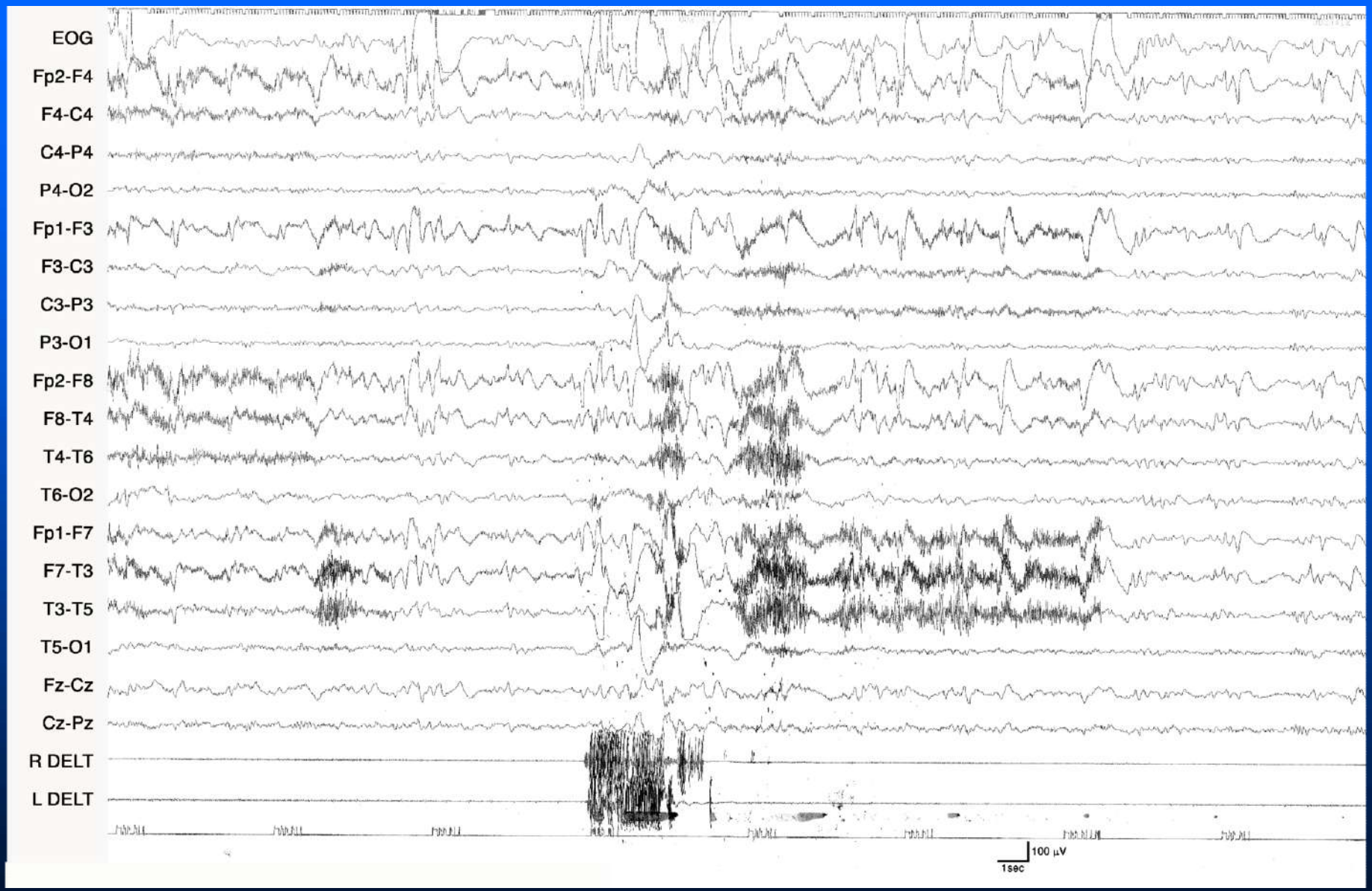

Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fz-Cz
Cz-Pz
MIL.C
21 yrs/97
100 µV
1 sec

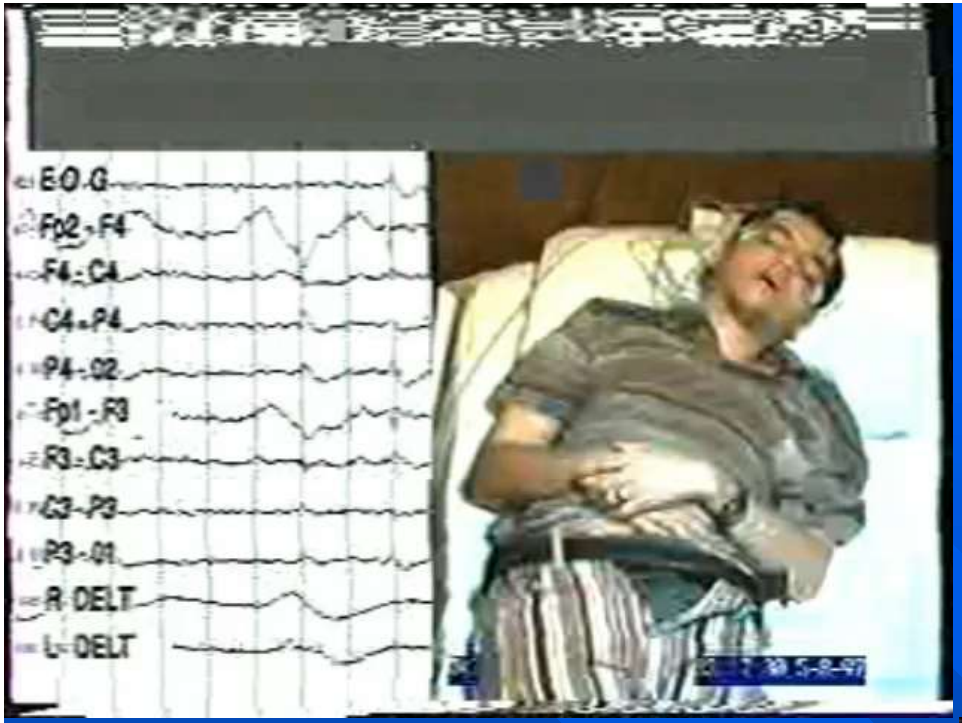

SLOW SLEEP
EOG
Fp2- F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fz-Cz
Cz-Pz
R DELT
L DELT
MIL. C.
22 yrs
S 743/97
100µV
1 sec

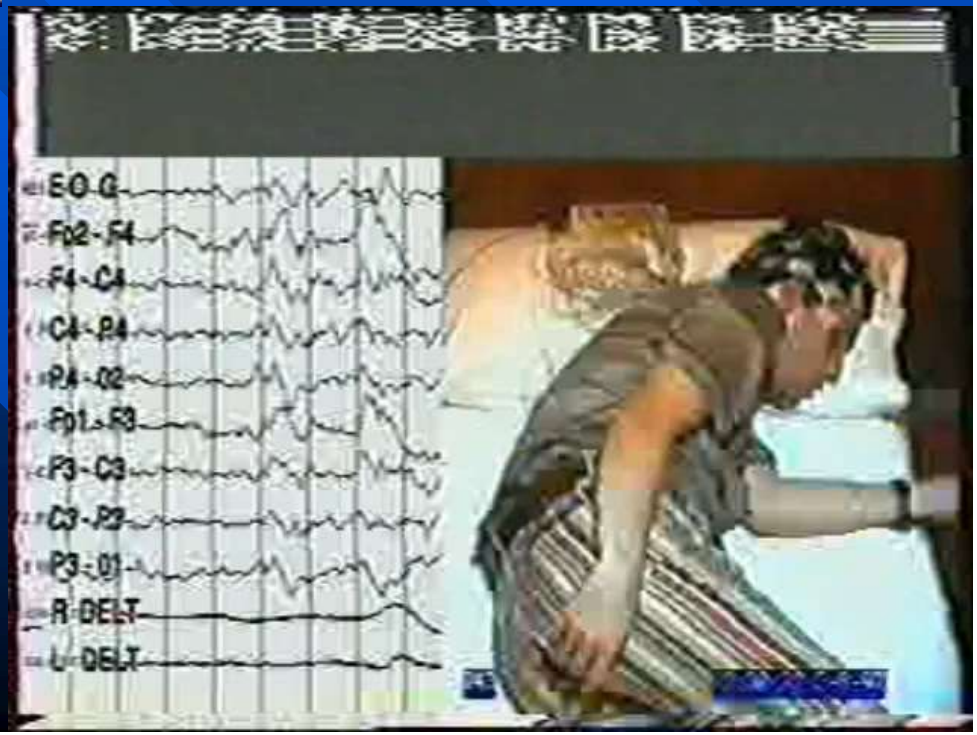

EOG
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fz-Cz
Cz-Pz
R DELT
L DELT
100 µV
1sec


EOG
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fz-Cz
Cz-Pz
R DELT
L DELT
100 µV
1sec


EOG
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fz-Cz
Cz-Pz
R DELT
L DELT
100 µV
1sec


EOG
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fz-Cz
Cz-Pz
R DELT
L DELT
100 µV
1sec


E-O-G
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
R-DELT
L-DELT


E-O-G
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F3
P3-C3
C3-P3
P3-O1
R-DELT
L-DELT

- Donna di 46 anni
- r(20)
- Deficit attentivo, mnesico e prattognosico
- Esordio delle crisi in epoca infantile
- Crisi di assenza di lunga durata (avvertite con senso di derealizzazione e di ansia) con automatismi motori, crisi versive o con automatismi oro-buccali, crisi focali notturne quotidiane o pluriquotidiane, a volte associate ad emissione di urlo
- Resistenza a CBZ, LTG, TPM, VPA, LEV, ZNS, ox-CBZ, LCS, CLB, PER, BRV

