## La sindrome di Angelman: il problema delle crisi

- Crisi o non crisi? Questo è il problema….
- Pedagogia dell'anamnesi: ovvero come raccontare una crisi al medico, sperando che non vada fuori strada…
- L'inizio della terapia AE: necessità ed abusi (ovvero, la punta-onda fa sempre male?)
- La scelta del farmaco "giusto": le scienze di base ci aiutano veramente in questo?

# Definizioni

- **Crisi epilettica:** manifestazione clinica di una scarica neuronale ipersincrona, di durata variabile, autolimitantesi, che interessa in modo prevalente la corteccia cerebrale
- **Epilessia:** sindrome clinica, eterogenea per eziologia e presentazione, caratterizzata dalla ripetizione di crisi epilettiche non sintomatiche di una lesione acuta del sistema nervoso
- **Crisi sintomatica acuta:** crisi epilettica conseguente ad un evidente evento patologico immediatamente precedente, cerebrale o sistemico; può costituire un evento isolato
- **Crisi sintomatica remota:** crisi epilettica conseguente ad una pregressa lesione cerebrale
- **Stato di male epilettico:** attività epilettica persistente che si manifesta come crisi prolungata o crisi seriate senza ricupero tra l'una e l'altra

# Tipi di crisi epilettiche

## Crisi autolimitanti

- generalizzate
- focali

## Crisi continue

- stato epilettico generalizzato
- stato epilettico focale

# Tipi di crisi epilettiche

## Crisi autolimitanti

- generalizzate
- focali

## Crisi continue

- stato epilettico generalizzato
- stato epilettico focale

- tonico-cloniche
- cloniche
- assenze tipiche
- assenze atipiche
- assenze miocloniche
- toniche
- spasmi
- miocloniche
- **mioclonie palpebrali**
- mioclonico-atoniche
- **mioclono negativo**
- atoniche

# Tipi di crisi epilettiche

## Crisi autolimitanti

- generalizzate
- focali
  - sensoriali
  - motorie
  - gelastiche
  - emicloniche
  - secondariamente generalizzate
    - con sintomi sensoriali elementari (es. occipitali)
    - con sintomi sensoriali **esperienziali** (es. temporo-parieto-occipitali)

## Crisi continue

- stato epilettico generalizzato
- stato epilettico focale

# Tipi di crisi epilettiche

## Crisi autolimitanti

- generalizzate
- focali
  - sensoriali
  - motorie
    - cloniche elementari
    - toniche asimmetriche
    - con automatismi tipici (lobo temporale)
    - con automatismi ipercinetici
    - mioclono negativo focale
    - motorie inibitorie
  - gelastiche
  - emicloniche
  - secondariamente generalizzate

## Crisi continue

- stato epilettico generalizzato
- stato epilettico focale

# Tipi di crisi epilettiche

## Crisi autolimitanti

- generalizzate
  - tonico-clonico
  - clonico
  - di assenza
  - tonico
  - mioclonico
- focali

## Crisi continue

- stato epilettico generalizzato
- stato epilettico focale

# Tipi di crisi epilettiche

## Crisi autolimitanti

- generalizzate
- focali

## Crisi continue

- stato epilettico generalizzato
- stato epilettico focale
  - epilessia parziale continua di Kojevnikov
  - aura continua
  - stato epilettico limbico (stato psicomotorio)
  - stato emiconvulsivo con emiparesi

# Mioclono corticale

# Mioclono non corticale

# Myoclonus in Angelman syndrome: is it always of cortical origin?

Maurizio Elia, Raffaele Ferri, Maria Bottitta, Paolo Bosco, Sebastiano A. Musumeci

(presented at the 1st World Conference of the International Angelman Syndrome Organization, Tampere Finland, July 4-8, 2000)

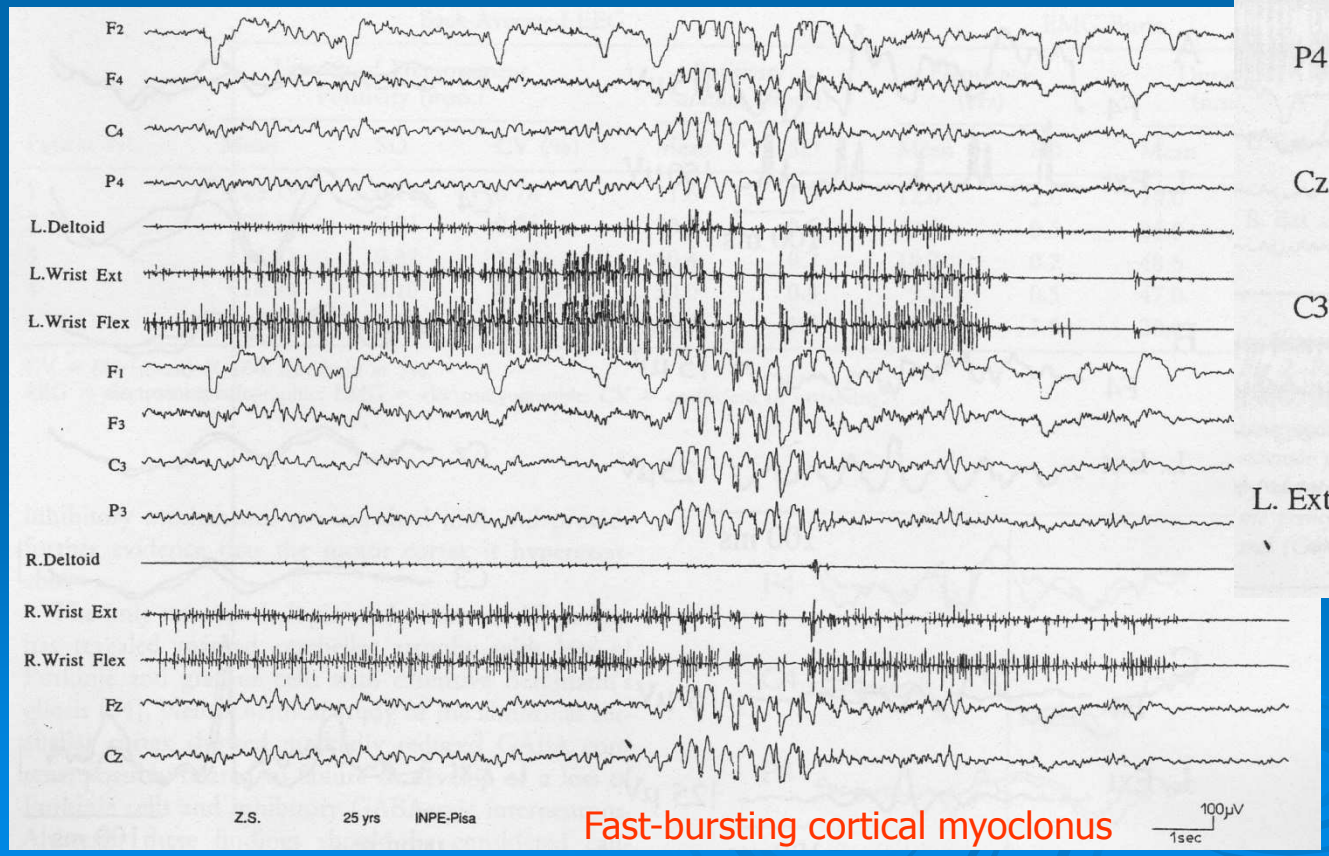
- Fifteen subjects with AS (7 males, age range 4 - 26 years, mean age 11.64 years, DS 6.61 years) were included in this study
- Back averaging of EEG interictal activity related to EMG potentials was performed in all cases; in 11 subjects median nerve somatosensory evoked potentials (SEPs) were recorded and the eventual presence of C-reflex assessed Only in two subjects, both of them with deletion of the region 15q11-13, a negative cortical wave 60 to 75 milliseconds before the myoclonic jerk was found. No ‘giant’ SEPs or C-reflex were found
- Our findings allow us to exclude the presence of a cortical reflex myoclonus in AS

