Epileptic Encephalopathy With Continuous Spike And Wave During Sleep: Caratterizzazione clinica, neurofisiologica e neuropsicologica

Valentina De Giorgis, MD PhD
Martina Zanaboni, Spec. in Neuropsicologia e Psicoterapia
**the «TRUE EPILEPTIC ENCEPHALOPATHY»**

The cognitive and behavioural difficulties are the direct result of the underlying epileptic activity and any targeted treatment.

- **Subclinical Electric Status Epilepticus induced by sleep**
  Patry et al., 1971

- **Encephalopathy related to status epilepticus during slow sleep (ESES)**
  Tassinari et al., 1977

- **Epilepsy with continuous spikes and waves during slow sleep (ECSWS)**
  Tassinari et al., 1985 – Palayiotopoulos, 2005

- **Continuous spikes and waves during sleep (CSWS)**
  Commission on Classification and Terminology of ILAE, Engel 2006

- **Epileptic Encephalopathy with Continuous Spike and Waves during Sleep (ESES)**
  Commission on Classification and Terminology of ILAE, Berg et al., 2010
**CSWS: TYPICAL SYMPTOMS**

*Hallmark: a significant increase in EEG abnormalities during sleep with presence of neurocognitive impairment*

<table>
<thead>
<tr>
<th>Clinic</th>
<th>EEG</th>
<th>NPS characterization</th>
<th>Treatment</th>
<th>Clinical Study</th>
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</thead>
</table>
| ++ Neuropsychological impairment
  Global or Selective cognitive or Language regression |
| ++ Typical EEG pattern
  continuous epileptiform activity in NREM sleep |
| + Epilepsy, with focal or generalized seizures
  clonic; tonic–clonic; absence; focal-motor; focal-complex; negative myoclonus |
| +/- Motor deterioration
  ataxia, dyspraxia, dystonia or unilateral deficits |
ETIOLOGY

A complex interplay between brain development, maturation processes and susceptibility genes

- **Structural**
  Perinatal infarction, Brain malformation, Thalamic injury, Shunted Hydrocephalus, POLYMICROGYRIA

- **Genetic**
  GRIN2A: cognitive disability, focal epilepsy, ESES, autistic-like disability
  CNKSR2: epilepsy-aphasia spectrum
  SRPX2: RE, verbal dyspraxia, and intellectual disability, autism

- **Idiopathic – Self limited**
  Regular development before epilepsy onset, no brain lesions
  ECTS (Rolandic) – Atypical ECTS – Panayiotopoulos - Gastaut

- **Unknown – Cryptogenic**
  Developmental delay before epilepsy onset, dysmorphic features, comorbidities
CSWS

- **Encephalopathy with SES**
  different seizure types, combinations of cognitive, motor, and behavioural disturbances, and CSWS EEG pattern

- **Landau-Kleffner Syndrome**
  acquired aphasia, seizures, neuropsychological deficit, behavioural disturbances and CSWS

- **Acquired epileptiform opercular syndrome**
  oro-facio-lingual deficits, focal motor seizures involving the face and occasionally rolandic, partial complex, or atypical absences, neuropsychological deficit and CSWS

- **Atypical Benign epilepsy with centro-temporal spikes (BECTS)**
  early age at onset, frequent spikes or spike-wave discharges in awake, severe neuropsychological impairment and CSWS pattern
CSWS – 3 MAIN GROUPS

Static frames of an evolutive multifactorial age-related condition

- **PERVASIVE**
  Language, memory, spatial orientation, ADHD, autistic-like behaviours

- **COMBINED – multiple concomitant disfunctions**
  Temporal (language in LKS), frontal, occipital, parietal dysfunction, spatio-temporal or motor disturbances (negative myoclonus, dyspraxias, gait disorders)

- **SELECTIVE**
  Unique specific impairment restricted to a limited number of cortical columns

**Figure 1.** EEG and MEG. In Patient 1, persistent 1-2 Hz generalised spikes and waves, dominant in the occipito-temporal region, were recorded on EEG (A), and dipole clusters in and around the posterior inferior temporal cortex were recorded on MEG (B). In Patient 2, persistent 3-5 Hz generalised spikes and waves, dominant in the occipito-temporal region, were recorded on EEG (C), and dipole clusters in and around the posterior inferior temporal cortex were recorded on MEG (D).
Epileptic encephalopathy with continuous spikes and waves in the occipito-temporal region during slow-wave sleep in two patients with acquired Kanji dysgraphia

Ichiro Kuki, Hisashi Kawakami, Shin Okazaki, Hiroko Ikeda, Kiyotaka Tomiwa
Department of Pediatric Neurology, Child Medical Center, Osaka City General Hospital, Osaka, Japan
Received April 16, 2014; Accepted August 8, 2014

Figure 2: Schematic illustration of Kanji tasks and representative errors in writing Kanji.
In the examples given, the patients were presented with words written in Kanji (first columns on the left) and they wrote the Kanji for these words (second column, handwriting). The correct Kanji are shown in the third columns, and the types of dysgraphia are explained in the fourth column.

Figure 3: A.V.'s performance in the copying task (NEPSY [24]). The tendency to copy parts of the objects separately is shown with this task example. The model figures are in the upper row above A.V.'s performance.
CSWS - EVOLUTION

I STAGE
Pre-CSWS period
Infrequent nocturnal motor focal seizures
EEG:
- nonREM potentiation of spiking
- focal-multifocal SW (CT-F-PO)

II STAGE
CSWS period
Frequent seizures
Absences, Myoclonic, Atonic, Clonic
EEG:
- Abnormal background
- Widespread spikes of higher amplitude
- SWI >85%
Cognitive, Language, Behavior, Motor deterioration

III STAGE
CSWS evolution
Seizures remit
EEG:
- Normalization of interictal activity
Cognitive, Language improvement (but not normalization)

OUTCOME AND PROGNOSIS

CSWS disappear after 11-12y
Seizures usually disappear with puberty
Residual moderate to severe neurocognitive impairments persist
Poor prognosis when:
- Symptomatic/structural
- Early onset seizures
- Resistance to AEDs
- DURATION OF CSWS

CRITICAL PERIOD & PLASTICITY
CSWS: TYPICAL EEG pattern

diffuse bilateral
and/or unilateral or focal localization
rhythmic high-amplitude spikes and waves

occuring in slow sleep (NREM)
persisting on 3 or more recordings over a period of at least 1 month
CSWS: EPILEPTIFORM ACTIVITY