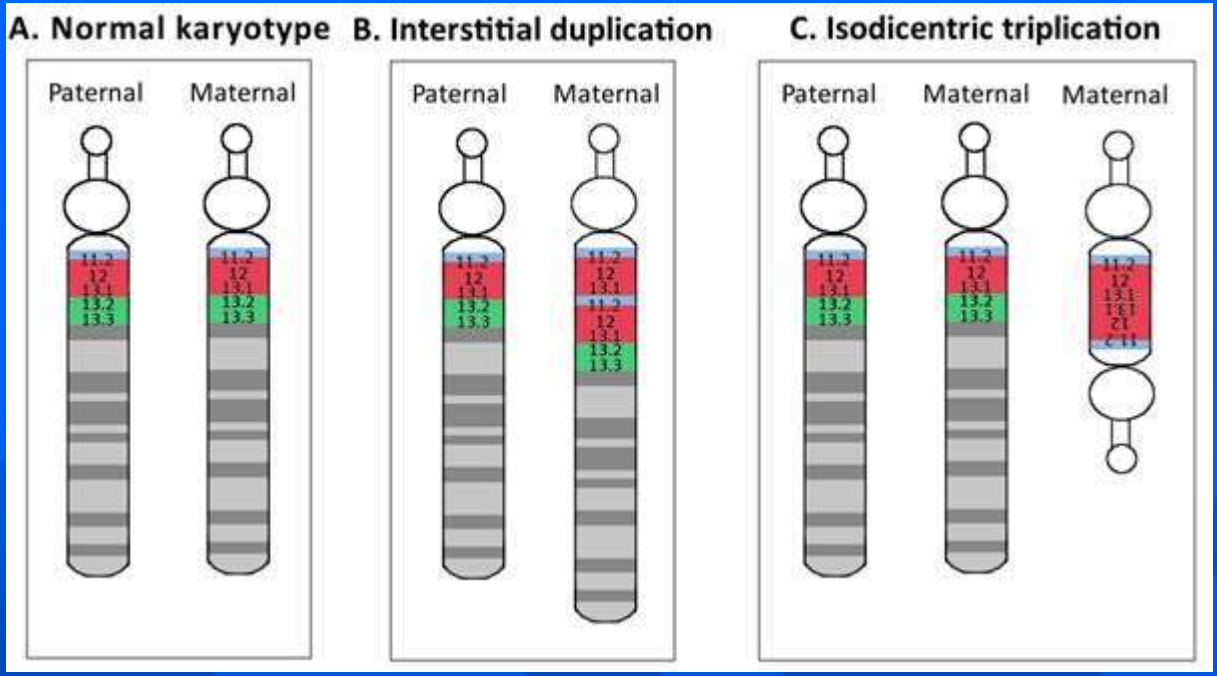
Video r(20)_2

- Bambina di 12 anni
- 46, XX, r(20)(p13q13.3)
- Disabilità intellettiva di grado lieve; condotte oppositive
- Non deficit neurologici, MRI nella norma
- Esordio delle crisi a 3 anni circa: rottura del contatto, deviazione dello sguardo, irrigidimento, pallore in addormentamento o al risveglio (cluster di 10-20 crisi) resistenti al VPA
- A 4 anni e 8 mesi circa episodi di rottura del contatto, sguardo fisso della durata di 15’ circa che sono divenuti nel tempo plurisettimanali
- A 9 anni introdotta in terapia la LTG; ridotta frequenza delle crisi in veglia (per lo più una volta al giorno per una settimana, ma con intervalli liberi anche di 2 settimane); semeiologia: manifestazione di paura, clonie degli arti superiori, rottura del contatto, sguardo fisso, quindi emissione di grido e automatismi motori (tende a scappare) di durata 5-10’; non più crisi in sonno

Video r(20)_ 3

Sindrome Dup15q

- La sindrome Dup15q è causata dalla presenza di almeno una copia extra di origine materna della regione critica Prader-Willi/Angelman (PWACR) - 15q11.2-q13.1



La copia o le copie extra più comunemente possono essere generate con uno dei seguenti due meccanismi:

1) Un cromosoma sovrannumerario di origine materna isodicentrico 15q11.2-q13.1– idic(15) – che comprende tipicamente due copie extra della regione 15q11.2-q13.1, risultante nella tetrasomia per la regione 15q11.2-q13.1 (*~80%* dei casi)

2) Una duplicazione interstiziale 15q11.2-q13.1 sul cromosoma di origine materna che tipicamente include una copia extra di 15q11.2-q13.1 nel cromosoma 15, risultante nella trisomia per la regione 15q11.2-q13.1 (~20% of cases)

Inv dup 15 pathophysiology

- Increased dosage of the PWS/ASC gene region between BP2 and BP3 positively correlates with phenotypic severity (Mann et al., 2004); however, the clinical heterogeneity among patients cannot be explained by variations in BPs, suggesting that additional factors contribute to clinical complexity
- Epigenetic differences exist between individuals with the same genetic copy number variant, stochastic, environmentally determined, or influenced by genetic background (Hogart et al., 2007)
- Imbalance of 15q11-q13 dosage may alter normal parental homolog pairing, DNA methylation, and the GABA receptor synaptic activity (GABRB3, GABRA5, and GABRG3) (Battaglia et al., 2016)

Epidemiologia (1)

- La prevalenza della sindrome idic(15) nella popolazione generale è stimata essere 1:30.000 (Schinzel and Niedrist, 2001)
- Nei pazienti indirizzati al CGH-array per disturbi del neurosviluppo (ritardo dello sviluppo, disabilità intellettiva o disturbo dello spettro autistico) o per anomalie congenite multiple, la prevalenza di dup15q è approssimativamente 1:508 (Moreno-De-Luca et al., 2013)

Epidemiologia (2)

- Nelle coorti di pazienti con disturbo dello spettro autistico, la prevalenza di dup15q è 1:253-1:522 (Depienne et al., 2009; Malhotra & Sebat, 2012; Moreno-De Luca et al., 2013)
- Nelle coorti di pazienti con disabilità intellettiva, la prevalenza di dup15q è 1:584 (Malhotra & Sebat, 2012)

Electroclinical features of epilepsy in patients with InvDup(15)

Alberto Verrotti[a], Fiammetta Sertorio [a], Sara Matricardi[b], Pietro Ferrara[c], Pasquale Striano [d]

a. Department of Pediatrics, University of L'Aquila, L'Aquila, Italy. E-mail address: alberto.verrottidipianella@univaq.it; fiammetta.sertorio@gmail.com

b. Department of Pediatrics, University of Chieti, Chieti, Italy. E-mail address: sara.matricardi@yahoo.it

c. Institute of Pediatrics, Catholic University, Roma, Italy. E-mail address: pietro.ferrara@unicatt.it

d. Pediatric Neurology and Muscular Diseases Unit, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, G. Gaslini Institute, Genova, Italy. E-mail address: strianop@gmail.com

(Seizure 2017;47:87-91)

Patients

- Of the 16 articles retrieved by the search, 12 were case reports and one was a survey, involving a total number of 144 patients with Inv Dup (15) and epilepsy
- Of these 144 patients with Inv Dup(15), 94 (65.27%) had multiple seizure types, and 4 had an unconfirmed history of seizures
- Gender was reported only for 24 of the 98 patients with multiple seizure types, who were 13 females and 11 males

Age at seizure onset

- Age at seizure onset was reported only for 23/98 patients (23.46%)
- Before age 12 months in 8 (34.78%) patients
- Between 1 and 10 years of age in 10 (43.48%)
- Between 10 and 15 years in 3 (13.04%)
- After age 15 years in 2 (8.7%) patients

Seizure types

Seizure types	GTC	IS	F	T	At	M	AA	SE	Gen	GT	UC	CP	GC	DA	AT	PSG
N	38	30	28	27	26	25	23	18	6	4	4	2	2	2	1	1
%	40,43	31,91	29,79	28,72	27,66	26,60	24,47	19,15	6,38	4,26	4,08	2,13	2,13	2,13	1,06	1,06

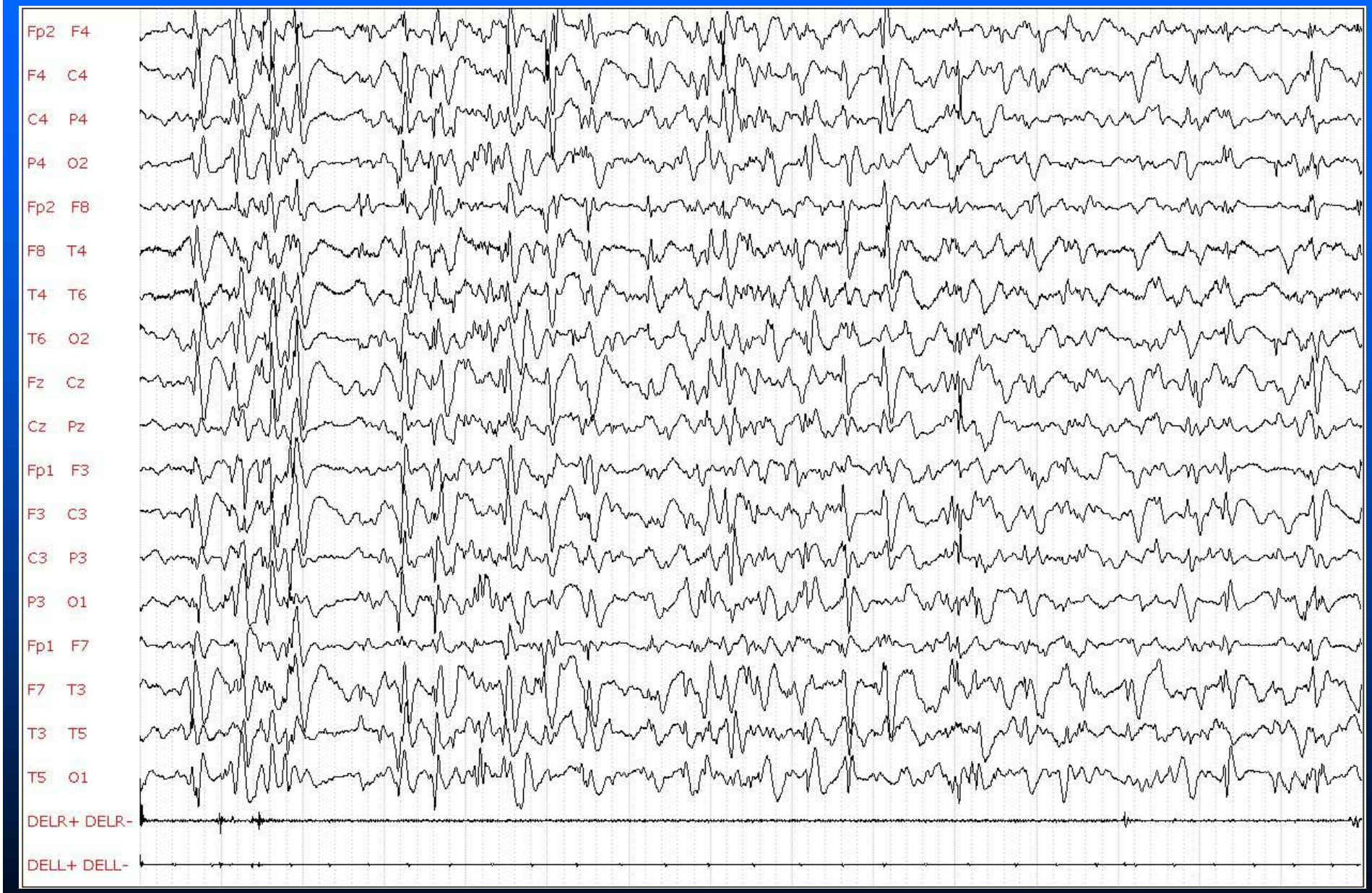
GTC: generalized tonic-clonic seizures; IS: infantile spasms; F: focal; At: atonic; AA: atypical absences; SE: status epilepticus; Gen: generalized; GT: generalized tonic; CP: complex partial; GC: generalized clonic; DA: drop attacks; AT: axial tonic; PsG: partial with secondary generalization