# Cortical Myoclonus in Angelman Syndrome

Renzo Guerrini, MD,* Timothy M. De Lorey, PhD,† Paolo Bonanni, MD,* Anne Moncla, MD,‡ Charlotte Dravet, MD,§ Georges Suisse, MD,‖ Marie Odile Livet, MD,§ Michelle Bureau, MD,§ Perrine Malzac, PhD,‡ Pierre Genton, MD,§ Pierre Thomas, MD,‖ Ferdinando Sartucci, MD,¶ Paolo Simi, PhD,# and José M. Serratosa, MD†

**Angelman syndrome (AS) results from lack of genetic contribution from maternal chromosome 15q11–13. This region encompasses three $GABA_A$ receptor subunit genes (β3, α5, and γ3). The characteristic phenotype of AS is severe mental retardation, ataxic gait, tremulousness, and jerky movements. We studied the movement disorder in 11 AS patients, aged 3 to 28 years. Two patients had paternal uniparental disomy for chromosome 15, 8 had a >3 Mb deletion, and 1 had a microdeletion involving loci D15S10, D15S113, and GABRB3. All patients exhibited quasicontinuous rhythmic myoclonus mainly involving hands and face, accompanied by rhythmic 5- to 10-Hz electroencephalographic (EEG) activity. Electromyographic bursts lasted 35 ± 13 msec and had a frequency of 11 ± 2.4 Hz. Burst-locked EEG averaging in 5 patients, generated a premyoclonus transient preceding the burst by 19 ± 5 msec. A cortical spread pattern of myoclonic cortical activity was observed. Seven patients also demonstrated myoclonic seizures. No giant somatosensory evoked potentials or C-reflex were observed. The silent period following motor evoked potentials was shortened by 70%, indicating motor cortex hyperexcitability. Treatment with piracetam in 5 patients significantly improved myoclonus. We conclude that spontaneous, rhythmic, fast-bursting cortical myoclonus is a prominent feature of AS.**

Guerrini R, De Lorey TM, Bonanni P, Moncla A, Dravet C, Suisse G, Livet MO, Bureau M, Malzac P, Genton P, Thomas P, Sartucci F, Simi P, Serratosa JM. Cortical myoclonus in Angelman syndrome. Ann Neurol 1996;40:39–48




Fast-bursting cortical myoclonus

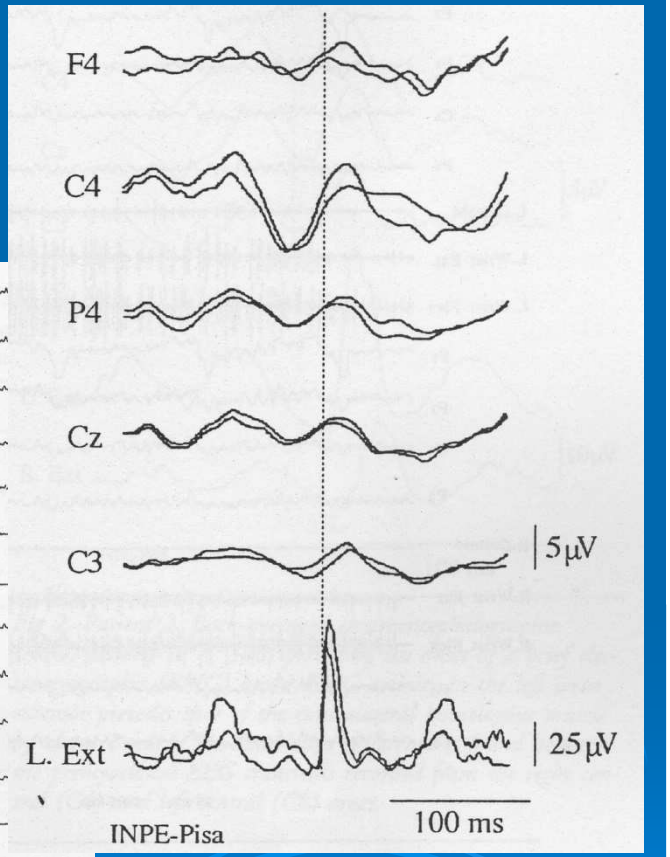


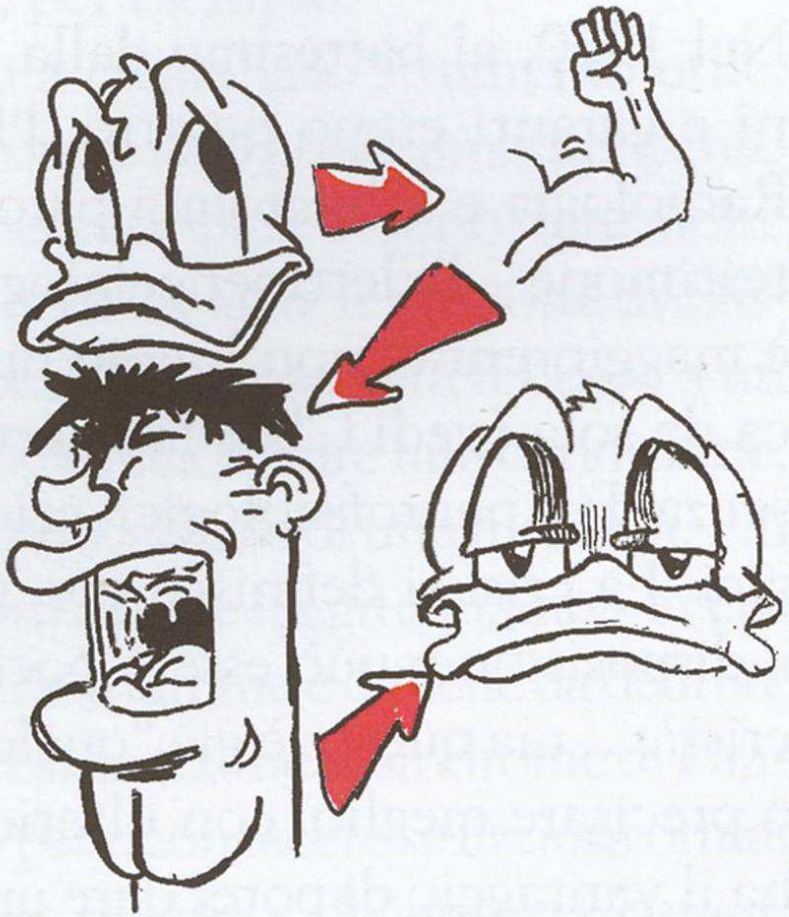
Table 1
Comparison between AS patients aged less than 15 (group A) and age-matched normal controls (group C)