Morphology Parameters for a syndromic and/or etiological assessment

Amplitude

EEG

Topography

Before ESES: FC – CT – T – P – O – Vertex
During ESES: migration to frontal regions
ESES offset: moving back to the original topography

Developmental Stages

AEDs

Clinic

NPS characterization

Treatment

Clinical study
CSWS: EPILEPTIFORM ACTIVITY

Morphology
Parameters for a syndromic and/or etiological assessment

Amplitude

Clinic

EEG

NPS characterization

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CSWS: EPILEPTIFORM ACTIVITY

Morphology

Parameters for a syndromic and/or etiological assessment

Amplitude

Definition

Clinic

EEG

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Treatment

Clinical study
CSWS: EPILEPTIFORM ACTIVITY

- **Morphology**
- **Amplitude**

Parameters for a syndromic and/or etiological assessment

**Definition**

**Clinic**

**EEG**

**NPS characterization**

**Treatment**

**Clinical study**
CSWS: TYPICAL EEG pattern

**WAKEFULNESS:**
Focal Slow Activity reflecting the main epileptic focus
Burst of diffuse SW (abesences) +/-diffuse PoliWS (atonic – myoclonic)

**NREM:**
- SW slower and more rhythmic during slow sleep (from a secondary bilateral/unilateral synchronization of the focal / multifocal SW)
- Transition between diffuse, hemisferic and focal pattern
- Fragmented EEG

**REM:**
- Focal SW (similar to wakefulness)
- Brief bursts of diffuse SW (arousal)
CSWS: TYPICAL EEG pattern
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## CSWS: MEASURES

**SPIKE AND WAVE INDEX**: percentage of NREM sleep occupied by spikes and waves (time occupied by epileptiform activities)

<table>
<thead>
<tr>
<th>Methods</th>
<th>Visual estimation</th>
</tr>
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<tr>
<td></td>
<td>Computer-aided spike detection</td>
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<tr>
<th>Cut off</th>
<th>85/90% - 50% - 25%</th>
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<td>Lack of the accepted criteria for the diagnosis of ESES</td>
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<th>Fluctuating</th>
<th>In the same patient during the course of ESES</th>
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<td></td>
<td>Within the same night (++ first part of night)</td>
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</table>
**CSWS: MEASURES**

**SPIKE AND WAVE INDEX**: percentage of NREM sleep occupied by spikes and waves (time occupied by epileptiform activities)

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**Methods**
- Visual estimation
- Computer-aided spike detection
- Cut off: 85/90% - 50% - 25%
- Lack of the accepted criteria for the diagnosis of ESES
- Fluctuating: In the same patient during the course of ESES, Within the same night (++ first part of night)

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**Definition**

- Clinic EEG
  - NPS characterization
  - Treatment Clinical study

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*Figure 1.* Frequency distribution of SWI - computed according to Larsson et al., 2009 with max ISI=3 - based on 1913 consecutive recordings. The x-axis corresponds to SWI during sleep and the y-axis to the number of recordings within a given SWI interval. (Data from PG1).
CSWS: MEASURES

**SLEEP STRUCTURE**

Presence/absence of sleep graphoelements
Alternating NREM/REM stages

Markers of fragmentation/instability
in sleep microstructure

**SPINDLES**  Consolidation of memory – maintenance of cognitive functions – EXECUTIVE FUNCTIONS
(working memory – cognitive flexibility – problem solving)

Chatburn, 2013
Astill et al., 2014
Vermeulen et al., 2018
CSWS: MEASURES

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Presence/absence of sleep graphoelements
Alternating NREM/REM stages

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CSWS: MEASURES

**Definition**

Clinic EEG NPS characterization

**Treatment**

Clinical study

**Presence/absence of sleep graphoelements**

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**SPINDLES**

Consolidation of memory – maintenance of cognitive functions – executive functions (working memory – cognitive flexibility – problem solving)

Chatburn, 2013

Astill et al., 2014

Vermeulen et al., 2018

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[Image of EEG waves]
CSWS: MEASURES

**SLOW WAVES DOWNSCALING**
Absence of progressive renormalization (downscaling) of synaptic strength occurring during sleep – Altered overnight decrease of slow wave slope

Wakefulness → Learning Process → Synchronization of large cortical areas → High synaptic strength

Overnight → Synaptic weakening/elimination → decrease of the SWA slope → Physiologic sleep-related synaptic downscaling

*References*
- Tononi & Cirelli, 2014
- Esser et al., 2007
- Riedner et al., 2007
- Bolsterli et al., 2017
NEW NEUROIMAGING TECHNIQUES AND BEYOND

- **EEG-fMRI**

- **DIFFUSION TENSOR IMAGING TRACTOGRAPHY**
  age-dependent difference and heritability of the perisylvian language network, altered white matter connectivity, motor networks related to behavior, cognitive and motor tasks

Parlatini et al., 2017

Budisavljevic et al., 2014

- **EEG COHERENCE STUDIES**
  functional brain connectivity as a measure of functional association between 2 brain regions

\[
\text{Coherence } (f) = \left( \frac{G_{xy}(f)}{G_{xx}(f) G_{yy}(f)} \right)^2
\]

Mott et al., 2019
CSWS: COGNITION

Cognitive regression/Stagnation (>12pts)
Language regression
Learning disabilities
Behavioural disturbances (ADHD)

Geographical Prominence of SWA
Temporal: LKS
Fronto-Central: Rolandoic
Occipital: visuo-spatial

Common-to-all basic diagnostic assessment
- Intelligence
- Language
- Memory
- Attention
- Visuo-spatial
- Executive Functions

Arzimanoglou & Cross., 2019
treatment goals include not only the improvement in seizure control, but even more important a reduction in EEG abnormalities and consequently neuropathological deficits.