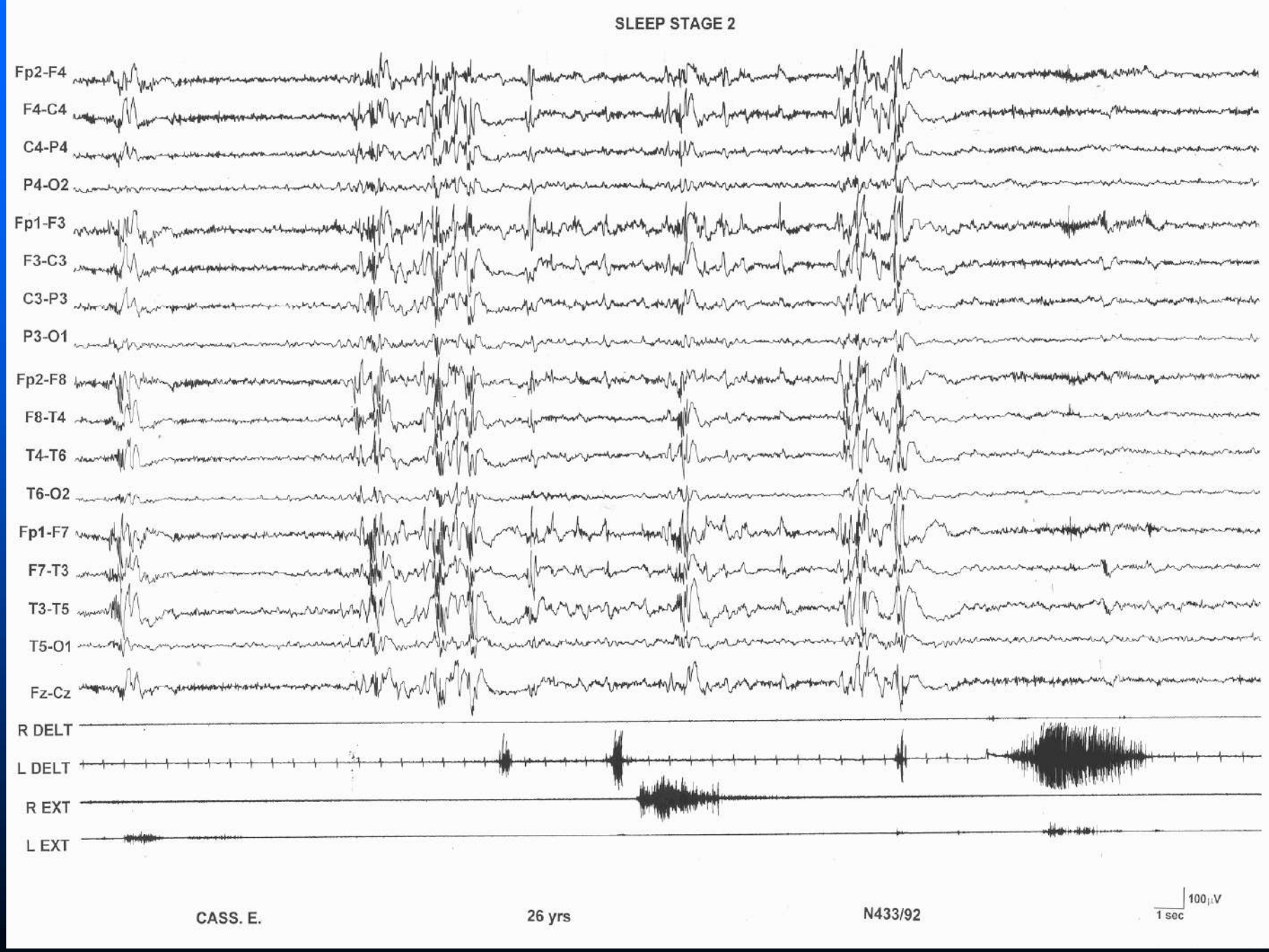
Total seizure control by AEDs was reported in 10.52% of cases (PB + PHT; CNZ + VPA; CBZ; GBP + CBZ + PB; VPA + VGB; VPA + LTG; ox-CBZ)

Interictal EEG

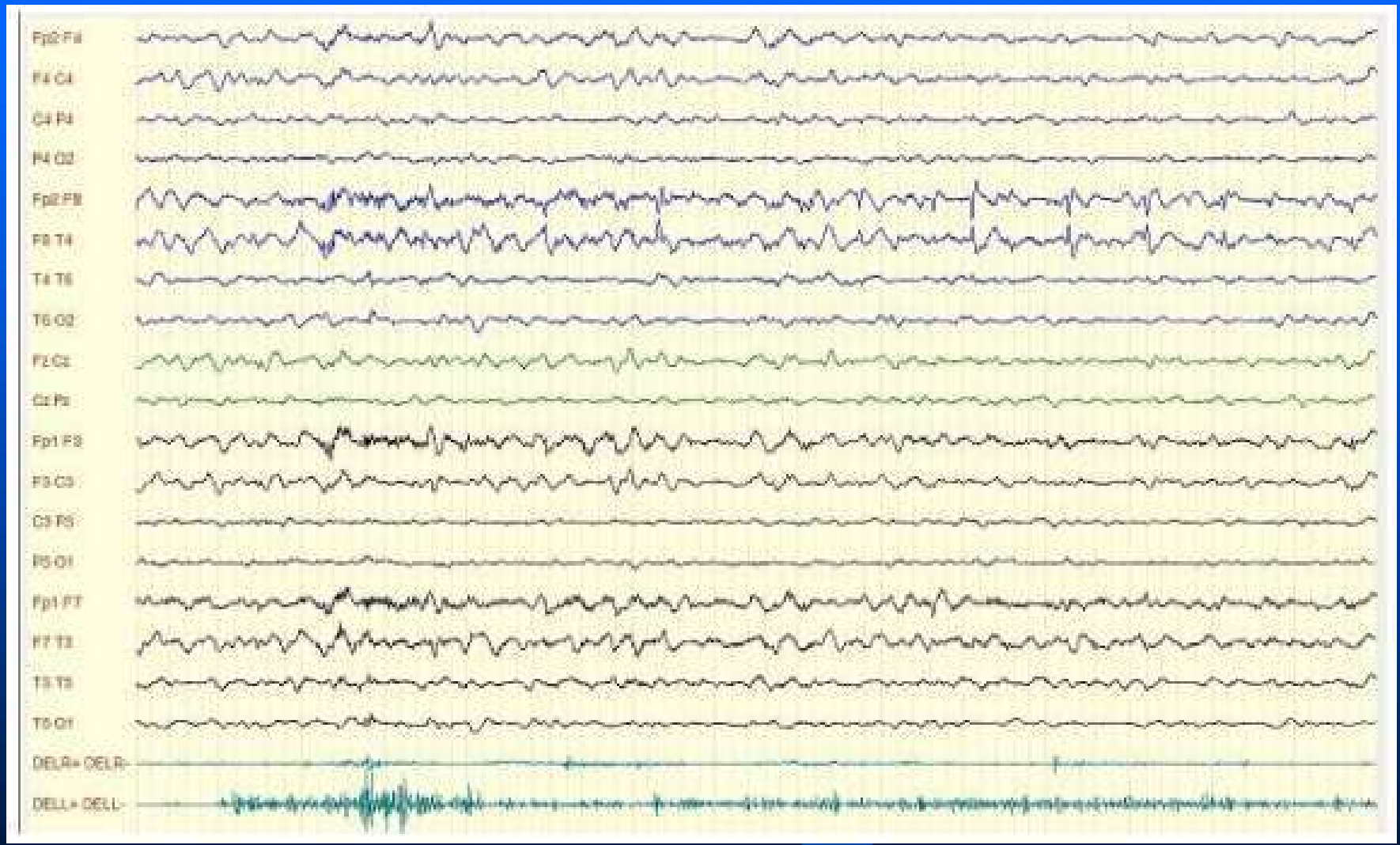
- Generalized spike activity (8 patients)
- Generalized spike and wave complexes (11 patients)
- Generalized polyspikes (4 patients)
- Multifocal diffuse abnormalities (3 patients)
- Epileptiform discharges in the left temporal lobe or parasagittal and midline regions (2 patients)
- Hypsarrhythmia, theta activity, bilateral fast rhythm during sleep, slow irregular waves in the left temporal-parietal region, and non-specific abnormalities (1 case each)

I.A., male, 2 yrs old - Sleep




SLEEP STAGE 2
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fz-Cz
R DELT
L DELT
R EXT
L EXT
CASS. E.
26 yrs
N433/92
100 µV
1 sec

M.G.A., male, 8 yr old - Wakefulness



T.U., male, 42 yr old - Wakefulness

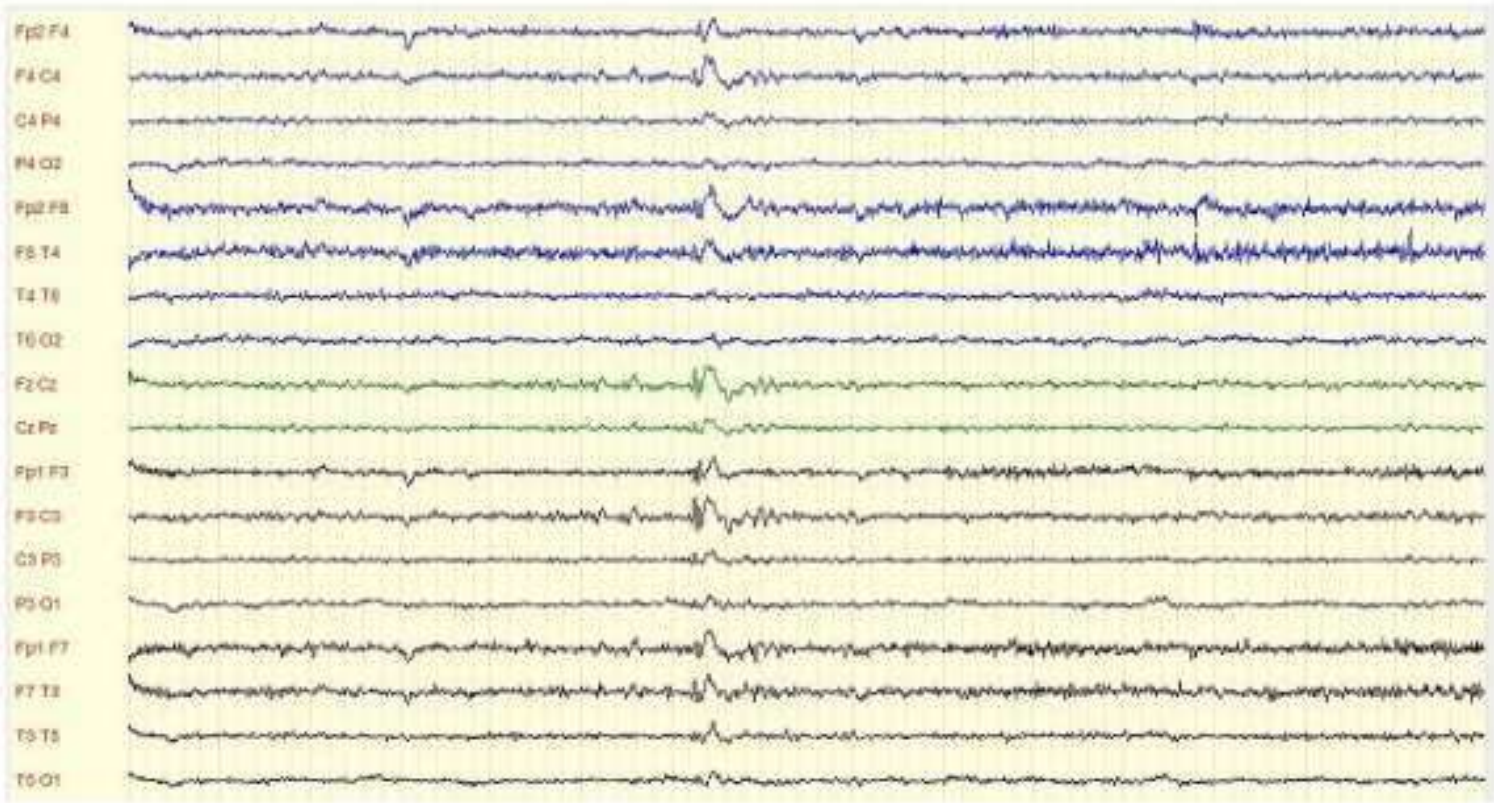


Fig. 15 – C: in veglia sono presenti complessi PO, singoli sincroni sulle regioni fronto-temporali dei due emisferi.

