Epilepsy & Behavior Reports 16 (2021) 100488

Contents lists available at ScienceDirect

Epilepsy & Behavior Reports

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

Case Report

6-year course of sleep homeostasis in a case with epilepsy-aphasia spectrum disorder

Nadine Oser [a,1], Martina Hubacher [a,1], Annette Nageleisen-Weiss [a], Pieter van Mierlo [b,c], Reto Huber [d,e,f], Peter Weber [a], Bigna K. Bölsterli [d,2], Alexandre N. Datta [a,*,2]

[a] Department of Pediatric Neurology and Developmental Medicine, University of Basel Children's Hospital, Basel, Switzerland
[b] Epilog NV, Ghent, Belgium
[c] Medical Image and Signal Processing Group, Ghent University, Belgium
[d] Department of Pediatric Neurology and Children's Research Center, University Children's Hospital Zurich, University of Zurich, Switzerland
[e] Child Development Center and Children's Research Center, University Children's Hospital Zurich, University of Zurich, Switzerland
[f] Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric Hospital, University of Zürich, Switzerland

ARTICLE INFO

Article history:
Received 27 May 2021
Revised 27 August 2021
Accepted 24 September 2021
Available online 30 September 2021

Keywords:
Self-limited focal epilepsy with centro-temporal spikes (SLECTS)
Benign epilepsy with centro-temporal spikes (BECTS)
Rolandic epilepsy
Electrical status epilepticus during sleep (ESES)
Slow waves
Functional magnetic resonance tomography (fMRI)
Neuropsychology

ABSTRACT

The epilepsy-aphasia spectrum consists of epilepsies with a strong activation of epileptic discharges during non-rapid-eye-movement (NREM) sleep, variable seizure burden and language problems. The homeostatic decrease of slow waves (SW) during NREM sleep (i.e. their amplitude/slope and power) has been related to brain recovery and cognitive function. Epileptic discharges during NREM-sleep were related to an impairment of the decrease of the slope of SW and to cognitive deficits. In this longitudinal case study, we aim to relate this electrophysiological marker, i.e. overnight change of slope of SW, to imaging and behavior.

We report a young girl with a fluctuating course in the epilepsy-aphasia spectrum, ranging from the benign end with self-limited childhood epilepsy with centrotemporal spikes (SLECTS) to the severe end with epileptic encephalopathy with continuous spike waves during sleep (CSWS) with two phases of cognitive regression. She was documented over a period of six years including 12 PSGs, six language fMRIs and seven neuropsychological assessments. We longitudinally studied focal and total spike wave index (SWI), detected SW during NREM sleep, calculated their slopes (first and last hour of NREM sleep and overnight change).

Deterioration of overnight decrease of the slope of SW was paralleled by the occurrence of the EEG picture of bilateral synchronous electrical status epilepticus during sleep (ESES) and neuropsychological deficits, and this impairment was reversible with resolution of ESES and was accompanied by cognitive improvement. A laterality switch from left to right sided language dominance occurred during recovery from the second regression phase. This might reflect a compensating process. Later, the laterality switched back to the left, possibly facilitated by a low SWI on the left hemisphere.

The qualitative analysis of this case supports the view that the longitudinal course of the overnight change of the slope of SW, as an objective, quantitative EEG measure, is related to the course of cognitive function and functional language MR analysis.

1. Introduction

The epilepsy-aphasia spectrum consists of a group of self-limited focal childhood epilepsies with variable severity regarding EEG-pathology, neurodevelopment and seizures. They share common genetic grounds such as mutations in GRIN2A [1–3] and exhibit a striking increase of interictal epileptic discharges (IED) during non-rapid-eye-movement (NREM) sleep. The spectrum ranges from the self-limited childhood epilepsy with centro-temporal spikes (SLECTS), the most common focal epilepsy in children, with none or mild and specific cognitive deficits to the Landau-Kleffner Syndrome (LKS) with language regression with auditory agnosia and epileptic encephalopathy with continuous spike waves during

* Corresponding author.
E-mail address: alexandre.datta@ukbb.ch (A.N. Datta).
[1] Shared first authorship.
[2] Shared last authorship.

https://doi.org/10.1016/j.ebr.2021.100488
2589-9864/

slow sleep (CSWS), i.e. electrical status during sleep in the EEG (ESES) with more global developmental regression. Atypical courses of SLECTS evolving to the clinical picture of LKS or CSWS are rare but known [4–6]. IED in the electroencephalogram (EEG) during sleep have been proposed to be causal for the development of neuropsychological deficits [7–13]. However, the mechanisms are unclear and objective and reliable markers for the risk to develop cognitive deficits to guide treatment are still lacking. Additionally, it is still unknown what reverses a cognitive regression.