Avoid: PB, PHT, CBZ, OXC
Intravenous methylprednisolone pulse therapy for children with epileptic encephalopathy

**Definition**

**Clinic**

**EEG**

**NPS characterization**

**TREATMENT**

**Clinical study**

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<table>
<thead>
<tr>
<th>Case/sex</th>
<th>Epilepsy syndrome</th>
<th>Neurological problems before epilepsy</th>
<th>Neurological problems at the start of PT</th>
<th>Outcome after PT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F</td>
<td>ESES</td>
<td>Minimum motor development</td>
<td>Severe mental retardation (TIQ 38)</td>
<td>No change</td>
</tr>
<tr>
<td>2/M</td>
<td>ESES</td>
<td>Normal</td>
<td>Mild mental retardation (TIQ 68)</td>
<td>School-learning ability and minimum IQ improved (TIQ 70)</td>
</tr>
<tr>
<td>3/F</td>
<td>ESES</td>
<td>Normal</td>
<td>Mild mental retardation (TIQ 63)</td>
<td>Borderline mental impairment (TIQ 75)</td>
</tr>
<tr>
<td>4/F</td>
<td>ESES</td>
<td>Normal</td>
<td>Normal IQ (TIQ 86)</td>
<td>Normal IQ (TIQ 90)</td>
</tr>
<tr>
<td>5/M</td>
<td>ESES</td>
<td>Normal</td>
<td>Severe mental retardation (TIQ 20)</td>
<td>No change</td>
</tr>
<tr>
<td>6/M</td>
<td>ESES</td>
<td>Normal</td>
<td>Aphasia and moderate performance impairment (PIQ 50)</td>
<td>Language gain (about 20 words) and performance improvement (PIQ 65)</td>
</tr>
</tbody>
</table>

No significant or persistent side effects were noted, in particular only a modest transient hyperglycemia in the 24 hours after infusion in 1 patient and a modest weight gain in 1 patient.

- Significant reduction (p<0.013) of seizure frequency
- The frequency of epileptic seizures was reduced by more than 50% in 4/6
- 4 patients showed a dramatic improvement on EEG with reduction of abnormal SWDs (p<0.0028)
AIM OF THE STUDY
To find possible correlations between clinical variables and ESES/CSWS outcome, with the aim to identify possible factors involved in a worse long-term cognitive and behavioral outcome in patients affected by ESES/CSWS with a SWI ≥ 50

RESULTS
71 patients (36 males and 35 females)
Mean follow-up: 6.1 years (range 2-11).
Mean age at first seizure onset: 3.9 years (range 0-12)
Mean age at ESES/CSWS onset: 5.7 years (range 2-14)
Mean ESES/CSWS duration: 1.84 years (range 0.4-4)

17 pt: ischemic birth injuries (porencephaly, periventricular leukomalacia)
4 pt: brain infections (3 congenital cytomegalovirus infections, 1 meningitis)
3 pt: focal or diffuse cortical dysplasia, 1 pt: ganglioloma
1 pt: thalamic cavernous angioma
1 pt: Leber Congenital Amaurosis
5 genetic alterations (cromosom translocation, del4q13.1, dup-inv 15q)
At T0 most patients presented seizures during night sleep (47.9%).
At T1 both in daytime and sleep (49.2%).
At T2 seizure freedom 59.1% (7pt night, 9pt day, 7 pt both).

SWI was measured through a nocturnal polygraphic monitoring EEG recording in all patients during ESES/CSWS period (t1) and we found a mean SWI of 78% on our patients with a range from 50% to 95%.
FOCAL SLOW ACTIVITY IN SLEEP

73.4% of patients

even if this pattern apparently doesn’t correlate with ESES outcome (seizures, neuropsychological and motor findings, drug-resistance)
WHAT’S NEW

- **Patients who presented** sleep disorder **before ESES/CSWS onset** were those who showed worst cognitive outcome \((p<0.05)\) and more evident drug resistance \((p<0.05)\).

- **Motor impairment** was seen at ESES onset in 16% of patients.

- **Negative outcome** was evident in patients who essayed the higher number of AEDs \((p<0.05)\).

- Brain MRI examination was found to be normal in 57.6% of our patients. CSWS develops not only due to a macroscopic structural abnormality, but also as a result of a functional disorder of the brain.

- **Language disturbance** (39%) could be considered a pervasive and persistent symptom of the CSWS itself, regardless the etiology or natural history of the other symptoms.
TREATMENT EFFICACY

**Steroids** 48%
**Benzodiazepine** 20%
**Sulthiame** 18%
**Levetiracetam** 8%
**Etosuximide** 6%

**DRUG-RESISTANCE**

- Prevalent in lesional patients, not in idiopathic ones (p=0.002)
- In patients who had a developmental delay before ESES/CSWS (P=0.04)
16 «Idiopathic» Patients (8 M, 8 F)
Mean Age at onset 6.25
(range 2.4 – 9)
Follow-up 7.6 years
(3-16 aa)

Detailed neuropsychological assessment

<table>
<thead>
<tr>
<th>Area</th>
<th>Test</th>
<th>Parameter to be assessed</th>
<th>Borderline</th>
<th>Pathological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive assessment</td>
<td>WISC-IIIa</td>
<td>Cognitive profile</td>
<td>Q10; 85-71</td>
<td>Q&lt;0.05; 70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Q10; 85-71</td>
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<td></td>
<td>Q10; 85-71</td>
<td>Q&lt;0.05; 70</td>
</tr>
<tr>
<td>Reading</td>
<td>DDEBs (task 4 – word reading)</td>
<td>Accuracy</td>
<td>Z-score &lt; 2</td>
<td>Z-score &gt; 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Speed</td>
<td>Z-score &lt; 2</td>
<td>Z-score &gt; 2</td>
</tr>
<tr>
<td>Writing</td>
<td>DDEBs (task 10 – word dictation)</td>
<td>Accuracy</td>
<td>Z-score &lt; 2</td>
<td>Z-score &gt; 2</td>
</tr>
<tr>
<td>Calculation</td>
<td>BDE (forward and backward enumeration, number reading, number dictation, number repetition, number ordering)</td>
<td>Numerical competence</td>
<td>Weighted score 5-7</td>
<td>Weighted score &lt;5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BDE (multiplication, table, mental calculation, written calculation)</td>
<td>Calculation competence</td>
<td>Weighted score 5-7</td>
</tr>
<tr>
<td>Visual motor integration test</td>
<td>VMI</td>
<td>visuo-constructive abilities</td>
<td>10-25 percentile</td>
<td>&lt;10 percentile</td>
</tr>
<tr>
<td>Short term memory test</td>
<td>MBT</td>
<td>verbal, digits and visuo-constructive short term memory</td>
<td>Z-score &lt; 2</td>
<td>Z-score &lt; 2</td>
</tr>
<tr>
<td>Visuospatial attention battery</td>
<td>TCM</td>
<td>speed</td>
<td>10-25 percentile</td>
<td>&lt;10 percentile</td>
</tr>
</tbody>
</table>