C.E., female, 46 yr old - Wakefulness

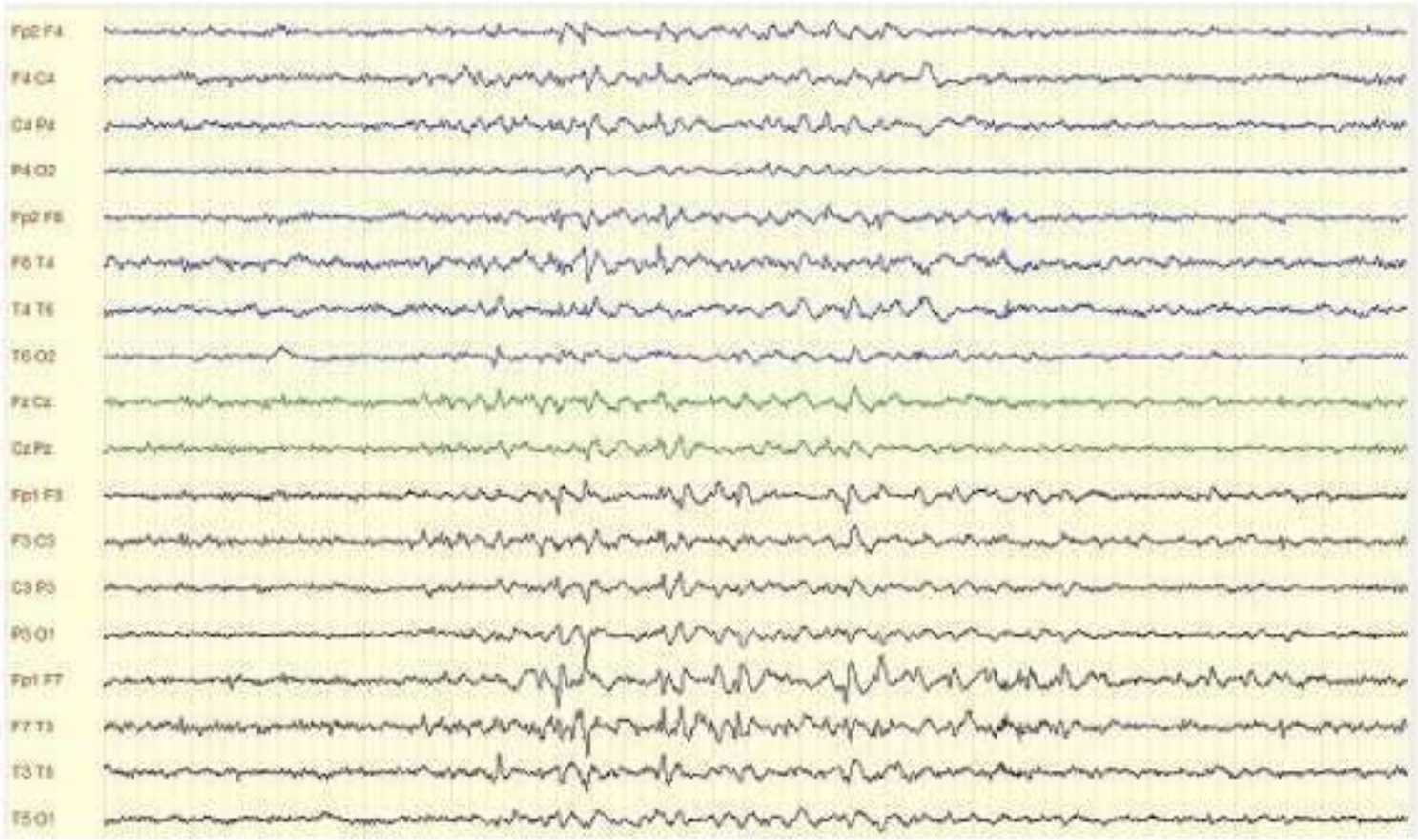
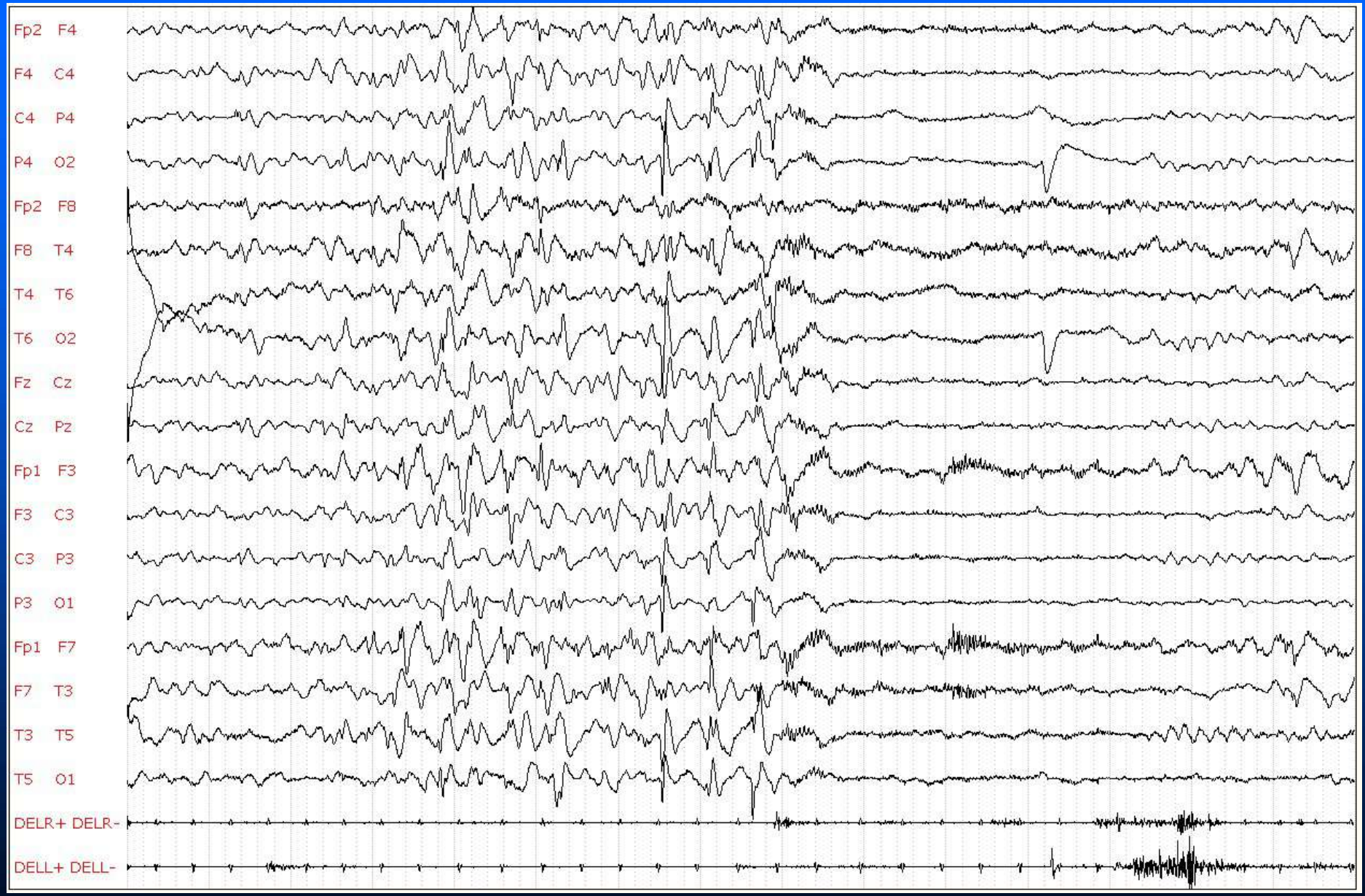


Fig. 5 – F: in veglia si osservano O theta angolari e PO degradate localizzate, per lo più in maniera indipendente, sulle regioni fronto-centro-temporali dei due emisferi, prevalentemente a sinistra.

Ictal EEG

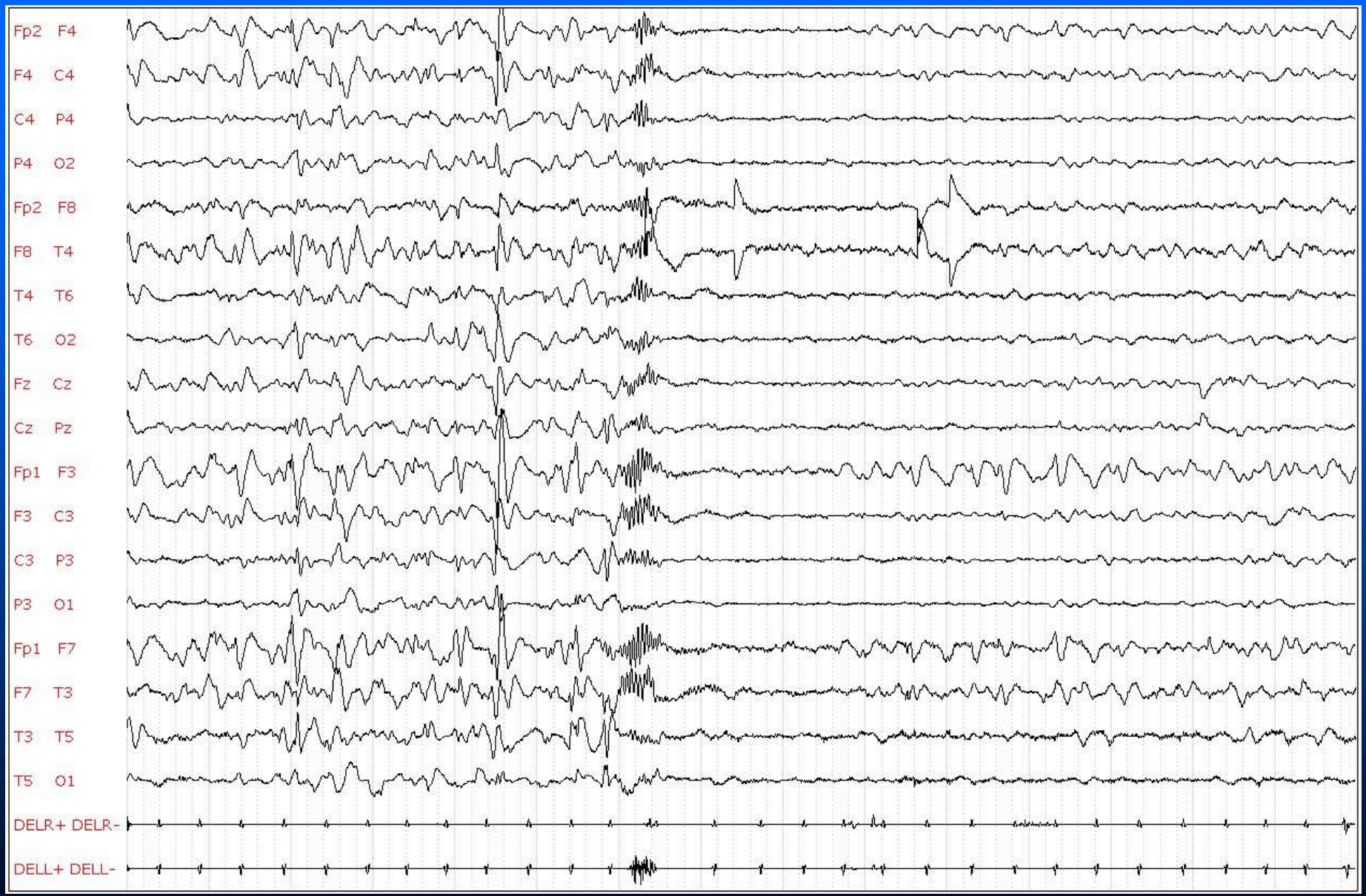
- Diffuse spikes followed by high-voltage spikes and waves in the right frontal-temporal region during an episode of head rotation to the right followed by rotation to the left, with tonic adduction of the arms, chewing movements, and loss of consciousness for 15 seconds (Buoni et al., 2000)
- Diffuse fast spikes followed by a voltage decrease (Buoni et al., 2000) during tonic spasms
- Mild diffuse attenuation of background activity with low-amplitude, rhythmic theta activity, correlated with brief tonic extension of the limbs; a year later, another ictal EEG showed diffuse delta bursts followed by an electrodecremental response, correlated with extensor spasms (Kim et al., 2012)