| | Group C (%) | Group A (%) | Chi-square | $P <$ |
|---|---|---|---|---|
| *Bedtime problems* | | | | |
| 1. Sleep less than 8 h | 9.63 | 70.27 | 117.68 | 0.00001 |
| 2. Latency to sleep >30 min | 6.61 | 32.43 | 30.04 | 0.00001 |
| 3. Reluctant to go to bed | 29.68 | 59.46 | 13.41 | 0.003 |
| 4. Bedtime variations | 38.63 | 48.65 | 1.11 | NS |
| 5. Difficulty getting to sleep at night | 8.96 | 56.76 | 78.98 | 0.00001 |
| 6. Anxiety/fear when falling asleep | 8.17 | 43.24 | 46.52 | 0.00001 |
| 7. Drink stimulant beverages in the evening | 27.32 | 27.03 | 0.02 | NS |
| 8. Need for light or TV in the bedroom | 27.21 | 32.43 | 0.26 | NS |
| 9. Need for a transitional object | 18.25 | 48.65 | 19.05 | 0.00001 |
| 10. Fluids or drugs to facilitate sleep | 0.67 | 32.43 | 172.46 | 0.00001 |
| *Sleep-wake transition disorders* | | | | |
| 11. Hypnic jerks | 5.04 | 59.46 | 149.35 | 0.00001 |
| 12. Rhythmic movements while falling asleep | 2.69 | 27.03 | 53.04 | 0.00001 |
| 13. Falling asleep sweating | 10.30 | 13.51 | 0.12 | NS |
| *Sleep quality* | | | | |
| 14. Poor sleep quality | 13.89 | 70.27 | 79.38 | 0.00001 |
| *Night awakenings* | | | | |
| 15. More than two awakenings per night | 6.83 | 62.16 | 125.73 | 0.00001 |
| 16. Waking up screaming in the night | 5.49 | 18.92 | 9.08 | 0.003 |
| 17. Waking up to drink or eat in the night | 13.55 | 24.32 | 2.59 | NS |
| 18. Getting up to use to the bathroom | 10.64 | 2.70 | 1.64 | NS |
| 19. Difficulty to fall asleep after awakenings | 4.82 | 56.76 | 141.58 | 0.00001 |
| *Abnormal movements during sleep* | | | | |
| 20. Nocturnal hyperkinesias | 29.00 | 67.57 | 23.12 | 0.00001 |
| 21. Unusual movements during sleep | 5.94 | 48.65 | 85.96 | 0.00001 |
| 22. Pains of unknown origin during sleep | 0.56 | 10.81 | 28.99 | 0.00001 |
| 23. Convulsions during sleep | 0.67 | 5.41 | 4.61 | 0.035 |
| *Sleep breathing problems* | | | | |
| 24. Sleep breathing difficulties | 6.83 | 18.92 | 5.98 | 0.015 |
| 25. Sleep apnea | 1.01 | 2.70 | 0.03 | NS |
| 26. Snoring | 14.67 | 32.43 | 7.30 | 0.007 |
| *Parasomnias* | | | | |
| 27. Night sweating | 15.90 | 18.92 | 0.07 | NS |
| 28. Sleepwalking | 3.14 | 5.41 | 0.08 | NS |
| 29. Sleep talking | 14.45 | 2.70 | 3.16 | NS |
| 30. Bed-wetting | 2.35 | 35.14 | 99.30 | 0.00001 |
| 31. Bruxism | 7.39 | 21.62 | 7.98 | 0.005 |
| 32. Sleep terrors | 1.34 | 5.41 | 1.69 | NS |
| 33. Nightmares | 10.64 | 0.00 | 3.30 | NS |
| *Morning symptoms* | | | | |
| 34. Difficulty in waking up in the morning | 35.95 | 35.14 | 0.01 | NS |
| 35. Variation of waking time | 25.87 | 37.84 | 2.04 | NS |
| 36. Sleep paralysis | 4.14 | 13.51 | 5.22 | 0.025 |
| *Daytime sleepiness* | | | | |
| 37. Daytime somnolence | 4.48 | 24.32 | 24.20 | 0.00001 |
| 38. Falling asleep at school | 0.34 | 8.11 | 22.45 | 0.00001 |
| 39. Sleep attacks | 1.46 | 2.70 | 0.01 | NS |

Table 2
Comparison between AS patients aged less than 15 (group A) and those aged more than 15 years (group B)

| | Group A (%) | Group B (%) | Chi-square | $P <$ |
|---|---|---|---|---|
| *Bedtime problems* | | | | |
| 1. Sleep less than 8 h | 70.27 | 50.00 | 0.87 | NS |
| 2. Latency to sleep >30 min | 32.43 | 25.00 | 0.02 | NS |
| 3. Reluctant to go to bed | 59.46 | 50.00 | 0.06 | NS |
| 4. Bedtime variations | 48.65 | 25.00 | 1.22 | NS |
| 5. Difficulty getting to sleep at night | 56.76 | 58.33 | 0.06 | NS |
| 6. Anxiety/fear when falling asleep | 43.24 | 8.33 | 3.45 | $0.1 > P > 0.05$ |
| 7. Drink stimulant beverages in the evening | 27.03 | 0.00 | 2.58 | NS |
| 8. Need for light or TV in the bedroom | 32.43 | 33.33 | 0.57 | NS |
| 9. Need for a transitional object | 48.65 | 8.33 | 4.62 | NS |
| 10. Fluids or drugs to facilitate sleep | 32.43 | 50.00 | 0.09 | NS |
| *Sleep-wake transition disorders* | | | | |
| 11. Hypnic jerks | 59.46 | 25.00 | 3.04 | $0.1 > P > 0.05$ |
| 12. Rhythmic movements while falling asleep | 27.03 | 25.00 | 0.06 | NS |
| 13. Falling asleep sweating | 13.51 | 16.67 | 0.04 | NS |
| *Sleep quality* | | | | |
| 14. Poor sleep quality | 70.27 | 66.67 | 0.02 | NS |
| *Night awakenings* | | | | |
| 15. More than two awakenings per night | 62.16 | 58.33 | 0.01 | NS |
| 16. Waking up screaming in the night | 18.92 | 25.00 | 0.00 | NS |
| 17. Waking up to drink or eat in the night | 24.32 | 0.00 | 2.14 | NS |
| 18. Getting up to use to the bathroom | 2.70 | 8.33 | 0.00 | NS |
| 19. Difficulty to fall asleep after awakenings | 56.76 | 41.67 | 0.33 | NS |
| *Abnormal movements during sleep* | | | | |
| 20. Nocturnal hyperkinesias | 67.57 | 75.00 | 0.02 | NS |
| 21. Unusual movements during sleep | 48.65 | 25.00 | 1.22 | NS |
| 22. Pains of unknown origin during sleep | 10.81 | 0.00 | 0.34 | NS |
| 23. Convulsions during sleep | 0.67 | 5.41 | 4.61 | 0.035 |
| *Sleep breathing problems* | | | | |
| 24. Sleep breathing difficulties | 18.92 | 16.67 | 0.06 | NS |
| 25. Sleep apnea | 2.70 | 16.67 | 1.12 | NS |
| 26. Snoring | 32.43 | 50.00 | 0.57 | NS |
| *Parasomnias* | | | | |
| 27. Night sweating | 18.92 | 0.00 | 1.33 | NS |
| 28. Sleepwalking | 5.41 | 16.67 | 0.40 | NS |
| 29. Sleep talking | 2.70 | 0.00 | 0.36 | NS |
| 30. Bed-wetting | 35.14 | 50.00 | 0.33 | NS |
| 31. Bruxism | 21.62 | 8.33 | 0.36 | NS |
| 32. Sleep terrors | 5.41 | 8.33 | 0.11 | NS |
| 33. Nightmares | 0.00 | 0.00 | | |
| *Morning symptoms* | | | | |
| 34. Difficulty in waking up in the morning | 35.14 | 41.67 | 0.00 | NS |
| 35. Variation of waking time | 37.84 | 25.00 | 0.21 | NS |
| 36. Sleep paralysis | 13.51 | 8.33 | 0.00 | NS |
| *Daytime sleepiness* | | | | |
| 37. Daytime somnolence | 24.32 | 16.67 | 0.02 | NS |
| 38. Falling asleep at school | 8.11 | 8.33 | 0.34 | NS |
| 39. Sleep attacks | 2.70 | 0.00 | 0.36 | NS |