Definition
Clinic
EEG
NPS characterization
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CLINICAL STUDY

Neurobehavioral consequences of continuous spike and waves during slow sleep (CSWS) in a pediatric population: A pattern of developmental hindrance
Valentina De Giorgi, Melissa Filippini, Joyce Ann Macasaet, Silvia Masnada, Pierangelo Veggio

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<table>
<thead>
<tr>
<th>Patient</th>
<th>ESES onset (year)</th>
<th>Duration of Follow-up (year)</th>
<th>Sex</th>
<th>T0 Comorbilities</th>
<th>T0 Comorbilities</th>
<th>T0 Seizures</th>
<th>T0 EEG discharge</th>
<th>T0 SWI</th>
<th>Diagnosis</th>
<th>ESES Therapy</th>
<th>T0 Intelligence Quotient</th>
<th>TI Intelligence Quotient</th>
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<tbody>
<tr>
<td>#1</td>
<td>5</td>
<td>6</td>
<td>M</td>
<td>delayed speech</td>
<td>behavioral problems</td>
<td>motor focal</td>
<td>Temporal left</td>
<td>80</td>
<td>Atypical</td>
<td>BECTS</td>
<td>HC + VPA + ETS</td>
<td>TIQ 76</td>
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<tr>
<td>#2</td>
<td>6.6</td>
<td>3</td>
<td>M</td>
<td>delayed speech</td>
<td>emotional social problems</td>
<td>atonic</td>
<td>Temporal right</td>
<td>50</td>
<td>LKS</td>
<td>HC + CLB + VPA</td>
<td>TIQ 84</td>
<td>VIQ 79</td>
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<tr>
<td>#3</td>
<td>5.5</td>
<td>6</td>
<td>M</td>
<td>delayed speech</td>
<td>hyperactivity</td>
<td>tonic</td>
<td>Temporal left</td>
<td>80</td>
<td>LKS</td>
<td>HC + LEV + ETS</td>
<td>TIQ 79</td>
<td>VIQ 74</td>
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<td>#4</td>
<td>9</td>
<td>10</td>
<td>F</td>
<td>delayed speech</td>
<td>behavioral problems</td>
<td>myoclonic</td>
<td>Frontal bilateral</td>
<td>70</td>
<td>ESES</td>
<td>STH + VPA + CLB</td>
<td>TIQ 74</td>
<td>VIQ 77</td>
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<td>HC + VPA</td>
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<td>3</td>
<td>M</td>
<td>emotional-social problems</td>
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<td>motor focal</td>
<td>Temporal right</td>
<td>80</td>
<td>Atypical</td>
<td>BECTS</td>
<td>HC + VPA</td>
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<tr>
<td>#7</td>
<td>2.4</td>
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<td>no</td>
<td>no</td>
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<td>Central bilateral</td>
<td>50</td>
<td>ESES</td>
<td>ETS + CLB</td>
<td>TIQ 88</td>
<td>VIQ 86</td>
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<td>8</td>
<td>M</td>
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<td>hyperactivity</td>
<td>motor focal</td>
<td>Central left</td>
<td>90</td>
<td>ESES</td>
<td>VPA + CLB</td>
<td>TIQ 87</td>
<td>VIQ 74</td>
</tr>
<tr>
<td>#9</td>
<td>4.5</td>
<td>9</td>
<td>F</td>
<td>no</td>
<td>behavioral problems</td>
<td>motor focal</td>
<td>Temporal left</td>
<td>80</td>
<td>ESES</td>
<td>STH + ETS</td>
<td>TIQ 99</td>
<td>VIQ 84</td>
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<td>#10</td>
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<td>12</td>
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<td>tonic–clonic</td>
<td>Temporal left</td>
<td>80</td>
<td>ESES</td>
<td>ETS + CLB</td>
<td>TIQ 75</td>
<td>VIQ 59</td>
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<td>6.25</td>
<td>16</td>
<td>F</td>
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<td>motor focal</td>
<td>Frontal right</td>
<td>80</td>
<td>ESES</td>
<td>VPA + CLB</td>
<td>TIQ 101</td>
<td>VIQ 93</td>
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<tr>
<td>#12</td>
<td>6.4</td>
<td>9</td>
<td>F</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>Central right</td>
<td>70</td>
<td>ESES</td>
<td>HC + VPA + ETS</td>
<td>TIQ 63</td>
<td>VIQ 52</td>
</tr>
<tr>
<td>#13</td>
<td>6.5</td>
<td>12</td>
<td>F</td>
<td>behavioral problems</td>
<td>hyperactivity</td>
<td>motor focal</td>
<td>Central bilateral</td>
<td>75</td>
<td>ESES</td>
<td>STH + CLB</td>
<td>TIQ 93</td>
<td>VIQ 81</td>
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<td>#14</td>
<td>8.4</td>
<td>8</td>
<td>M</td>
<td>hyperactivity</td>
<td>hyperactivity</td>
<td>motor focal</td>
<td>Temporal left</td>
<td>80</td>
<td>Atypical</td>
<td>BECTS</td>
<td>VPA + HC</td>
<td>TIQ 34</td>
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<tr>
<td>#15</td>
<td>11</td>
<td>5</td>
<td>M</td>
<td>emotional-social problems</td>
<td>emotional-social problems</td>
<td>motor focal</td>
<td>Temporal right</td>
<td>70</td>
<td>Atypical</td>
<td>BECTS</td>
<td>STH + VPA + LEV</td>
<td>TIQ 35</td>
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<tr>
<td>#16</td>
<td>6.25</td>
<td>5</td>
<td>M</td>
<td>no</td>
<td>behavioral problems</td>
<td>motor focal</td>
<td>Central right</td>
<td>80</td>
<td>Atypical</td>
<td>BECTS</td>
<td>HC + ETS + VPA</td>
<td>TIQ 69</td>
</tr>
</tbody>
</table>
Wechsler scales

T0 Baseline – T1 Remission

VIQ ↓: da 71.84 a 68.55
PIQ ↑: da 77 a 85
p-value 0.004
**Cognitive evolution and age at onset**