I.A., male, 1 yr old - Wakefulness



400 μV/cm —— 1 sec

I.A., male, 1 yr old - Wakefulness



400 μV/cm — 1 sec

F.A.F., female, 15 yr old - Sleep

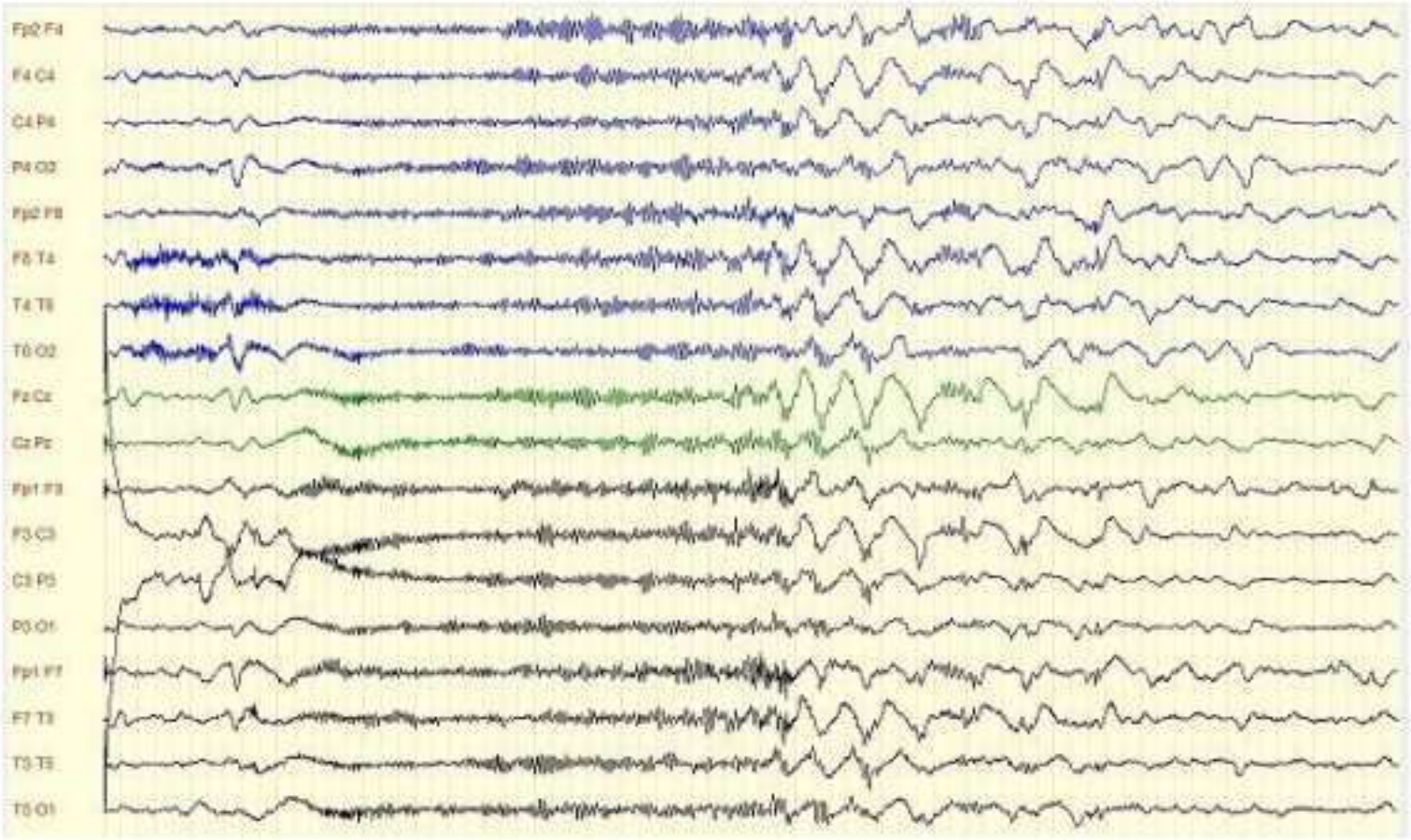
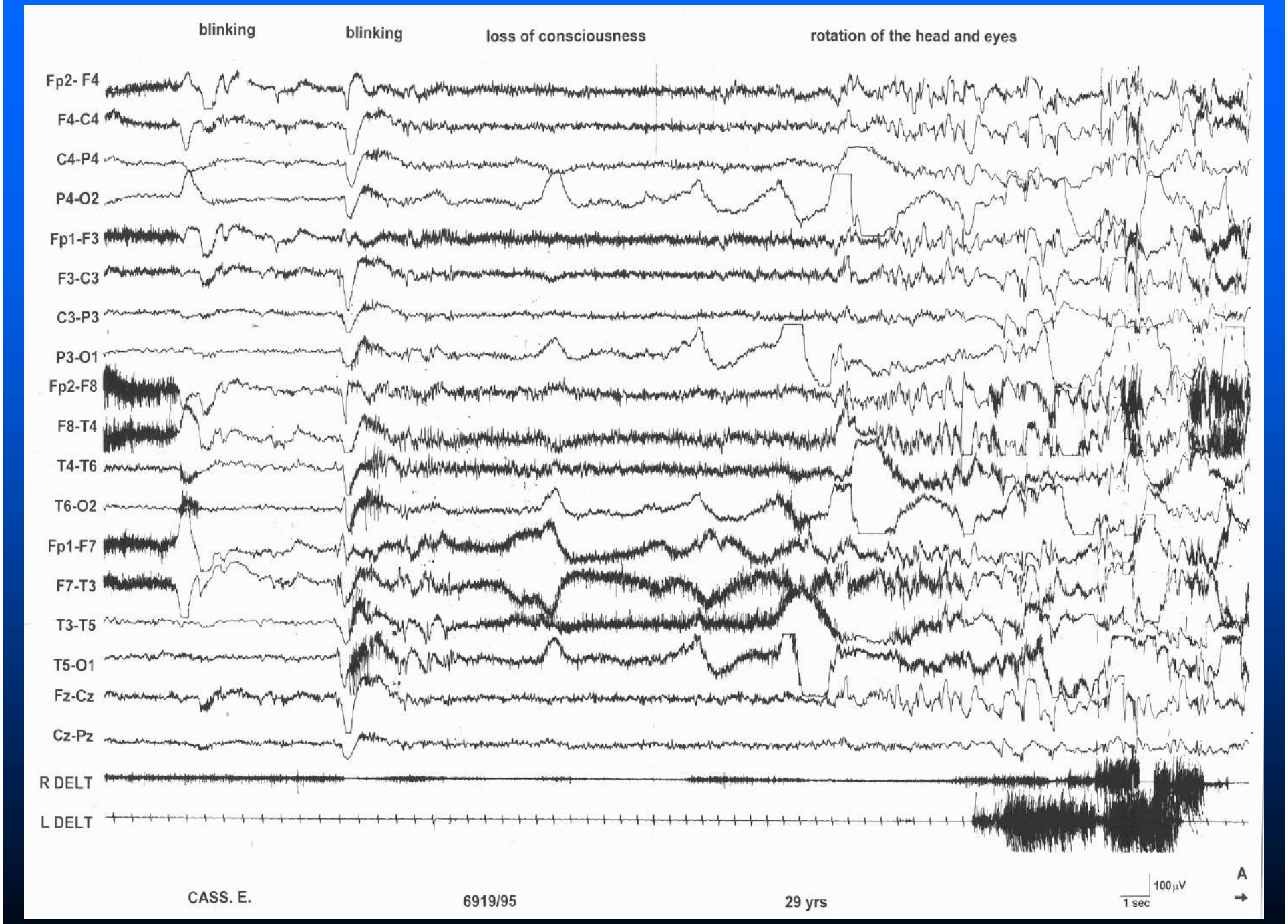
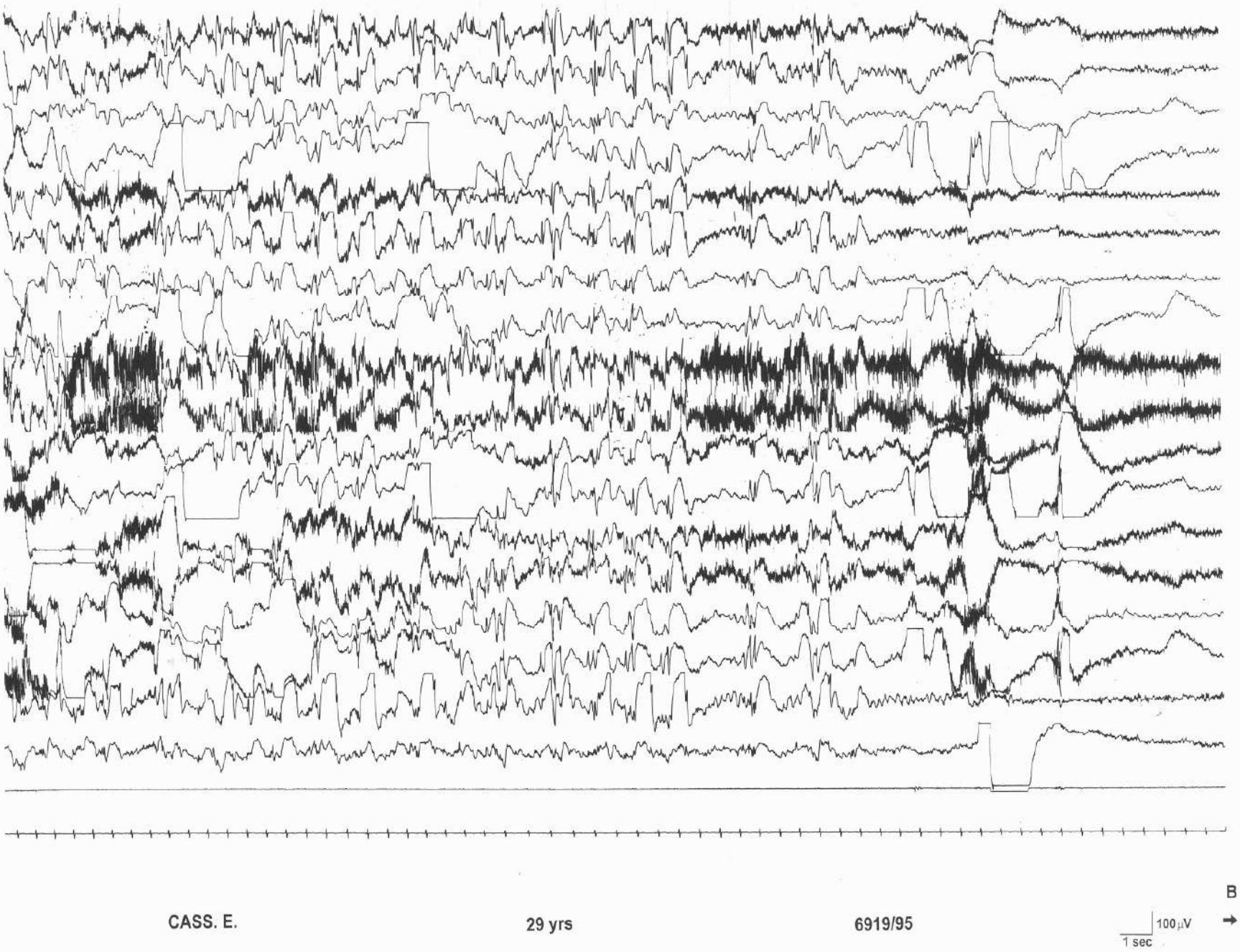