# SEMIOLOGIA CRISI



*Develop. Med. Child Neurol.* 1965, **7**, 681–688

# 'Puppet' Children

## *A Report on Three Cases*

***Harry Angelman***

**"Very frequently fits resembling a hypsarrhythmic state and a profound degree of mental retardation"**

# Seizures

- 31/34 subjects (91.2%) with seizures
- 2 of the patients without seizures had a mutation in UBE3A, 1 had UPD
- age at onset of seizures ranged from 1 month to 5 years (mean 1.92, SD 1.33)
- 17/31 subjects (54.83%) were seizure-free at the last visit; 2 of them took no AEDs at that time; recent data were not available for 1 subiect (#21)
- age at the last seizure ranged from 1 to 28 years (mean 10.47, SD 7.99)
- decreasing the dosage of AEDs in 2 patients led to recurrence of seizures (#1, #26)

# Epilepsy in patients with 15q11-13 deletion

| | Matsumoto et al., 1992 | Sugimoto et al., 1992 | Viani et al, 1995 | Guerrini et al., 1996 | Rubin et al., 1997 | Laan et al., 1997 | Minassian et al., 1998 | Our series |
|---|---|---|---|---|---|---|---|---|
| No. of cases/M | 8/3 | 3/2 | 18/13 | 9/3 | 3/3 | 36/20 | 9/4 | 20/12 |
| Epilepsy | 8/8 | 3/3 | 15/18 (83.3%) | 9/9 | 3/3 | 30/36 (83.3%) | 9/9 | 20/20 |
| Typical EEG | 8/8 | 3/3 | 18/18 | 9/9 | 3/3 | 30/36 (83.3%) | 9/9 | 20/20 |
| Age (last follow-up) | 4-26 yrs (15.63 ±6.63) | 1-6 yrs (3.33 ±2.52) | 1-28 yrs (7.97 ± 7.00) | 3-28 yrs (18.44 ±8.07) | 1-3 yrs (2.39 ±0.72) | 1yr 6 mos-39 yrs (11) | 2-41 yrs (17.11± 15.03) | 2-32 yrs (16.36 ± 8.58) |
| Age at seiz. onset | 3 mos-3 yrs (1.32 ±0.9) | 1 yr 2 mos-1 yr 7 mos | 9 mos-4 yrs 10 mos | 4 mos-5 yrs (1.42 ±1.59) | 1 -2 yrs (1.72 ±0.24) | 1 mo-5 yrs (2) | 6 mos-2 yrs (0.93 ± 0.62) | 1 mo-5 yrs (1.46 ±1.21) |
| Myoclonic status | 4/8 (50%) | 1/3 (33%) | 13/15 (86.7%) | 4/9 (44.4%) | 1/3 (33.3%) | 5/30 (16.7%) | 1/9 (11.1%) | 9/20 (45%) |
| Seizure-free (last visit) | 7/8 (87.5%) | ? | ? | ? | ? | 5/13 (38.5%) | 0/9 | 11/19 (57.9%) |