<table>
<thead>
<tr>
<th>Group</th>
<th>IQ Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: early onset (&lt; 6 aa)</td>
<td>TIQ: 61 to 62; VIQ: 63 to 59; PIQ: 66 to 69</td>
</tr>
<tr>
<td>Group 2: mid-onset (età 6-7 aa)</td>
<td>TIQ: 72 to 75; VIQ: 75 to 73; PIQ: 73 to 83</td>
</tr>
<tr>
<td>Group 3: late onset (&gt; 8 aa)</td>
<td>TIQ: 85 to 95; VIQ: 82 to 75; PIQ: 92 to 106</td>
</tr>
</tbody>
</table>

- Early Onset group had lower IQ values during follow-up (p value 0.02)
- Verbal scores were worse than Performance scores in all groups

Scores: TIQ: Group 1: 61 to 62; Group 2: 72 to 75; Group 3: 85 to 95  
VIQ: Group 1: 63 to 59; Group 2: 75 to 73; Group 3: 82 to 75  
PIQ: Group 1: 66 to 69; Group 2: 73 to 83; Group 3: 92 to 106
Visuo-spatial attention: range values (83% with better performance during follow-up Speed from 50° to 65° p - Accuracy from 50° to 75° p
Visuo-motor skills: scores in range in almost all patients Improvement during follow-up (T0-T1) from 45° to 64° p
Short term memory: scores in range in all patients
**Academic Skills**

**Writing accuracy**
Improved from pathological to borderline in non-word (standard deviation mean values: T0 = -2.5 and T1 = -1.5)
Stayed significantly pathological with respect to words (standard deviation mean values: T0 = -6.5 and T1 = -4)

**Reading speed**
Non-word reading performance remained borderline during the follow-up (standard deviation mean values: T0= -1.8 and T1= -1.3)
Word performance passed from borderline to normal scores (standard deviation mean values: T0= -1.9 and T1= -0.9)

**Reading accuracy**
Non-word reading improved from pathological to normal (standard deviation mean values: T0 = -2 and T1 = -0.6)
Word reading accuracy improved from pathological to borderline (standard deviation mean values: T0 = -1.9 and T1 = -1.3).
Lexical semantic route

(word writing accuracy)

temporo-occipital region next to fusiform gyrus

medial and inferior temporal gyrus
AGE OF CSWS ONSET

Worst evolution in **early onset patients**

*in whom the disease develops in a critical period of brain and synaptic maturation*

*At the end of follow-up the Neuropsychological picture did not refer to a deterioration*

Verbal IQ has the worst evolution but

after an accurate evaluation of cognitive subtest decline is not seen but a

**DEVELOPMENTAL HINDRANCE**
Whole Exome Sequencing

**GENETICS IN CSWS PATIENTS**

**GRIN2A**: cognitive disability, focal epilepsy, ESES, autistic-like disability

**SRPX2**: RE, verbal dyspraxia, and intellectual disability, autism

**CNVs**: 15q13.3, 15q11.2, 16p13.11, 1q21.1, 16p11.2, 22q11.2, 16p11.2

Selection of potential interesting variants for Sanger validation and Segregation Analysis

None of them were de novo variants

**Trios of 9 patients with Idiophatic ESES**
<table>
<thead>
<tr>
<th>Chr:Pos</th>
<th>PubMed/OMIM</th>
<th>Inheritance</th>
<th>Sanger seq</th>
<th>Gene Names</th>
<th>Sequence Ontology</th>
<th>Effect (Combined)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6:5231886</td>
<td>Eilepsy, juvenile absence, susceptibility to, 1</td>
<td>AD</td>
<td>EHHC1</td>
<td>mis sense variant</td>
<td>Missense</td>
<td></td>
</tr>
<tr>
<td>12:4818907</td>
<td>Chang et al. (2006) found that mice heterozygous for Hdac7 deletion were normal, but Hdac7 knockout was embryonic lethal. By embryonic day 11, all Hdac7-/- embryos showed widespread vascular rupture, pericardial effusion, and enlarged dorsal aorta. Electron microscopy showed a lack of tight junctions between adjacent endothelial cells in dorsal aorta and cardinal veins prior to death. Endothelial cell-specific Hdac7 deletion was also embryonic lethal. Hdac7-/- embryos showed a dramatic upregulation of Mmp10 in the perivascular region and downregulation of Timp1 in endothelial cell. Expression of class II HDACs in two mouse models of temporal lobe epilepsy.</td>
<td>lesions</td>
<td>HDAC7</td>
<td>splice_region variant</td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>MT:12345</td>
<td>SELLAS SYNDROME</td>
<td>?</td>
<td>NDS</td>
<td>missense variant</td>
<td>Missense</td>
<td></td>
</tr>
<tr>
<td>MT:13105</td>
<td>SELLAS SYNDROME</td>
<td>?</td>
<td>NDS</td>
<td>missense variant</td>
<td>Missense</td>
<td></td>
</tr>
<tr>
<td>12:4818913</td>
<td>The in vivo roles of S357/7u1m, Rac1 and JNK in cortical neuronal migration. Kawashch T, Chihama K, Nabeshima Y, Hosono M. EMBO J. 2009 Aug 15;28(16):4190-201.</td>
<td>?</td>
<td>Maternal</td>
<td>TIAM2</td>
<td>frameshift variant</td>
<td>LoF</td>
</tr>
<tr>
<td>6:1554503</td>
<td>Chang et al. (2006) found that mice heterozygous for Hdac7 deletion were normal, but Hdac7 knockout was embryonic lethal. By embryonic day 11, all Hdac7-/- embryos showed widespread vascular rupture, pericardial effusion, and enlarged dorsal aorta. Electron microscopy showed a lack of tight junctions between adjacent endothelial cells in dorsal aorta and cardinal veins prior to death. Endothelial cell-specific Hdac7 deletion was also embryonic lethal. Hdac7-/- embryos showed a dramatic upregulation of Mmp10 in the perivascular region and downregulation of Timp1 in endothelial cell. Expression of class II HDACs in two mouse models of temporal lobe epilepsy.</td>
<td>lesions</td>
<td>HDAC7</td>
<td>missense variant</td>
<td>Missense</td>
<td></td>
</tr>
<tr>
<td>17:222792</td>
<td>Autism disorder, cognitive disability. No epileptic seizures (recognised by parents) but during EEG we found an epileptiform activity with a typical picture of CSWS, confirmed during two-three nocturnal EEG polysomnographic registrations. Chang et al. (2006) found that mice heterozygous for Hdac7 deletion were normal, but Hdac7 knockout was embryonic lethal. By embryonic day 11, all Hdac7-/- embryos showed widespread vascular rupture, pericardial effusion, and enlarged dorsal aorta. Electron microscopy showed a lack of tight junctions between adjacent endothelial cells in dorsal aorta and cardinal veins prior to death. Endothelial cell-specific Hdac7 deletion was also embryonic lethal. Hdac7-/- embryos showed a dramatic upregulation of Mmp10 in the perivascular region and downregulation of Timp1 in endothelial cell. Expression of class II HDACs in two mouse models of temporal lobe epilepsy.</td>
<td>lesions</td>
<td>HDAC7</td>
<td>missense variant</td>
<td>Missense</td>
<td></td>
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<tr>
<td>8:6842381</td>
<td>epilepsy, familial temporal lobe, 5</td>
<td>AD, AR</td>
<td>CPA6</td>
<td>missense variant</td>
<td>Missense</td>
<td></td>
</tr>
<tr>
<td>3:381250</td>
<td>Changes in FCHO1/2 expression levels correlated directly with numbers of CCV budding events, ligand endocytosis, and synaptic vesicle marker recycling.</td>
<td>?</td>
<td>FCHO1</td>
<td>splice_region variant</td>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>
#5  ESES - maternal familiarity for Epilepsy (cousins and uncles) - mild cognitive impairment (IQ 63), learning disorder, attention deficit, memory disturbances - seizure onset 7.25 y - ESES onset 10.5 years