Fig. 9 – C: si registra un episodio critico in veglia, caratterizzato da brusca comparsa di attività reclutante diffusa per circa 6 secondi, seguita da OL di alto voltaggio e diffuse, prevalenti sulle regioni medio-anteriori. Clinicamente, la paziente presenta rottura del contatto e sguardo fisso.


blinking
blinking
loss of consciousness
rotation of the head and eyes
Fp2- F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fz-Cz
Cz-Pz
R DELT
L DELT
CASS. E.
6919/95
29 yrs
100 µV
1 sec
A


B
CASS. E.
29 yrs
6919/95
100 µV
1 sec

- Diagnosi di Inv Dup15 a 18 mesi
- Gemella monozigote con la stessa patologia
- Grave disturbo del neurosviluppo
- A 9 anni diagnosi di LLA
- All'EEG presenza di anomalie epilettiformi plurifocali (>in sonno) dai 5 anni
- A 10 anni e 10 mesi comparsa di crisi pluriquotidiane a tipo spasmo e spasmo tonico, isolate ed in grappoli
- Crisi rapidamente farmacoresistenti e successiva comparsa di crisi focali e pseudoassenze
- Deceduta a 13 anni in seguito a recidiva di LLA

Video inv dup 15

Accepted: 2 January 2018
DOI: 10.1111/ane.12902

ORIGINAL ARTICLE

WILEY Acta Neurologica Scandinavica

Electroclinical findings and long-term outcomes in epileptic patients with inv dup (15)

S. Matricardi[1] | F. Darra[2] | A. Spalice[3] | C. Basti[4] | E. Fontana[2] | B. Dalla Bernardina[2] | M. Elia[5] | L. Giordano[6] | P. Accorsi[6] | R. Cusmai[7] | P. De Liso[7] | A. Romeo[8] | F. Ragona[9] | T. Granata[9] | D. Concolino[10] | M. Carotenuto[11] | P. Pavone[12] | D. Pruna[13] | P. Striano[14] | S. Savasta[15] | A. Verrotti[4]

TABLE 1 Comparison of epileptic features with respect to the age of seizure onset

	Age at seizure onset <5 y (n = 32)	Age at seizure onset >5 y (n = 13)	*P*-value
Seizure freedom	11 (34.4%)	9 (69.2%)	.03
Epileptic syndrome			
West syndrome	8 (25%)	0 (0%)	.04
Lennox-Gastaut	14 (43.8%)	1 (7.7%)	.02
Generalized epilepsy	8 (25%)	4 (30.8%)	.69
Focal epilepsy	2 (6.3%)	8 (61.5%)	<.001
Cognitive and behavioural findings			
Severe/Moderte ID	32 (100%)	13 (100%)	ns
ASD/Psychosis	23 (71.9%)	6 (46.2%)	.10

AEDs: antiepileptic drugs; ID: intellectual disability; ASD: Autism spectrum disorder.

	Epileptic spasms (n = 9)	Epileptic spasms + other seizure types (n = 14)	*P*-value
Age at onset (mo) (mean, median and range)	6.8 (6; 4-12)	15.5 (7.5; 1-108)	.85
EEG findings at onset			
Classical hypsarrhythmia	7 (77.8%)	1 (7.1%)	<.001
Modified hypsarrhythmia	2 (22.2%)	9 (64.3%)	.04
Other forms of abnormal activity	0	4 (28.6%)	.07
Epileptic syndrome			
West Syndrome	7 (77.8%)	1 (7.1%)	<.001
Lennox-Gastaut	2 (22.2%)	13 (92.8%)	<.001
Seizure freedom	7 (77.8%)	1 (7.1%)	<.001
Cognitive and behavioural findings			
Severe/Moderte ID	9 (100%)	14 (100%)	ns
ASD/Psychosis	5 (55.6%)	12 (85.7%)	.10

ns: not significant; ID: intellectual disability; ASD: Autism spectrum disorder; EEG: electroencephalographic.

Int. J. Mol. Sci. **2015**, *16*, 4068-4082; doi:10.3390/ijms16024068

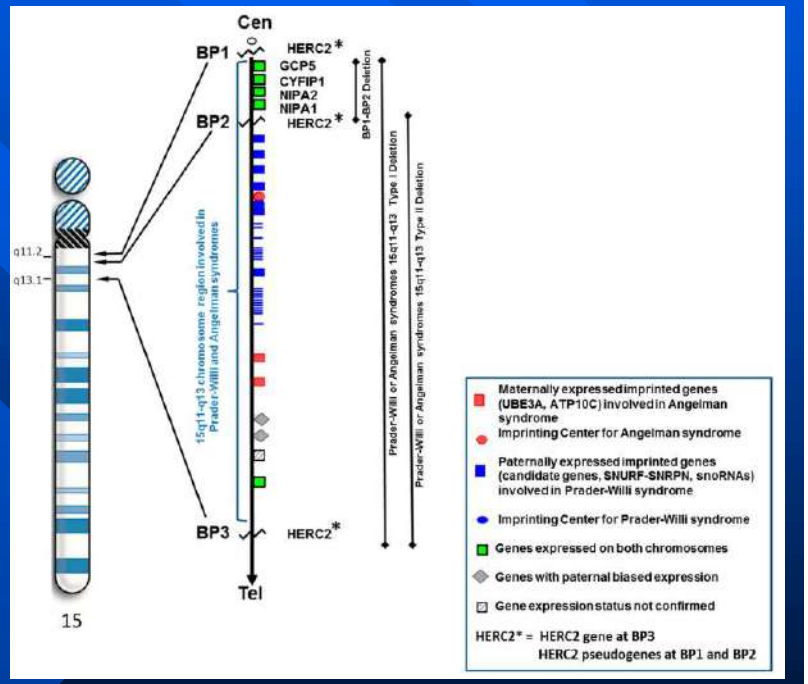
OPEN ACCESS
International Journal of
Molecular Sciences
ISSN 1422-0067
www.mdpi.com/journal/ijms

Review

The 15q11.2 BP1–BP2 Microdeletion Syndrome: A Review

Devin M. Cox [†,*] and Merlin G. Butler [†]

Abstract: Patients with the 15q11.2 BP1–BP2 microdeletion can present with developmental and language delay, neurobehavioral disturbances and psychiatric problems. Autism, seizures, schizophrenia and mild dysmorphic features are less commonly seen. The 15q11.2 BP1–BP2 microdeletion involving four genes (*i.e.*, *TUBGCP5*, *CYFIP1*, *NIPA1*, *NIPA2*) is emerging as a recognized syndrome with a prevalence ranging from 0.57%–1.27% of patients presenting for microarray analysis which is a two to four fold increase compared with controls. Review of clinical features from about 200 individuals were grouped into five categories and included developmental (73%) and speech (67%) delays; dysmorphic ears (46%) and palatal anomalies (46%); writing (60%) and reading (57%) difficulties, memory problems (60%) and verbal IQ scores ≤75 (50%); general behavioral problems, unspecified (55%) and abnormal brain imaging (43%). Other clinical features noted but not considered as common were seizures/epilepsy (26%), autism spectrum disorder (27%), attention deficit disorder (ADD)/attention deficit hyperactivity disorder (ADHD) (35%), schizophrenia/paranoid psychosis (20%) and motor delay (42%). Not all individuals with the deletion are clinically affected, yet the collection of findings appear to share biological pathways and presumed genetic mechanisms. Neuropsychiatric and behavior disturbances and mild dysmorphic features are associated with genomic imbalances of the 15q11.2 BP1–BP2 region, including microdeletions, but with an apparent incomplete penetrance and variable expressivity.



- Secondogenito di non consanguinei, disabilità intellettiva di grado profondo, disturbo dello spettro autistico
- Esordio crisi all'età di 7 anni circa, di tipo focale con compromissione della consapevolezza, pallore, automatismi motori (toccava la madre)
- La terapia antiepilettica è stata ripetutamente modificata nel tempo con l'introduzione di TPM (sospeso per inappetenza), NTZ (sospeso dopo pochi giorni per scialorrea), LEV (sospeso dopo pochi giorni per la presenza di numerosissime "assenze" e crisi con caduta), CBZ (sospesa dopo pochi giorni per la presenza di crisi con caduta), RFM (sospesa per la presenza di "assenze" e crisi con caduta), ESM (sospesa anch'essa per inefficacia), CLB (sospeso per la comparsa di sonnolenza), LCM (sospesa dopo pochi giorni per incremento delle crisi)
- Ha continuato a presentare crisi, soprattutto nel sonno notturno, caratterizzate da cianosi al volto, rottura del contatto della durata di 10' circa, seguite da sudorazione profusa per 30' circa
- A 18 anni circa, il paziente ha iniziato a presentare crisi pluriquotidiane, caratterizzate da fugace revulsione dei globi oculari o da automatismi di deglutizione e da caduta
- Obiettività neurologica: nella norma, RM-encefalo: nella norma
- Terapia all'ingresso in reparto: VPA 1.500 mg/die, PB 150 mg/die, clobazam (10 mg/die), risperidone (2 mg/die); sospeso il clobazam, inserita la lamotrigina (fino a 200 mg/die) + un ciclo di idrocortisone, con netto miglioramento clinico ed EEG

Video del 15q11.2

Sclerosi tuberosa

- Prevalenza: 1:5.800 nati vivi, 1:12.000 bambini di età < 10 aa
- Epilessia (~ 80%), disturbo dello spettro autistico (26-45%), disabilità intellettiva (~ 50%)
- AD, 2/3 casi sporadici
- Mutazioni a livello di due geni: TSC1 (9q34) e TSC2 (16p13.3)
- Il TSC1 (21 esoni) produce amartina, il TSC2 (41 esoni) produce tuberina
- Modello di malattia con più geni coinvolti: amartina e tuberina formano un complesso localizzato nel citosol e hanno funzione di soppressione tumorale, regolando la proliferazione cellulare

Sclerosi tuberosa - Criteri diagnostici

Updated diagnostic criteria for tuberous sclerosis complex 2012

A. Genetic diagnostic criteria

The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of tuberous sclerosis complex (TSC). A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment (www.lovd.nl/TSC1, www.lovd/TSC2, and Hoogeveen-Westerveld et al., 2012 and 2013). Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria, and are not sufficient to make a definite diagnosis of TSC. Note that 10% to 25% of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.