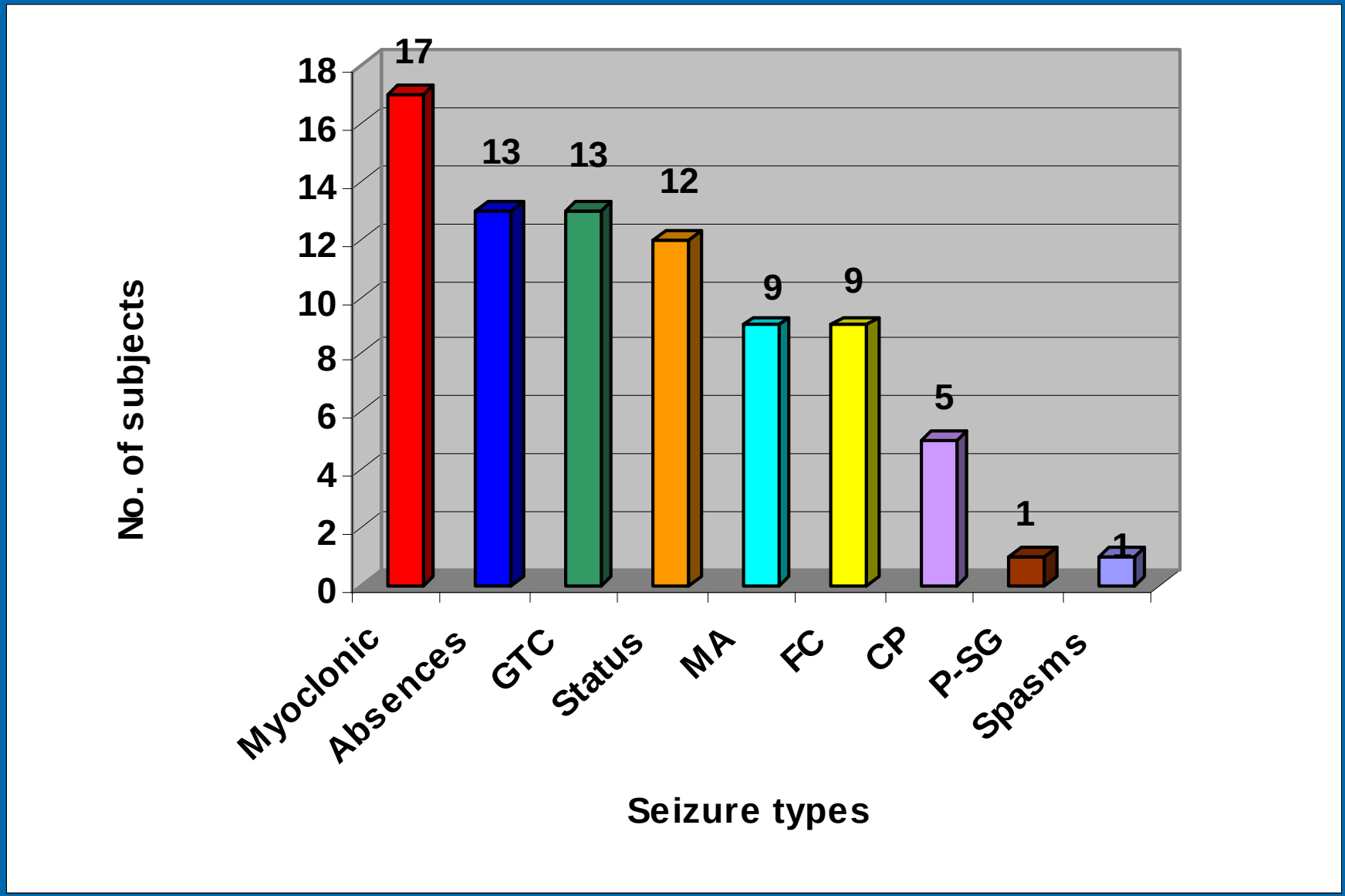
# Epilepsy in patients with UPD

| | Guerrini et al., 1996 | Minassian et al., 1998 | Our series |
|---|---|---|---|
| No. of cases/M | 2/2 | 4/4 | 4/2 |
| Epilepsy | 1/2 (50%) | 2/4 (50%) | 3/4 (75%) |
| Typical EEG | 2/2 | 3/4 (75%) | 4/4 |
| Age (last follow-up) | 7-15 yrs | 7-15 yrs (11.25 ± 4.34) | 3-15 (11.06 ± 5.48) |
| Age at seizure onset | 4 yrs | ? | 2-5 yrs (3.33 ± 1.53) |
| Myoclonic status | 0/1 | 0/2 | 0/3 |
| Seizure-free (last visit) | ? | 1/2 | 2/3 (66.7%) |

# Epilepsy in patients with UBE3A mutations

| | Minassian et al., 1998 | Moncla et al., 1999 | Laan et al., 1999 | Our series |
|---|---|---|---|---|
| No. of cases/M | 2/0 | 14/8 | 8/6 | 10/6 |
| Epilepsy | 2/2 | 11/14 (78.6%) | 5/8 (62.5%) | 8/10 (80%) |
| Typical EEG | 2/2 | 14/14 | 6/8 (75%) | 10/10 |
| Age (last follow-up) | 10-18 yrs | 5-36 yrs (17,57 ± 9,80) | 4-53 yrs (23.5 ± 14.84) | 3-32 yrs (16.42 ± 10.40) |
| Age at seizure onset | 18 yrs (case A64) | 6 mos-20 yrs (5.14 ± 5.43) | ? | 1-4 (2.5 ± 1.07) |
| Myoclonic status | 0/2 | ? | ? | 3/8 (37.5%) |
| Seizure-free (last follow-up) | 1/2 (50%) | 7/11 (63.6%) | 2/5 (40%) | 4/8 (50%) |