<table>
<thead>
<tr>
<th>Chr:Pos</th>
<th>PubMed/OMIM</th>
<th>Inheritance</th>
<th>Sanger seq</th>
<th>Gene Names</th>
<th>Sequence Ontology</th>
<th>Effect (Combined)</th>
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<tr>
<td>2:2597646</td>
<td>3712934723/5</td>
<td>AD</td>
<td>ASKL2</td>
<td>missense_variant</td>
<td>Missense</td>
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</table>

#6  ESES - from 2 to 4 year language disorder (word’s articulation) - seizure onset 2,25 years - ESES onset 5.5 years - moderate cognitive impairment, severe language disturbance (landau kleffner)

<table>
<thead>
<tr>
<th>Chr:Pos</th>
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<th>Gene Names</th>
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<td>3712934723/5</td>
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<td>KCNH1</td>
<td>splice_region_variant</td>
<td>Other</td>
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</table>

#7  ESES - mother’s uncle with unknown EPILEPSY , mother’s cousin with ABSENCE, son of a mother’s cousin with ABSENCE - Seizure onset 4.5 years - ESES onset 7.4 years - metaphonological disorder, attention deficit, (IQ98) - mild learning disorder, IQ 104

<table>
<thead>
<tr>
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<th>Gene Names</th>
<th>Sequence Ontology</th>
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<td>9:8331573</td>
<td>3712934723/5</td>
<td>AD</td>
<td>PTPRD</td>
<td>splice_region_variant</td>
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</table>

#6  ESES - from 2 to 4 year language disorder (word’s articulation) - seizure onset 2,25 years - ESES onset 5.5 years - moderate cognitive impairment, severe language disturbance (landau kleffner)

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<thead>
<tr>
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<td>15:579240</td>
<td>3712934723/5</td>
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<td>GCOM1,MYZAP</td>
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</table>

#6  ESES - from 2 to 4 year language disorder (word’s articulation) - seizure onset 2,25 years - ESES onset 5.5 years - moderate cognitive impairment, severe language disturbance (landau kleffner)

<table>
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#6  ESES - from 2 to 4 year language disorder (word’s articulation) - seizure onset 2,25 years - ESES onset 5.5 years - moderate cognitive impairment, severe language disturbance (landau kleffner)

<table>
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<td>#8</td>
<td>ES ES - maternal family of ES ES and ES ES - seizure onset 8.5 years - ES ES onset 9.4 years - impaired reading and perceptual visual disorder, visual agnosia (IQ80) - mild learning disorder (IQ116)</td>
<td></td>
<td></td>
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<td>Chr:Pos</td>
<td>PubMed/OMIM</td>
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<td>6:3219165</td>
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<td>NOTCH4</td>
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<td>disruptive</td>
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<td>1:1948025</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>Other</td>
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</tbody>
</table>

**Approximately 25% of the mutant mice showed signs of neurologic dysfunction, including ataxia and seizures. Imaging studies detected cerebral arteriovenous malformations.**

This gene is a member of the neublastoma breakpoint family (NBPF) which consists of dozens of recently duplicated genes primarily located in segmental duplications on human chromosome 1. This gene family has experienced its greatest expansion within the human lineage and has expanded, to a lesser extent, among primates in general. Members of this gene family are characterized by tandemly repeated copies of DUF1220 protein domains. Gene copy number variations in the human chromosomal region 1q21.1, where most DUF1220 domains are located, have been implicated in a number of developmental and neurogenetic diseases such as microcephaly, macrocephaly, autism, schizophrenia, mental retardation, and congenital kidney and urinary tract anomalies. Altered expression of some gene family members is associated with various types of cancer. This gene family contains numerous pseudogenes. Alternative splicing results in multiple transcript variants.

**N-Acetyl-D-Glucosamine Kinase Promotes the Axonal Growth of Developing Neurons.**


N-acetyl-D-glucosamine kinase interacts with dynein light-chain roadblock type 1 at Golgi outposts in neuronal dendritic branch points.

**p600 regulates spindle orientation in apical neural progenitors and contributes to neurogenesis in the developing neocortex.**


**Whole-exome sequencing identifies a variant of the mitochondrial MT-ND1 gene associated with epileptic encephalopathy: west syndrome evolving to Lennox-Gastaut syndrome.**


**MT:10277**

**Porencephaly 2**

**AD/incomplete penetrance**

**COL4A2**

**missense variant**

**Other**

**NAGK**

**splice acceptor variant**

**Other**

**ITSN1**

**inframe deletion**

**Missense**

**| #9 | ES ES - mild perinatal sufference - seizure onset 5 years - ES ES onset 10.5 years - mild cognitive impairment (IQ 65), learning disability, attention deficit |
<table>
<thead>
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<th></th>
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<tbody>
<tr>
<td>Chr:Pos</td>
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<td>5:1105603</td>
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<tr>
<td>11:117299</td>
<td></td>
</tr>
<tr>
<td>21:351443</td>
<td></td>
</tr>
</tbody>
</table>


**Increased Cell Proliferations and Neurogenesis in the Hippocampal Dentate Gyrus of Ahnak Deficient Mice.**


**SEIZURES**
Inconstant deviation of the head and eyes to the right shoulder, gasps, staring eyes, tightening the 4 limbs, vomiting and loss of consciousness, lasting between 3 to 10 minutes, followed by drowsiness and severe headache and nausea.