Brain plasticity in children with SLECTS results in a reorganisation of language networks, a more bilateral activation pattern of language production in fMRI [14,15]. A lack of compensatory mechanisms in bilateral synchronous ESES can lead to a verbal agnosia, which has been shown in a LKS case study [16].

Cognitive performance highly depends on sleep, especially NREM sleep, in adults [17] and during development [18]. The 'active consolidation hypothesis' and the synaptic homeostasis hypothesis (SHY) are the two most important hypotheses about the function of sleep for cognition [18]. In both, SW, a main characteristic of deep NREM sleep, play a key role for memory consolidation. The SHY describes that during wakefulness, by interaction with the environment, synaptic connections are built and strengthened, i.e. the basic mechanism of learning. This is energy and space consuming. To prevent synaptic saturation, a regenerative process, independent of environmental stimuli, providing synaptic homeostasis is needed. This occurs during NREM sleep and was hypothesised to be driven by SW. To enhance synaptic efficacy, previously used and newly generated neuronal paths are integrated and surplus synapses are weakened. This is resulting in consolidation of the memory traces [19–21]. Slow waves (0.5–4.5 Hz) in the surface EEG are generated by highly synchronous slow oscillations of neuronal activity. Amplitude and slope of SW as well as SW activity depend on the degree of neuronal network synchrony [22] and thus indirectly on synaptic efficacy. These SW characteristics are tightly related to each other, though it is the slope of SW that has been shown to be best related to synchrony. Therefore, the homeostatic synaptic down-selection may be indirectly measured in the sleep EEG as a decrease of the slope of SW. There exists evidence that spike waves during sleep are tightly linked to SW and are generated by hypersynchronous oscillations of neuronal networks [23,24]. Therefore, a relation of spike-waves during slow wave sleep and synaptic homeostasis seems plausible and was proposed to be a mechanism for the development of cognitive deficits in epilepsies with spike wave activation during sleep [11]. Indeed, reduced homeostatic decline of the slope of SW was discovered in various epilepsies in adults and children [25–29]. This alteration was related to localisation and rate of epileptic discharges [25,30,31] and first hints towards a relevance for cognitive (dys)-function were found [25,31,29]. In a longitudinal study, overnight-EEGs during times with high amounts of epileptic discharges during NREM sleep and after recovery, i.e. without epileptic discharges, were analysed. Here, hampered homeostasis of slope of SW renormalised with the recovery [31]. In conclusion, it might be hypothesised that altered synaptic homeostasis, measured by the decrease of the slope of SW, lead to cognitive problems and the renormalisation to cognitive improvement [11,32,31]. To the best of our knowledge, no studies of slow wave characteristics and their overnight changes has been performed yet in patients with epilepsies of the epilepsy-aphasia spectrum without clear-cut cognitive problems, i.e. SLECTS. However there exists some studies reporting a relation between SWI and impaired memory consolidation in these patients [33,34].

In this article, we report on the longitudinal course of the overnight decrease of slope of SW in overnight-EEGs, the rate of epileptic discharges (spike wave index, SWI), the functional language organisation assessed by fMRI and cognition by means of neuropsychological assessments in a girl with a fluctuating course within the epilepsy-aphasia spectrum, i.e. regarding cognition, EEG features and language lateralisation, over a time-period of six years.

2. Case report

Case previous history

The girl was born at term after a normal pregnancy and delivery. Her development of motor and cognitive skills was normal. She is right-handed and bilingual (Swiss, German, and Albanian). No problems in school were reported, concentration was good and homework completed fast and properly.

Course of epilepsy – seizures, electrophysiology

The patient had her first three seizures after having fallen asleep at 8.3 years. The semiology consisted of a tonic deviation of the right angle of the mouth followed by clonic twitching, hypersalivation and postictal aphasia. EEG showed bilateral asynchronous centro-temporal spike-waves with right hemispheric predominance. A quantitative evaluation of the PSGs is provided in Fig. 1B. A diagnosis of SLECTS was made and treatment with sulthiame initiated. Two months later, the left centro-temporal focus disappeared during wakefulness. At 8.9 years, she experienced her fourth seizure out of sleep with the same semiology. At 9.0 years a PSG showed secondary bilateral synchrony on EEG, but a clear predominance of right sided spike-waves consistent with right hemispheric electrical status epilepticus during sleep (ESES). Therefore, sulthiame was increased and clobazam added. No signs of regression were noted.