# Seizure types

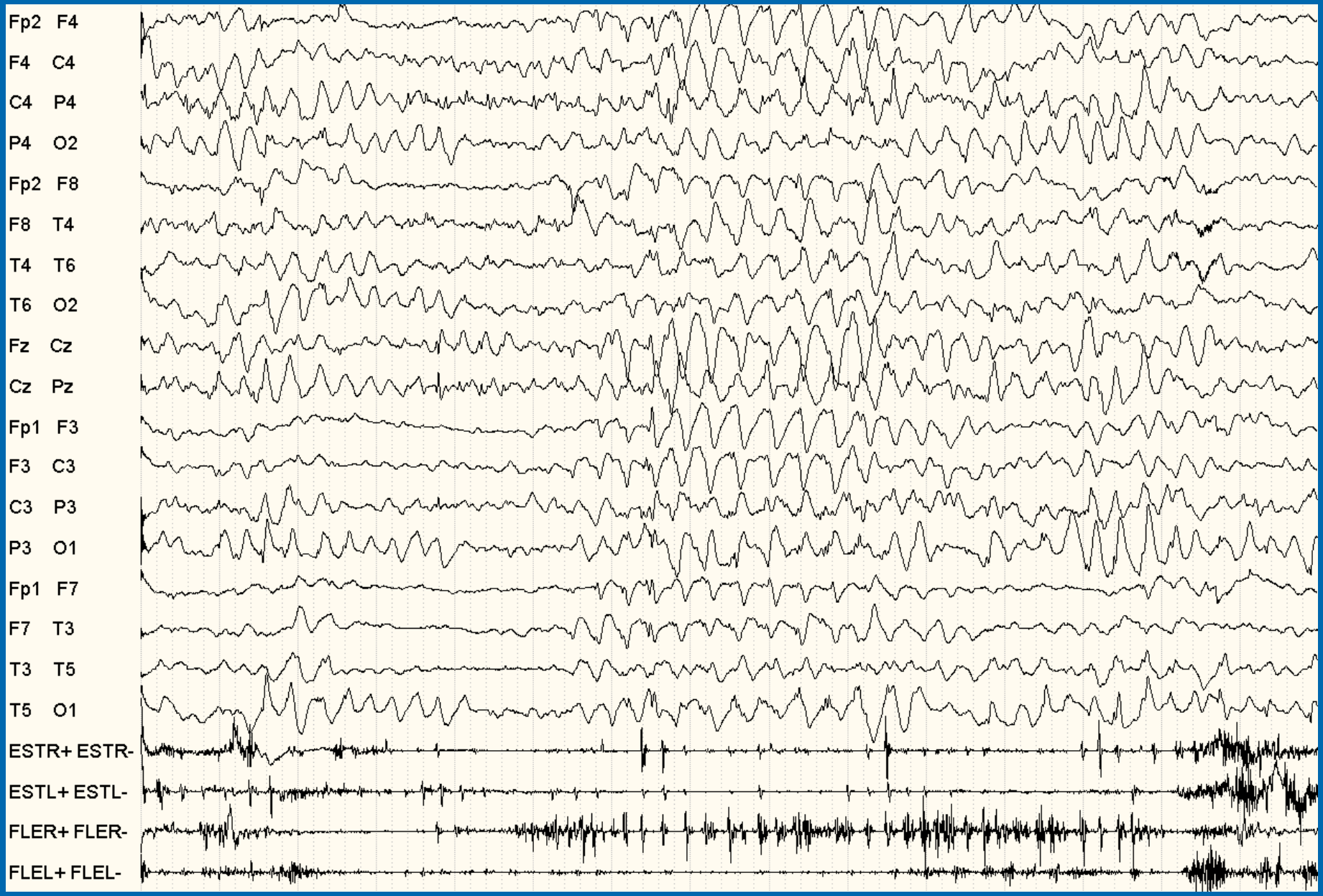


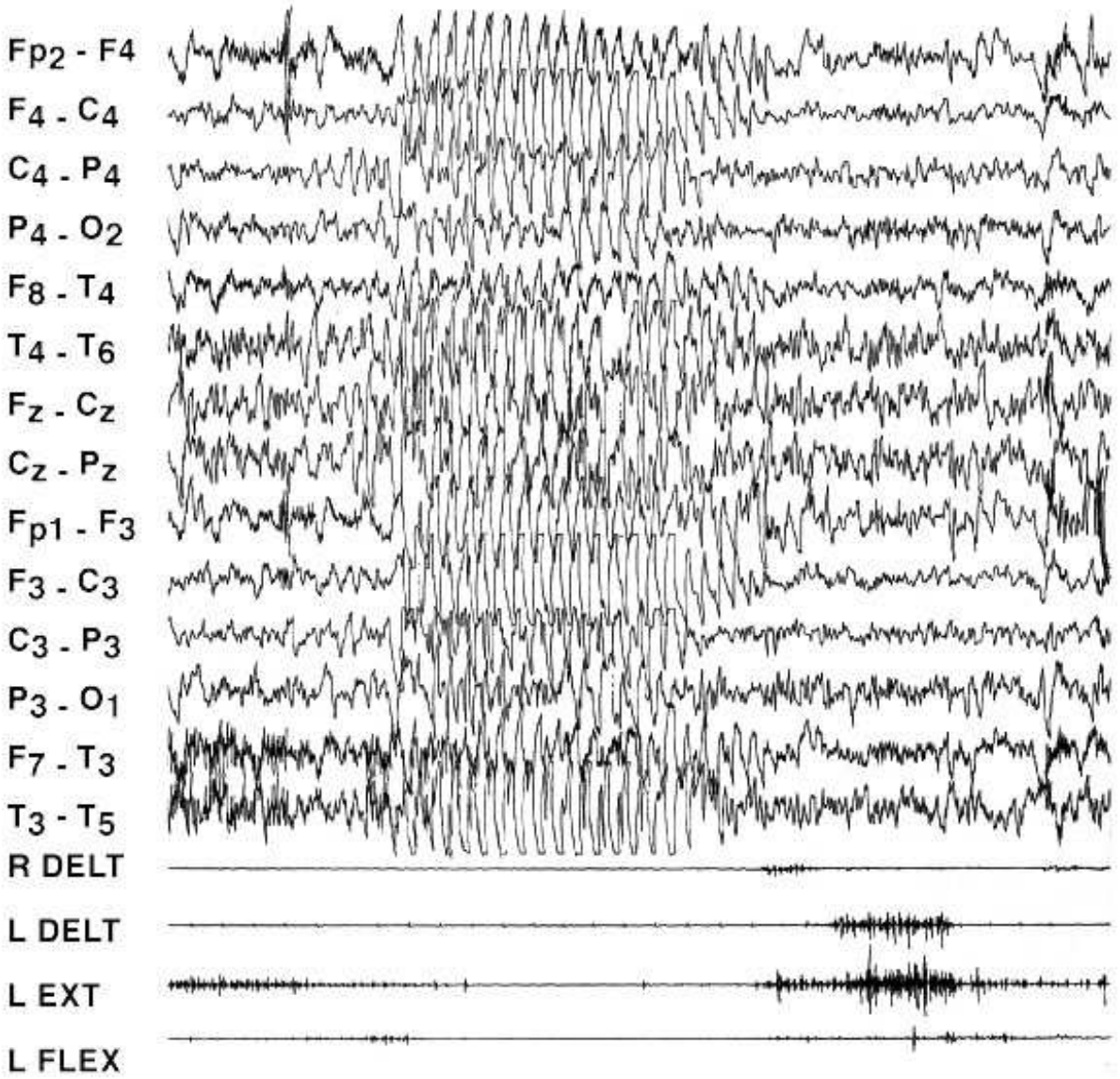
# Frequency of the seizures*

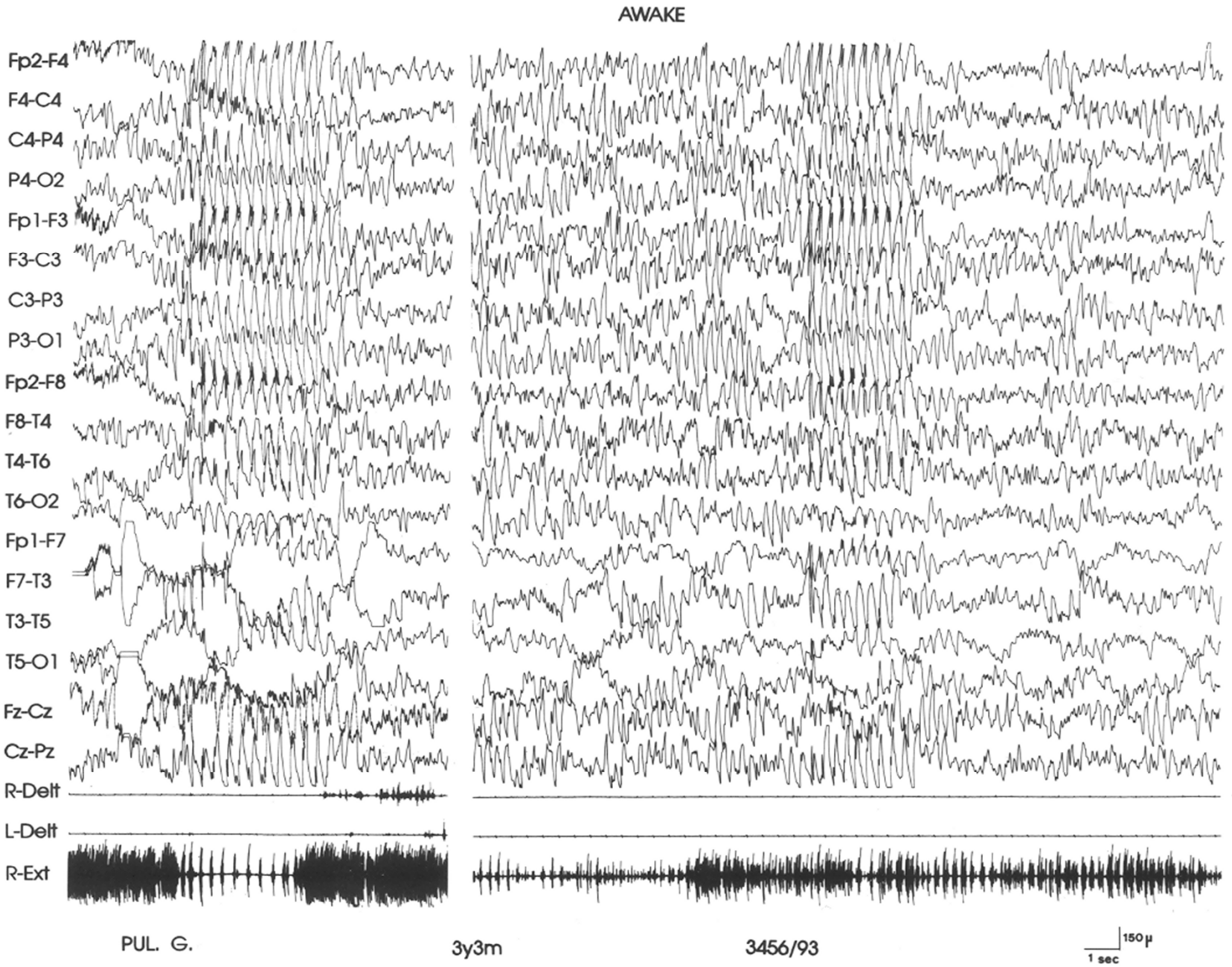
| | |
|---|---|
| >1/day | 1 |
| >1/week | 2 |
| >1/month | 1 |
| >1/year | 5 |
| sporadic | 4 |