**NEUROPSYCHOLOGICAL PROFILE**
Deficiency in the decoding processes of the written code with severely impaired visually-cognitive skills.

**CLINICAL STUDY**

Bilateral parieto-occipital epileptic foci

CSWS pattern during sleep
SEIZURE
at age 9.5 years
on waking, while in bed with her parents, the girl presented loss of contact with glare, generalized tremor and hypertone guttural sounds and light scalpel with upper limbs and hands claw, lasting about 4-5 minutes, then followed by a long period of general hypotonia with persistence of fiery look and absence of contact.

NEUROPSYCHOLOGICAL PROFILE
borderline cognitive level (WISC-III TIQ 80, VIQ 103, PIQ 60)
a significant reading impairment (-2 SD)
insufficient comprehension deficit in organizational and planning skills
slowness in writing in italics
lacking speed in arithmetic skills
deterioration in visual-perceptive disorder
with very severe visual agnosia and a disturbance of spatial orientation

CLINICAL STUDY

Temporo-occipital epileptic foci.

CSWS pattern during sleep
Single-subject result. Single-subject IED-related BOLD findings in the 2 ICOE patients. The hemodynamic changes have been warped to the PALS-B12 atlas in Caret, bottom and lateral view. Results are displayed using a threshold of $p < 0.05$ corrected for FWE for both. No decreases in BOLD signal were detected in any patient.

A linear relationship was observed between the number of IEDs and positive BOLD signal changes in the left postcentral gyrus (BA3) (global maximum), the left fusiform gyrus (BA37), and the right lingual gyrus (BA 18). No significant correlation was found with the age at seizure onset or epilepsy duration.

SEVERE VISUAL-PERCEPTIVE DISORDER

VISUAL AGNOSIA +

DISTURBANCE OF SPATIAL ORIENTATION

ADEQUATE IQ

(discrepancy between PIQ and VIQ)

visuo-spatial

visuo-motor impairment
during ESES/CSWS period
CLINICAL RELEVANCE

EXTRASTRIATE VISUAL SYSTEM

- Selective impairment of functions
- Limited number of cortical columns
- Posterior ventral occipito-temporal cortex
  (faces, objects, and letters)

*EEG paroxysms interfere with physiological functions, and possibly, with neuroplasticity processes involved in higher cortical functions* [Tassinari and Rubboli, 2006]

- Need for appropriate neuropsychological testing, individually tailored to specific deficits and interpreted in the light of the neurophysiology and functional neuroimaging
# CSWS: COGNITION

**Cognitive regression/Stagnation (>12pts)**  
*Language regression*  
*Learning disabilities*  
*Behavioural disturbances (ADHD)*

**Geographical Prominence of SWA**  
Temporal: LKS  
Fronto-Central: Rolandic  
Occipital: visuo-spatial

**Common-to-all basic diagnostic assessment**  
- Intelligence  
- Language  
- Memory  
- Attention  
- Visuo-spatial  
- Executive Functions

**Practices that may need a consensual attitude**  
- Repet at regular intervals (once a year?) a core battery of neurocognitive test  
*Arzimanoglou et al., 2019*
Sviluppo neuropsicologico:

- Specializzazione cerebrale progressiva delle funzioni
- Plasticità= Cambiamenti funzionali e strutturali cerebralì che permettono lo svilupparsi delle funzioni (Johnson, 2009)
NEUROPSICOLOGIA ED EPILESSIA

Anomalie epilettiformi, crisi epilettiche e il substrato neuronale anomalo

SNC dinamico, plasticità, ambientale, ambiente

- Mancato sviluppo
- Rallentamento
- Regressione di una funzione

Disfunzioni più generali e diffuse

(Smith, 2010)
La spiegazione **patofisiologica dell'impatto negativo dell'attività epilettica dipende dall’organizzazione del cervello**

- **Pruning**
- costruzione dei network corticosubcorticale

Le anomalie epilettiche compromettono questi processi

- Maintiene connessioni non più utili (in base all’età del bambino e alla richieste dell’ambiente)
- Impedisce consolidamento di nuove connessioni sinaptiche tra le regioni (Maquet et al., 1995)

**EE precoce** (pruning precoce): precoce specializzazione cerebrale - sistema che elabora troppi tipi di input o perde capacità acquisite in precedenza (**ritardo globale/regressione**)

**EE con esordio in età scolare**= pruning impedito o aberrante _ no specializzazione cerebrale e ciò potrebbe influire sulla capacità del sistema di multitasking e di **integrare le abilità di base in funzioni superiori** (Karmiloff-Smith, 2012)= intelligenza normale ma con disturbi specifici, come il linguaggio, le funzioni esecutive, la memoria e l'apprendimento (lettitura, scrittura e aritmetica).
**VALUTAZIONE**

*Quando?* All’esordio controlli 6-9 mesi  
*Come?* «minimum routine screening for cognitive and behavioral difficulties»  
*Perché?* Ritardo nello sviluppo di competenze  
Caratterizzazione delle funzioni  
Follow up  
Supporto

---

Fixed Factors
- Nature of underlying pathology (consider developmental timescale and reorganisation/plasticity)
- Laterality of pathology
- Location of pathology
- Age of onset of pathology/seizures
- Age of onset of treatment
- Impact on education
- Gender
- Intellectual capacity

Remedial Factors
- Medication
- Interictal/subclinical EEG abnormalities
- Seizure control
- Mood
- Motivation
- Quality of sleep
- Proximity of last seizure to assessment

Neuropsychological Test Profile

Course of Disease
- History of status epilepticus
- History of generalised seizures
- History of head injuries/comorbidities
"l'attività epilettica stessa può contribuire a gravi deficit cognitivi e comportamentali al di sopra e al di là di quanto ci si potrebbe aspettare dalla sola patologia sottostante (ad esempio malformazione corticale), così come il fatto che tali menomazioni possono peggiorare nel tempo. ”
(Bergel, 2010)
Tipo di sonda eletroclínica

Pattern EEG

Crisi epilettiche tipo e frequenza

Risposta al trattamento o/farmaci

Fattori psicosociali e ambientali

Durata ESES

onset

Tipo di sonda eletroclínica

Pattern EEG

Crisi epilettiche tipo e frequenza

Risposta al trattamento o/farmaci

Fattori psicosociali e ambientali

Durata ESES

onset
ESES «maladaptive plasticity» Issa, 2014

- ESES = maladaptive plasticity durante i «periodi critici/ sensibili nello sviluppo» = deficit indotti dalla riorganizzazione di nuovi circuiti neuronali disadattivi

I disturbi cognitivi osservati sembrano fortemente collegati a periodi critici/sensibili dello sviluppo.