At 9.5 years PSG showed a deterioration: Now, sleep graphoelements were almost absent and sleep architecture was perturbated bilateral synchrony increased. The patient had short seizures with jerks of both angles of the mouth even during wakefulness. Her parents reported that she had problems understanding instructions at school, she was less attentive.

The combination of a considerably high SWI with involvement of both hemispheres with neuro-developmental deterioration made more aggressive treatment inevitable and oral hydrocortisone was initiated. After 3.5 months, at 9.8 years, parents and teachers reported a clear-cut improvement of attention and understanding. In contrast to that, PSG did not show a reduction of epileptiform activity then. At 10.1 years old, after 6 months of hydrocortisone treatment she showed a good school performance again and she did not feel impaired at school in any way anymore. SWI decreased and epileptic activity became asynchronous.

At 10.4 years, patient restarted to have focal seizures. Sulthiame was further increased. Neuropsychological assessment at 10.8 years revealed a decline of processing speed, auditive retentivity as well as working memory. At 10.9 years, PSG showed a bilateral synchronous ESES. Although EEG deterioration was associated with neuropsychological decline parents refrained from another corticosteroid trial and levetiracetam was added. Seizures stopped but EEG did not improve.

At 11.2 years, she restarted to have diurnal and nocturnal seizures with unilateral to bilateral cloni on both angles of her moths and eyelids. Because of the advantage of less severe side effects compared to continuous hydrocortisone, dexamethasone pulse therapy (3 days every two weeks) was started and a certain improvement in attention and processing speed occurred. Seizures completely disappeared.