B. Clinical diagnostic criteria

Major features

1. Hypomelanotic macules (≥3, at least 5-mm diameter)
2. Angiofibromas (≥3) or fibrous cephalic plaque
3. Ungual fibromas (≥2)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Cortical dysplasias *
7. Subependymal nodules
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma
10. Lymphangioleiomyomatosis (LAM)†
11. Angiomyolipomas (≥2)†

Minor features

1. "Confetti" skin lesions
2. Dental enamel pits (>3)
3. Intraoral fibromas (≥2)
4. Retinal achromic patch
5. Multiple renal cysts
6. Nonrenal hamartomas

Definite diagnosis: Two major features or one major feature with ≥2 minor features

Possible diagnosis: Either one major feature or ≥2 minor features

* Includes tubers and cerebral white matter radial migration lines.

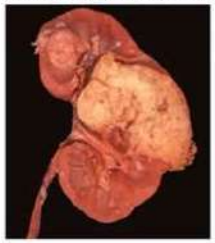
† A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.

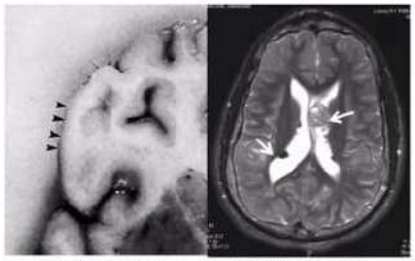
Tuberous Sclerosis Complex (TSC)

- Autosomal dominant disorder, involving tumor or hamartoma formation in multiple organs (kidney, heart, lungs, skin, eye, brain).

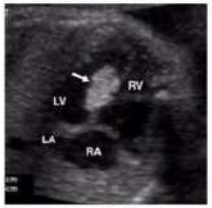
Hypopigmented macule ("ashleaf spot") | Shagreen patch | Facial angiofibromas

Kidney angiomyolipoma

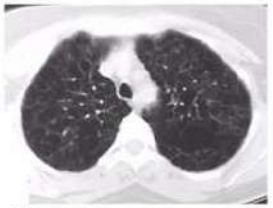




Cortical tuber | Subependymal nodules and giant cell astrocytoma



Cardiac rhabdomyoma



Pulmonary lymphangioleiomyomatosis

(Northrup et al., 2013)

TABLE 3 Type of epilepsy and treatment outcomes in overall epilepsy cohort and in patients diagnosed at <2 years at baseline

Characteristics	Overall epilepsy cohort (N = 1852), n (%)	Early onset seizure group, (N = 1461), n (%)
Epilepsy type		
Focal seizures[a]	1250 (67.5)	984 (67.4)
Infantile spasms[a]	720 (38.9)	684 (46.8)
Focal seizures only	765 (41.3)	530 (36.3)
Infantile spasms only	246 (13.3)	221 (15.1)
Co-occurrence of infantile spasms and focal seizures	380 (20.5)	375 (25.7)
Treatment outcomes for infantile spasm		
Resolved spontaneously	23 (3.3)	34 (5.0)
Controlled with treatment	530 (76.3)	506 (74.5)
Not controlled with treatment	108 (15.5)	106 (15.6)
Unknown	34 (4 9)	33 (4.9)
Treatment outcomes for focal seizures		
Resolved spontaneously	9 (0.7)	10 (1.0)
Controlled with treatment	713 (58.2)	552 (56.6)
Not controlled with treatment	466 (38.0)	384 (39.3)
Unknown	38 (3.1)	30 (3.1)

(Nabbout et al., 2019)

TABLE 2 | Summary of history of epilepsy in patients with Tuberous Sclerosis Complex.

Article	Epilepsy/seizures present in TSC	Age at onset, mean	Epileptic spasms, *n*	Epilepsy/seizure type	Refractory epilepsy (%)	Seizure frequency
Benova et al. (38)	20	8.1 mo	5	n/r	n/r	Daily ($n = 14$); weekly ($n = 2$); monthly ($n = 4$)
Capal et al. (51)	95	5.6 mo	39	Focal szs ($n = 21$); mixed ($n = 42$) Generalized szs ($n = 4$); unclassified ($n = 6$)	n/r	n/r
Caylor et al. (39)	3	n/r	1	Frontal lobe epilepsy ($n = 1$); Focal szs ($n = 1$);	1 (33%)	n/r
Chou et al. (20)	23	<1 y ($n = 13$); <2 y ($n = 19$)	10	n/r	11 (48%)	n/r
Cusmai et al. (41)	44	<1 y	29	Focal motor szs ($n = 19$); generalized szs ($n = 1$)	14 (32%)	n/r
Doherty et al. (42)	44	n/r	23	n/r	n/r	n/r
Gul Mert et al. (21)	83	25.46 mo	21	Focal ($n = 23$); multifocal ($n = 12$); generalized ($n = 26$)	15 (18%)	n/r
Huang et al. (22)	26	≤6 mo ($n = 11$); 7–12 mo ($n = 8$); ≥12 mo ($n = 4$)	7	Complex partial ($n = 4$); simple partial ($n = 4$); generalized ($n = 7$); clonic ($n = 1$); tonic ($n = 1$; myoclonic ($n = 1$)	n/r	n/r
Iscan et al. (23)	15	24.7 mo	4	Generalized ($n = 3$); mixed ($n = 4$); Complex partial ($n = 2$) myoclonic ($n = 1$); febrile ($n = 1$)	n/r	n/r
Jeste et al. (13)	34	5.75 mo	n/r	n/r	6 (18%)	Monthly (26%); weekly (7%); daily (27%)
Kilincaslan et al. (44)	6	<6 mo ($n = 3$); <2 y ($n = 2$); 7 y ($n = 1$)	4	Complex partial ($n = 2$); simple partial ($n = 2$); atonic/atypical absence ($n = 1$)	6 (100%)	>1 a day ($n = 4$); >1 a week ($n = 2$)
Kopp et al. (24)	87	0.9 y	51	Complex partial history ($n = 78$); mixed seizures history ($n = 18$)	n/r	Mean per month 39.9 ($n = 66$)
Kosac and Jovic (25)	39	2.8 y	10	Focal szs (84.6%); Secondary generalized szs (39.3%)	n/r	n/r
Metwelay et al. (32)	21	<6 mo ($n = 12$); >6 mo ($n = 9$)	13	Generalized ($n = 3$); Focal ($n = 4$); Partial with secondary generalization ($n = 1$)	16 (76%)	n/r
Mizuguchi et al. (45)	29	n/r	n/r	n/r	n/r	n/r
Moavero et al. (34)	51	<1 y ($n = 38$); <2 y ($n = 13$)	10	n/r	32 (63%)	n/r
Muzykewicz et al. (52)	208	n/r	92	n/r	141 (68%)	n/r
Numis et al. (18)	91	1.9 y	44	n/r	60 (66%)	1.75 per week
Overwater et al. (47)	25	n/r	7	n/r	14 (56%)	n/r
Pascual-Castroviejo et al. (26)	45	n/r	23	n/r	n/r	n/r
Saltik et al. (27)	21	<1 y (76.1%)	5	Focal szs ($n = 20$); diffuse tonic-clonic ($n = 3$); atonic ($n = 3$); absence ($n = 1$)	13 (62%)	n/r
Samir et al. (35)	30	<6 mo ($n = 16$); ≥6 mo ($n = 14$)	17	Focal szs ($n = 5$); secondary generalization ($n = 8$)	19 (63%)	n/r
Spurling Jeste et al. (12)	36	5.8 mo	26	n/r	n/r	n/r
Vignoli et al. (29)	42	7.9 mo	11	n/r	11 (26%)	Monthy ($n = 7$); Weekly ($n = 10$)
Wataya-Kaneada et al. (30)	143	n/r	n/r	n/r	20 (14%)	n/r
Wilbur et al. (31)	74	12 mo median	26	Focal (66%); epileptic spasms (26%); generalized (5%)	n/r	n/r
Wong et al. (55)	21	33 mo	8	n/r	3 (14%)	n/r
Yang et al. (50)	113	n/r	55	n/r	n/r	n/r

n/r, not reported; Szs, seizures; TCS, Tuberous Sclerosis Complex.

(Specchio et al., 2020)

- Ragazzo di 15 anni
- Diagnosi prenatale di TSC per la presenza di rabdomiomi cardiaci e madre affetta da TSC; conferma genetica per mutazione TSC2
- Disabilità intellettiva di grado lieve, ADHD e DOP
- All'età di 4 mesi presenza all'EEG di anomalie epilettiformi frontali
- Alla RM amartomi plurifocali prevalenti nelle regioni temporo-frontali
- Esordio delle crisi focali in veglia a 2 anni e due mesi: il bambino improvvisamente interrompe l'attività, si guarda intorno spaventato e disorientato, sorride a brevi riprese e riprende il contatto. Le crisi durano circa 25"-40", all'EEG ed è costituita da un ritmo rapido fronto-temporale destro seguito dopo da 10" un'attività di onda aguzza-onda lenta diffusa a tutto l'emisfero destro ed estesa alle regioni frontali di sinistra.
- Introduzione CBZ, inizialmente efficace, ma sospesa per rash cutaneo e linfopenia; controllo delle crisi con TPM in monoterapia dall'età di 3 anni

Video TSC2

European Journal of Paediatric Neurology 33 (2021) 75–85

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

CACNA1A-associated epilepsy: Electroclinical findings and treatment response on seizures in 18 patients

Marie Le Roux [a, *], Magalie Barth [b], Sophie Gueden [a], Patrick Desbordes de Cepoy [c], Alec Aeby [d], Catheline Vilain [e], Edouard Hirsch [f], Anne de Saint Martin [g], Vincent des Portes [h], Gaëtan Lesca [i], Audrey Riquet [j], Laurence Chaton [k], Nathalie Villeneuve [l], Laurent Villard [m, n], Claude Cances [o], Luc Valton [p, q], Florence Renaldo [r], Anne-Isabelle Vermersch [s], Cecilia Altuzarra [t], Marie-Ange Nguyen-Morel [u], Julien Van Gils [v], Chloé Angelini [v], Arnaud Biraben [w], Lionel Arnaud [x], Florence Riant [y], Patrick Van Bogaert [a, z]

CACNA1A gene (19p13) encodes the principle pore-forming subunit of the P/Q-type calcium channel, alpha-1 (also known as Cav2.1). P/Q-type calcium channels are high-voltage-activated (HVA) calcium channels and are abundantly expressed in the cerebellum, thalamus, cortex and hippocampus, mediating neurotransmission via fast synaptic transmission at central and peripheral nerve terminals