* subjects presenting seizures at the last visit (n=13)

# S.A., male, 5 yrs old - 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
R DELT
L DELT
L EXT
L FLEX
BUS ELI 11 yrs 17 / 06 /98 FBF MI
50 µ V
1 sec


AWAKE
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
R-Ext
PUL. G.
3y3m
3456/93
150 µ
1 sec

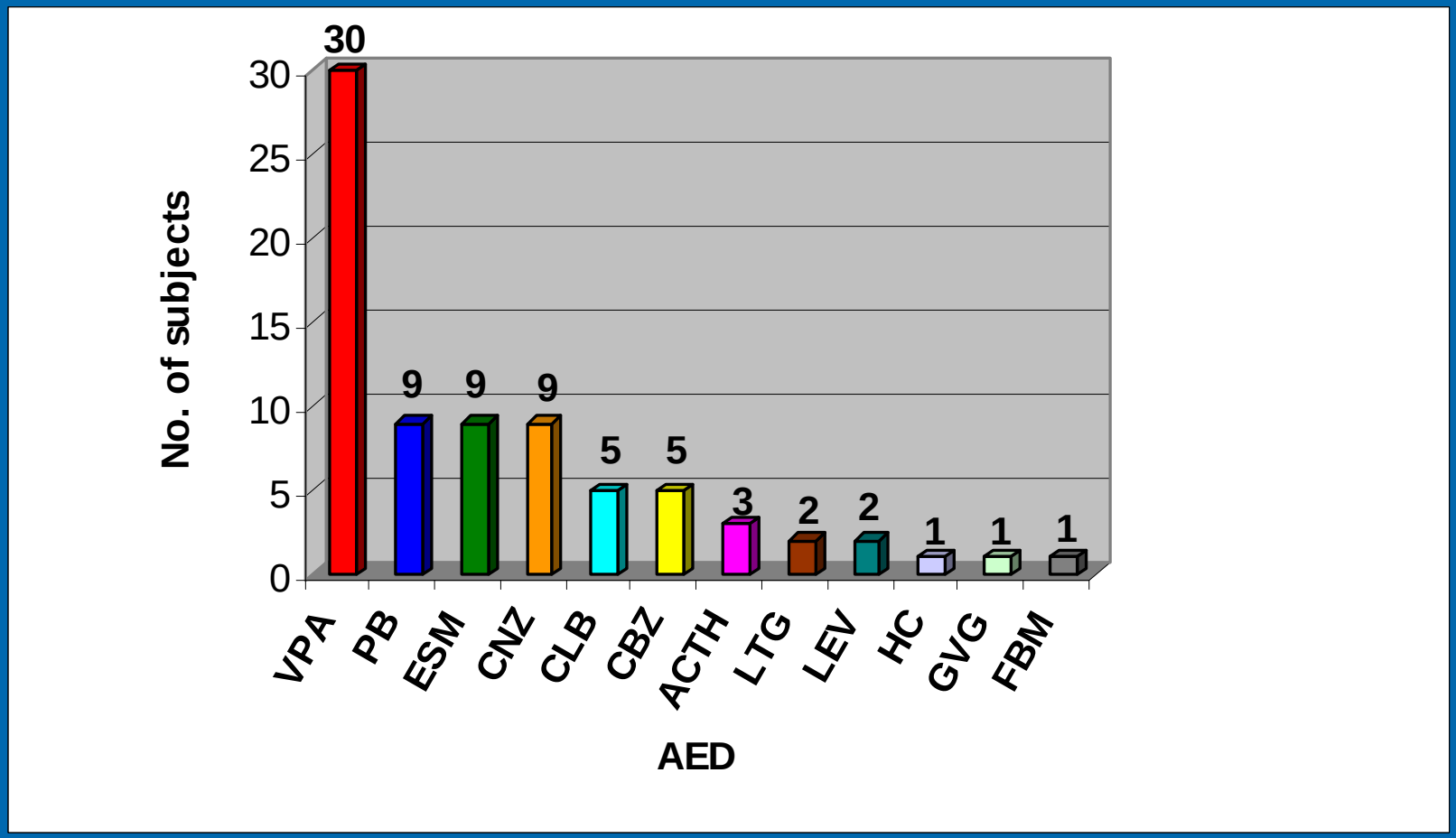
# EEG

- in 31/34 subjects (91.2%) at least one EEG recording showed diffuse discharges of spike-and-wave (SW) complexes
- in 30/34 subjects (88.2%) EEG disclosed multifocal posterior SWs
- in 3/34 patients (8.82%) multifocal frontal paroxysmal abnormalities (SWs) were present
- in 6/34 patients (17.65%), multifocal frontal and posterior SWs were found
- in 3 cases focal (central or temporal) SWs were present
- in 18/28 sleep recording spindles and K complexes were recognizable