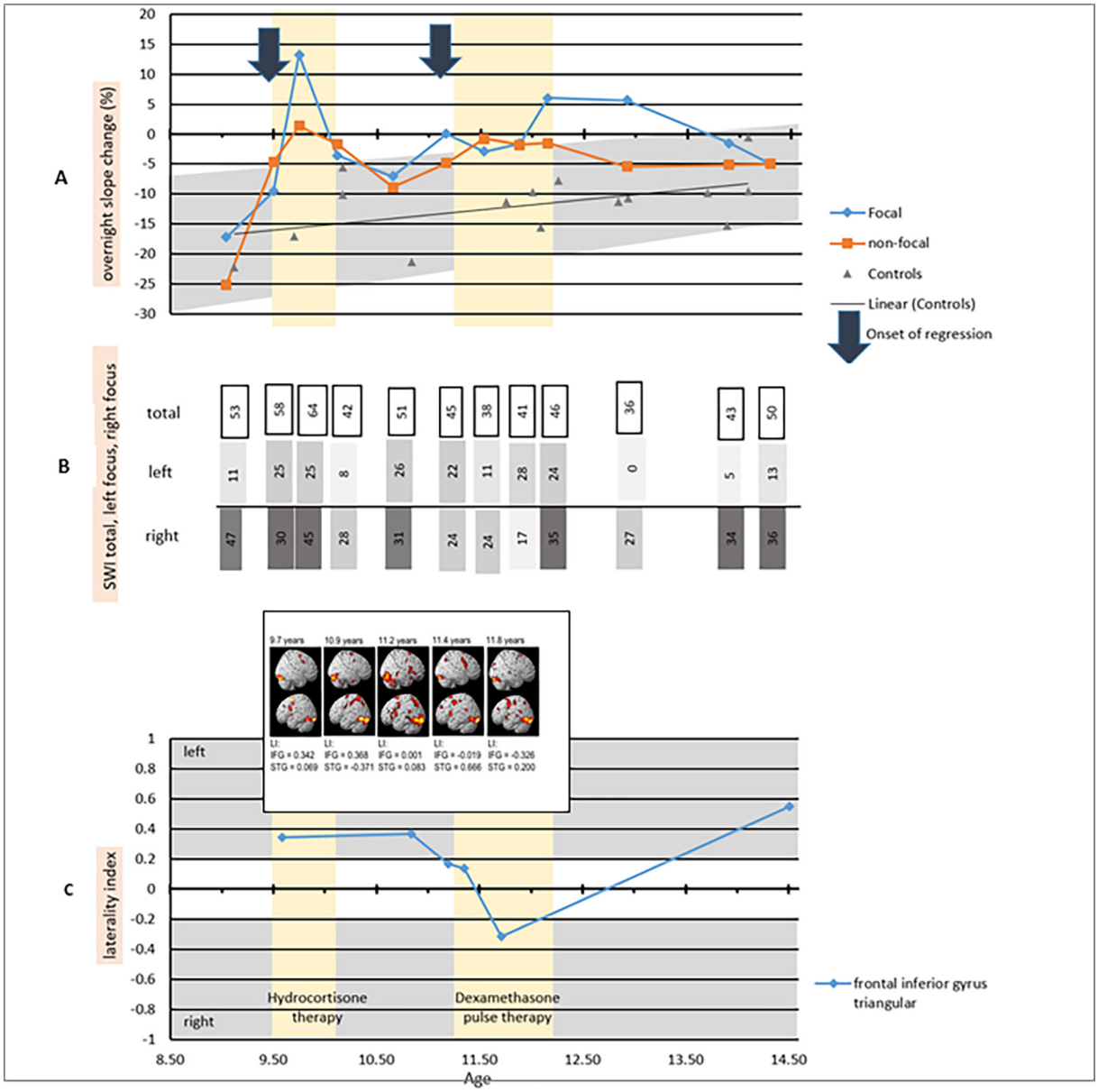

Fig. 1. A: Focal and non-focal slope of SW. Cognitive regression onset marked with an arrow. B: Total night SWI, SWI of the strongest left and of the strongest right focus (the more spike waves, the darker the grey). C: Language laterality index for the frontal inferior gyrus over time measured by functional MRI, silent generation of simple sentences. Hydrocortisone and pulsatile dexamethasone treatment phases marked in dark yellow. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

PSG findings at 11.5 years clearly improved. Epileptiform activity was still seen, was asynchronous but the most active epileptiform focus had switched to the left hemisphere. Dosage of dexamethasone pulses was halved for another 6 months. Her global IQ increased from low to middle level. At 12.2 years, PSG worsened with an increase of epileptic activity; the patient was doing fine, showed normal school performance and therfore wanted to stop steroids; at 12.3 years, dexamethasone was discontinued.

At 13.2 years, sulthiame was tapered off. Between 13.6 years and 14 years also levetiracetam was tapered off. At the age of 13.9 years, PSG showed again more but almost unilateral asynchronous epileptic activity. The girl remained seizure-free and school performance was good. At 14.4 years, even though the EEG slightly worsened but remained bilateral asynchronous, she still showed good school performance and was seizure-free.

3. Methods

3.1. Polysomnography (PSG)

PSGs were obtained at the age of 9.0, 9.5, 9.7, 10.1, 10.7, 11.2, 11.5, 11.9, 12.2, 12.9, 13.9 and 14.4 years. Most recordings included 19 EEG electrodes placed according to the 10–20 system and electrooculography (EOG), some had a reduced EEG montage (F3, F4, C3, C4, O1, O2).

The first and last hour of NREM sleep were identified in the hypnogram. Automated spike detection was performed to detect epileptic interictal discharges (IED) using the Persyst P13 algorithm (Persyst Inc., USA). The spike wave index (SWI) was calculated over the complete recording (Epilog NV, Belgium). The SWI defines the percentage of seconds in which an IED occurred with

respect to the total number of seconds studied. The total SWI was calculated by considering all IED detections at all electrodes. The SWI of the left and right focus were also separately calculated by considering only the strongest source of IEDs over the left and over the right hemisphere, respectively.

Analyses of overnight changes of the slope of SW (0.5–2 Hz) during NREM sleep was performed as published [30] using the software package MATLAB (The Math-Works Inc., Natick, MA, U. S.A.). Basically, after visual and semiautomatic artefact removal an automatic SW (0.5–2 Hz) detection algorithm according to Riedner et al. 2007 [35] was applied in all average referenced EEG channels. Because EEGs were highly pathological due to an abundance of spike and waves, SW associated with spikes (in spike and wave complexes) were detected as well. Because the relation between SW and neuronal synchrony was only shown in physiological SW, an automatic spike detection algorithm was used to exclude spike and wave complexes from further analysis [30]. Then, the slope of the detected SW was calculated as the amplitude of the negative peak divided by the time between the negative peak and the following zero-crossing. For the first (FH) and the last hour (LH) of NREM sleep the slope at the amplitude of 75 μV was calculated (see also [26]). Overnight changes are reported as percentual change. These percentual changes between the slopes of SW in the first and the last hour of artefact-free NREM sleep were averaged for "focal" electrodes containing the epileptic "focus", i.e. the electrodes in the localisations with highest amplitude spike waves, and for the "non-focal" electrodes, i.e. all remaining electrodes, separately. To display normal developmental evolution of overnight changes of SW slopes during NREM, previously published [30,36,37] PSGs of 15 healthy girls between nine and 14.5 years were analysed following the same procedure as described. In these subjects a mean overnight change of slopes over all 19 electrodes was calculated for each recording. To compare our case to this control data, linear regression was based on data from the 15 healthy girls ($y = 1{,}7109x - 32{,}286$; $r^2 = 0{,}2467$) and differences from the regression line (Δy) are provided for each measurement of our clinical case.