1) i disturbi iniziano e finiscono quasi nello stesso momento in cui iniziano e finiscono i periodi critici.

2) L’attività epilettica durante il sonno guida la plasticità in senso disadattivo durante il periodo critico e la fine del periodo critico cementa quei cambiamenti disadattivi deficit nps persistenti

3) Il sonno non REM è importante per plasticità del periodo critico e quindi potrebbe spiegare perché l'interruzione del sonno non permette i nuovi apprendimenti
Gruppo 1°: BECTS IEDs NREM sleep <50% Gruppo 1B BECTS IEDs NREM sleep tra 50% e 85%

50% di rischio di sviluppo di deficit verbali

Verbal deficit= digit span worward and backword, lettura, produzione lessicale
Gruppo 1°: caduta nel digit span deficit WM mostra un ruolo chiave nello sviluppo degli apprendimenti e della comprensione linguistica

Gruppo 2: Atypical BECTS with ESES IEDs NREM sleep >85%

100% di rischio di sviluppo di deficit verbali e disturbi dell’apprendimento

Disturbo dell’apprendimento rappresenta un deficit legato ad un processamento di alto livello che coinvolge l’integrazione tra le abilità cognitive di base (memoria, attenzione, linguaggio, percezione)

Conclusione: Lo sviluppo ed il mantenimento dei deficit nps dipende dalla frequenza di IED durante il sonno NREM perché non permettono di consolidare gli apprendimenti
Soggetti: ECTS all’esordio, drug naif, QI norma

Domini: Linguaggio, EF, apprendimenti scolastici, abilità visuomotorie e visuospatiali, memoria a breve termine

Risultati: Deficit: linguaggio, EF, apprendimenti scolastici

Ipotesi: Deficit delle FE
EPILESSIA E FE

- Alta frequenza di disfunzioni delle FE in questa popolazione
- Deficit nelle FE predicano una scarsa qualità della vita (MacAllister, 2014)
FE E VITA QUOTIDIANA

Apprendimento di nuove azioni e comportamenti non automatici

Pianificazione e presa di decisioni

Monitoraggio e modifica dell’azione

Letto-scrittura
Linguaggio
successo scolastico

Relazioni sociali
Qualità della vita
Status economico
<table>
<thead>
<tr>
<th>Aspects of life</th>
<th>The ways in which EFs are relevant to that aspect of life</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental health</td>
<td>EFs are impaired in many mental disorders, including:</td>
<td></td>
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<tr>
<td></td>
<td>- Addictions</td>
<td>Baler &amp; Volkow 2006</td>
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<tr>
<td></td>
<td>- Attention deficit hyperactivity (ADHD)</td>
<td>Diamond 2005, Lui &amp; Tannock 2007</td>
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<td></td>
<td>- Conduct disorder</td>
<td>Fairchild et al. 2009</td>
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<td></td>
<td>- Depression</td>
<td>Taylor-Tavares et al. 2007</td>
</tr>
<tr>
<td></td>
<td>- Obsessive compulsive disorder (OCD)</td>
<td>Penadés et al. 2007</td>
</tr>
<tr>
<td></td>
<td>- Schizophrenia</td>
<td>Barch 2005</td>
</tr>
<tr>
<td>Physical health</td>
<td>Poorer EFs are associated with obesity, overeating, substance abuse, and poor treatment adherence</td>
<td>Crescioni et al. 2011, Miller et al. 2011, Riggs et al. 2010</td>
</tr>
<tr>
<td>Quality of life</td>
<td>People with better EFs enjoy a better quality of life</td>
<td>Brown &amp; Landgraf 2010, Davis et al. 2010</td>
</tr>
<tr>
<td>School readiness</td>
<td>EFs are more important for school readiness than are IQ or entry-level reading or math</td>
<td>Blair &amp; Razza 2007, Morrison et al. 2010</td>
</tr>
<tr>
<td>School success</td>
<td>EFs predict both math and reading competence throughout the school years</td>
<td>Borella et al. 2010, Duncan et al. 2007, Gathercole et al. 2004</td>
</tr>
<tr>
<td>Job success</td>
<td>Poor EFs lead to poor productivity and difficulty finding and keeping a job</td>
<td>Bailey 2007</td>
</tr>
<tr>
<td>Marital harmony</td>
<td>A partner with poor EFs can be more difficult to get along with, less dependable, and/or more likely to act on impulse</td>
<td>Eakin et al. 2004</td>
</tr>
<tr>
<td>Public safety</td>
<td>Poor EFs lead to social problems (including crime, reckless behavior, violence, and emotional outbursts)</td>
<td>Broidy et al. 2003, Denson et al. 2011</td>
</tr>
</tbody>
</table>
EXECUTIVE FUNCTION

«Le funzioni esecutive rappresentano le abilità necessarie per programmare, mettere in atto e portare a termine con successo un comportamento finalizzato a uno scopo»
CONCLUSIONE

ESES = esempio paradigmatico dell’EE

“Estrema attivazione di anomalie epilettiche durante il sonno NREM causa deficit nelle funzioni neurocognitive e comportamentali al di là di altri fattori intervenienti ((i.e., structural lesions, abnormal preexisting cognitive and behavioral background).

Le anomalie epilettiche protratte in un Sistema in via di sviluppo e l’alta plasticità causano deficit nps e comportamentali anche in bambini sani o peggioramento nei bambini con deficit preesistente

Importante:

- EEG- diagnosi, identificazione del focus, IEDs NREM
- Nuove tecnologie diagnostiche: tecniche di neuroimmagine (fMRI, PET, MEG)
- Valutazione neuropsicologica – rischio adattamento qualità della vita
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Thanks