# Clinical and EEG pattern: DD

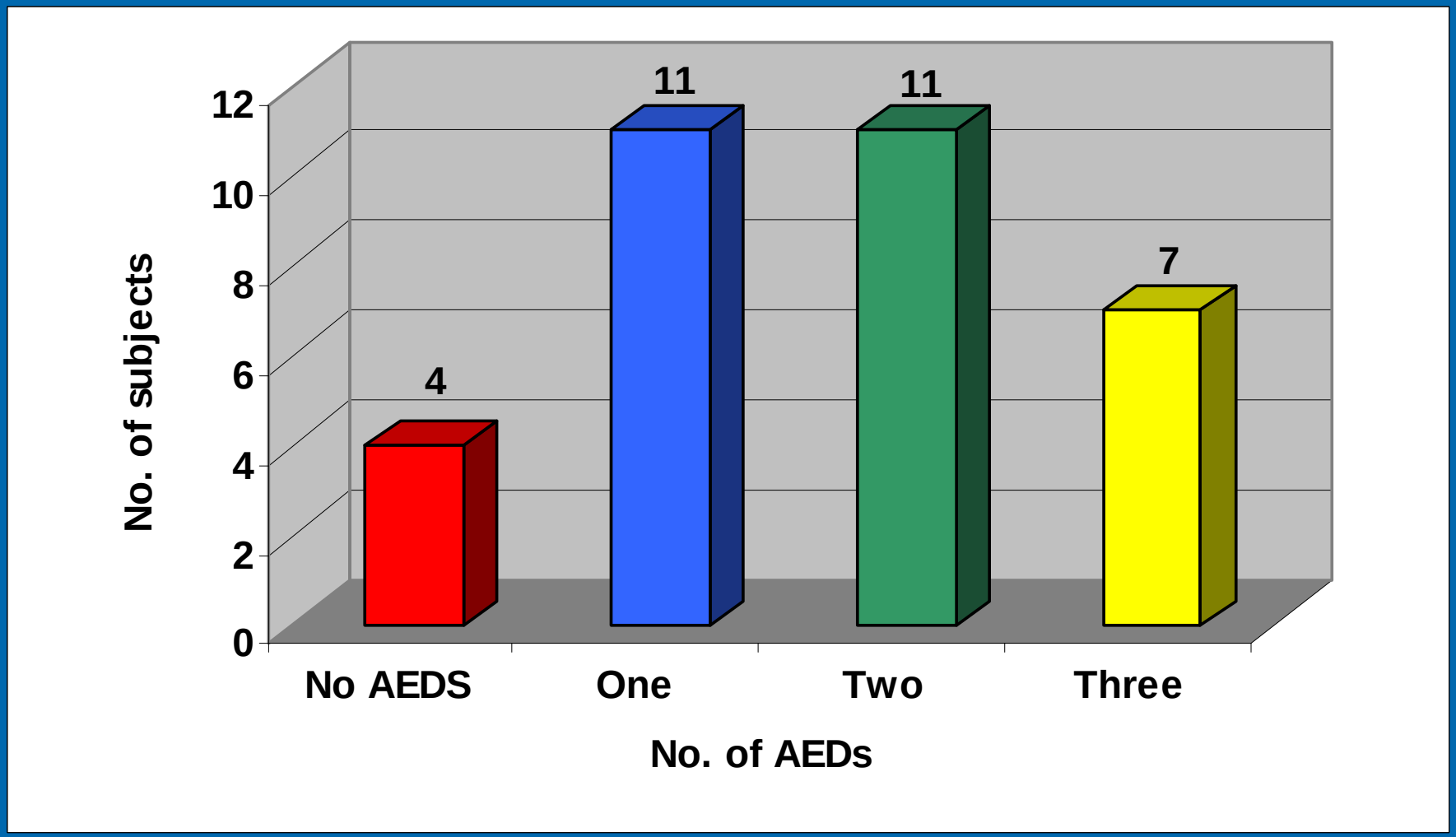
- ***fetal and neonatal anoxic injury*** **(cerebral palsy)**
- ***newborn continuous partial epilepsy*****: initial neurological picture is normal; the jerks are more rhythmic; a severe progressive intellectual deterioration quickly appears**
- ***epileptic encephalopathy*****: cognitive deterioration;drug-resistant seizures; presence of tonic and atonic seizures**
- ***Wolf-Hirschhorn syndrome (4p-)*****: slow BA & 2-3 Hz high-voltage slow-wave bursts biparietally, mainly elicited by eye closure; SW complexes, and high-voltage bifrontal slow-wave bursts**
- ***trisomy 12p syndrome*****: diffuse SW complexes; myoclonic-like absences; "myoclonic status" never reported**

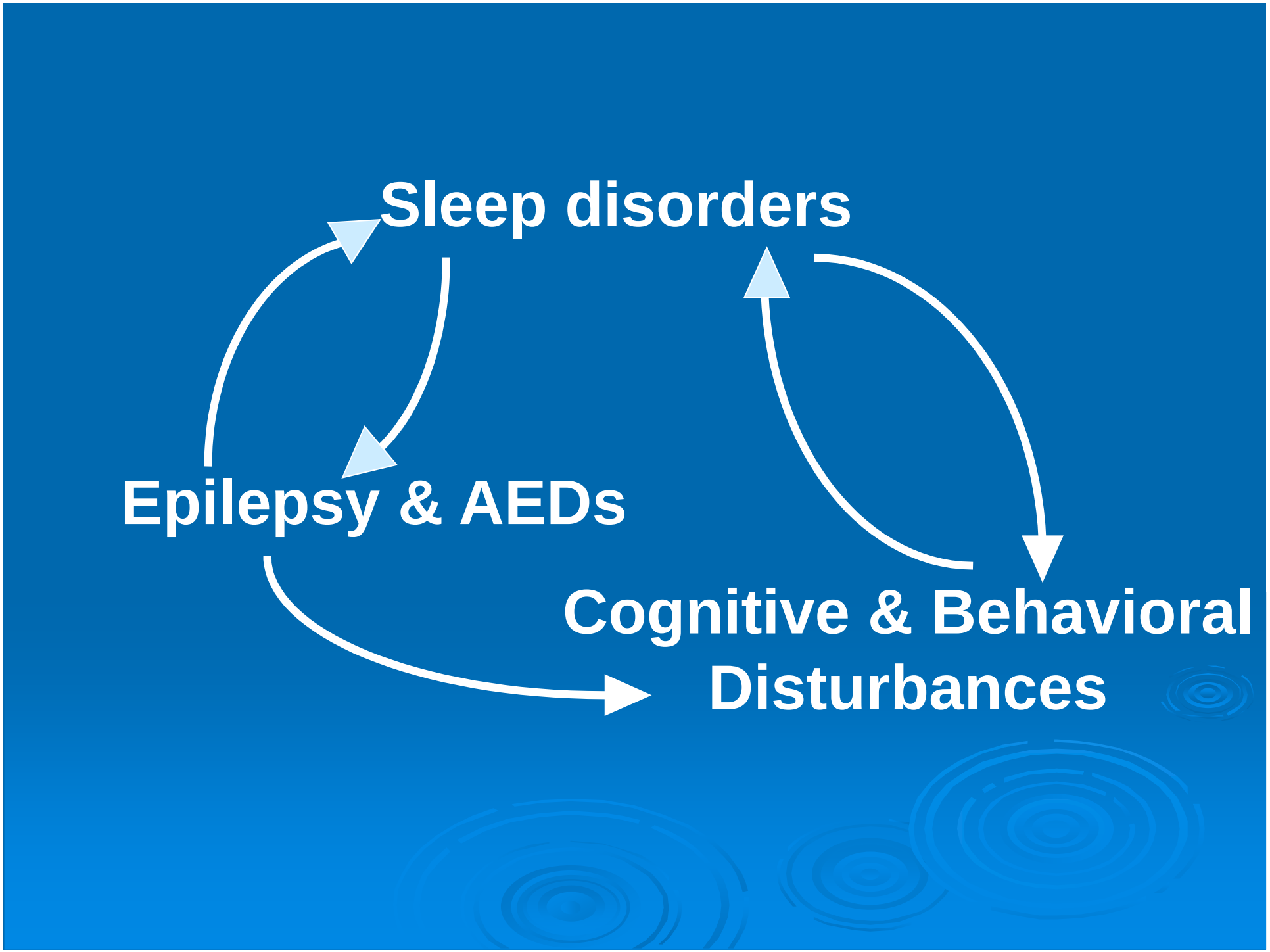
# AEDS*




*only 3/34 patients (# 2,14, 17) never took AEDS; 2 of them had no seizures
1 patient (#28) discontinued AEDs
1 patient without seizures (#3) was treated with AEDs

# Number of AEDS at the last visit




Sleep disorders
Epilepsy & AEDs
Cognitive & Behavioral Disturbances