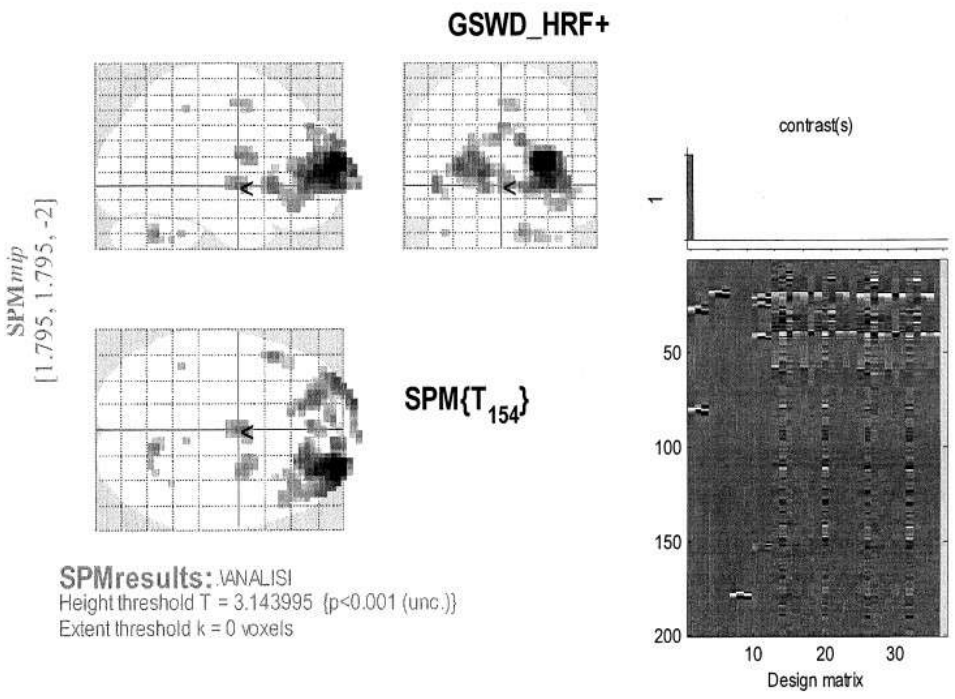
Table 2
Patients electro-clinical features.
G, generalized; F, focal; MF, multifocal; U, unknown; MJ, myoclonic jerks; ES, epileptic spasm; TC, tonic-clonic; F-GT, focal seizure evolving to a bilateral convulsive seizure; BA, behavioural arrest; SE, status epilepticus; SW, spike-waves; SBA, slow background activity; Mo, month(s); N, normal; NA, not available.

Patient	At onset Type, Age (Mo)	Follow up			Status epilepticus	EEG findings		Hemiplegic accesses (duration)	Epilepsy type
		Type(s)	Trigger(s)	Frequency		Interictal activity	Ictal activity		
1	F (SE), 7	**F:** clonic; **G:** TC, ES; **U:** MJ	Fever, viral infection	Weekly	F/G	SBA, MF sharp waves and SW complexes	F and G SW discharge	Hemispheric delta activity (Mo)	Combined G/F
2	F (SE), 17	**F-GT:** tonic, atonic; **G:** TC, MJ	Fever, bath, strong emotions	Daily	F/G	SBA, G sharp waves and SW complexes	G SW discharge, F theta rhythmic discharge	Hemispheric delta activity (Weeks)	Combined G/F
3	F (SE), 24	**F-GT:** BA ± autonomic features	Fever, external climate changes, stress	Weekly	F	SBA, F sharp waves and SW complexes	F theta rhythmic discharge	Not recorded	F
4	F: BA, 12	**F:** versive, BA (+/-automatisms)	–	Daily	–	SBA, G sharp waves and SW complexes	F beta rhythmic discharge	–	F
5	G-TC, 12	**G:** absence, TC	Fever	Daily	–	SBA, G SW complexes	3 Hz G SW discharge	–	G
6	G-TC, 36	**G:** TC	Fever	Rare	–	N	Not recorded	–	G
7	Atypical absence, 36	**G:** atypical absence	–	Daily	–	SBA, G sharp waves and SW complexes	G SW discharge (<3 Hz)	–	G
8	NA, 19 years	**G:** tonico-clonic; atypical absence	–	NA	–	SBA, G sharp waves complexes	Not recorded	Not recorded	G
9	F (SE), 2	**F:** clonic	–	Rare	F	N	F SW discharge	–	F
10	Atypical absence, 38	**G:** atypical absence	–	Daily	–	SBA, G sharp waves and SW complexes	Not recorded	–	G
11	Atypical absence, 36	**G:** atypical absence, TC	–	Daily	–	SBA, G sharp waves and SW complexes	G SW discharge (<3 Hz)	–	G
12	G-TC (SE), 12	**F-GT:** tonic, atonic, versive	Fever, bath, menstruation, noises	Weekly	F/G	SBA; MF sharp waves and SW complexes, diffuse fast rhythms in sleep	F beta rhythmic discharge	Hemispheric delta activity (Mo)	Combined G/F
13	F (SE), 48	**F-GT:** clonic; **U:** BA	Fever	Daily	F/G	SBA	F delta periodic complexes	Hemispheric theta rhythmic activity (Mo)	U
14	G-TC, 6 years	**G:** TC; **F:** clonic	Head trauma, viral infection	Rare	F	G sharp waves and SW complexes	F SW discharge	Abnormal background structure (Mo)	Combined G/F
15	G-TC (SE), 4,5	**F-GT:** clonic; **G:** TC, tonic; **U:** BA	Fever, head trauma	Weekly	F/G	SBA, G sharp waves and SW complexes (bifrontal predominance)	G beta rhythmic discharge	Hemispheric delta activity (Hours)	Combined G/F
16	G-TC (SE), 12	**G:** TC, tonic; **F:** clonic, motor automatisms; **U:** BA, MJ	Fever, stress	Daily	F/G	G or MF SW complexes, diffuse fast rhythms in sleep	F theta rhythmic activity, G beta rhythmic discharge	Hemispheric delta activity (Hours)	Combined G/F
17	Absence, 36	**G:** absence	–	Daily	–	G SW complexes	3 Hz G SW discharge	–	G
18	Absence, 36	**G:** absence	–	Daily	–	G and MF SW complexes	3 Hz G SW discharge	–	G

Table 3
Therapeutic profiles and seizure outcomes of *CACNA1A* epileptic patients.
AED, anti-epileptic drug; LEV, Levetiracetam; VPA, Sodium Valproate, ESM, Ethosuximide; OXC, Oxcarbamazepine; PB, Phenobarbital; CBZ, Carbamazepine; LTG, Lamotrigine; TPM, Topiramate; BZD, Benzodiazepine; LCS, Lacosamide; ZNS, Zonisamide; VNS, vagus nerve stimulation; KD, ketogenic diet; ACTZ, Acetazolamide; * stopped because of poor tolerability.

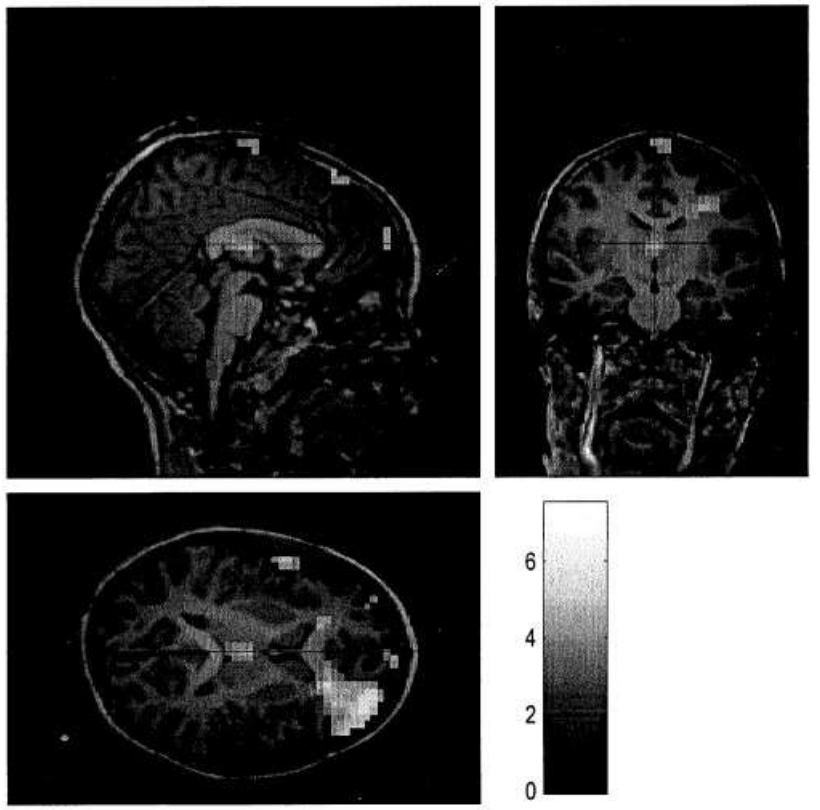
	AEDs					Other treatments		
Patient	Seizure free	Seizure reduction	No effect	Actual AED	Seizure free	Seizure reduction	No effect	Actual treatments	Epilepsy outcome
1		TPM, VPA, LTG	LEV, BZD	VPA, LTG			ACTZ, Pyridoxine, KD	ACTZ, Pyridoxine	Refractory
2		TPM, LCS, CBZ, VPA	LEV, BZD, LTG	VPA, LCS, BZD	ACTZ		KD	ACTZ	Refractory
3		CBZ, TPM, LCS	VPA, LEV	TPM, LCS			ACTZ, Flunarizine	–	Refractory
4		LEV, TPM		LEV, TPM				–	Refractory
5	TPM	ESM, VPA	LTG	TPM, VPA				–	Fluctuation course
6				–				–	Early seizure freedom
7		VPA	LTG, ESM	LTG		ACTZ	KD	ACTZ	Delayed seizure freedom
8		TPM, PB		–		ACTZ		ACTZ	Delayed seizure freedom
9	LEV			LEV				–	Early seizure freedom
10		VPA, OXC	CBZ	VPA, OXC				–	Refractory
11		OXC, TPM, LTG	ESM	TPM, LTG				–	Refractory
12		LEV, ZNS	BZD, VPA, OXC, CBZ	OXC, ZNS, BZD, LEV			Pyridoxine, VNS	VNS	Refractory
13		LEV		LEV		Flunarizine	Pyridoxine	Pyridoxine, Flunarizine	Fluctuation course
14	LEV			LEV				–	Early seizure freedom
15		TPM, VPA, PB	CBZ, BZD, LTG, LEV, ESM	VPA, TPM, PB, BZD, ESM				–	Refractory
16		LTG, TPM, OXC, LEV	VPA, CBZ, BZD, ZNS	LTG, ZNS, BZD			Pyridoxine, KD, VNS	Pyridoxine	Refractory
17		TPM, LTG, ESM	VPA, LEV	TPM		KD	VNS	–	Refractory
18		VPA, LTG	ESM*	VPA, LTG				–	Refractory

- Ragazza di 17 anni
- Funzionamento intellettivo limite
- Obiettività neurologica e MRI nella norma
- Variante gene CACNA1A c.2667delG (A890Pfs*3), frameshift, eterozigote
- A 16 mesi ha presentato una crisi GTC febbrile (T°C 38,5)
- All'età di 2 anni e mezzo ha iniziato a presentare episodi caratterizzati da rottura del contatto, talvolta da revulsione dei globi oculari, di breve durata, pluriquotidiani
- Resistenza a VPA, LEV, ESM, LTG
- Attualmente le assenze sono divenute sporadiche (VPA + ESM)



L'analisi del segnale BOLD evidenzia il coinvolgimento bilaterale della corteccia premotoria/motoria, supplementare motoria, del precuneo e del giro temporale superiore; ulteriore e successivo aumento del segnale BOLD a livello talamico bilateralmente

(cortesia Prof. Meletti)



Video CACNA1A