3.2. Language functional magnetic resonance imaging (fMRI)

At the age of 9.6, 10.2, 10.8, 11.2, 11.4, 11.7 and 14.5 structural and functional MRI-investigations were performed to get an insight in functional language organisation.

To measure functional activation of language production, the paradigm *silent generation of simple sentences* was applied, where a noun was visually presented on a screen for 5000 milliseconds. The activation blocks were followed by control condition blocks with a fixation cross.

Data acquisition was made on a 3-Tesla MRI (Magnetom SKYRA, Siemens Healthcare, Erlangen, Germany). Structural imaging was performed using a sagittal T1-weighted 3D high-resolution magnetisation prepared rapid gradient echo sequence (MPRAGE), with TR = 2000 ms, TE = 3,4 ms, TI = 1000 ms and an isotropic spatial resolution of $1 \times 1 \times 1$ mm^3. fMRI was carried out using an echo planar sequence (EPI) with a voxelsize of $3 \times 3 \times 3$ mm^3, 38 slices, a FOV of 228 mm, a slice thickness of 3 mm, TR = 2500 msec and TE = 28 msec.

For functional data analysis, the statistical parametric mapping software package (SPM12) was used. Pre- and postprocessing were done according to standard procedures including longitudinal serial registration of structural 3D-T1 images, realignment of functional images, co-registration to the averaged structural T1-weighted image, normalisation to standard MNI-Template and smoothing with 8 mm isotropic Gaussian filter [38]. Next, movement parameters were added as covariates to the first level analysis and passive conditions were subtracted from active conditions to contrast the functional language activation. Contrast images were uncorrected with a threshold of p = 0.001 and a cluster size of 10 voxel.

To quantify hemispherical activation of the expressive language area, the lateralisation index (LI) [39] was calculated for the frontal inferior triangular region (including Brodmann Area 44 and 45). A mask was created using the WFU PickAtlas (RRID:SCR_007378).

3.3. Neuropsychological examination

At the age of 8.7, 9.1, 9.8, 10.8, 11.2, 11.8 and 14.5 years, the girl underwent neuropsychological test sessions on different modules (Tables 1a-f, supplement), to avoid retest-effects. The last two assessments at the ages of 11.7 and 14.5 could not be completed because of mal-compliance.: To assess global mental abilities the Wechsler Intelligence Scale for Children (WISC-IV), the Coloured Progressive Matrices test (CPM), which is a language and culture free intelligence scale and the Intelligence and Development Scale (IDS) were used. To study specific linguistic abilities, writing and reading, we applied the modules of the Potsdam-Illinois Testbattery for Psycholinguistic Abilities (P-ITPA). We took the Verbal Learn- and Memory test (VLMT) [40], which is a German version of the Auditory Verbal Learning Test" and the Rey-Osterrieth complex figure (ROCF), a test for figural memory to check memory performance. The Mottier test was used for phonological processing. Depending on the requirements, various other tests were used (e.g. d2-R to test selective attention).

4. Results

4.1. Course of SWI and slope of SW

Evolution of overnight change of slope of SW (in short: slope) is displayed in Fig. 1A. The exact details including the exact values are in supplement 1. The numbers of the focal and total SWI over the course are provided in Fig. 1B.

The distribution of the sleep stages and sleep efficiency were normal (suppl. Table 3).

4.4. Course of language lateralisation

Course of language lateralization expressed as LI is displayed in Fig. 1C. The child had a normal cranial anatomical MRI at 8.4 years. At 9.7 years, the first fMRI was performed. A typical left hemispheric language activation pattern was seen. At 10.2 years, performance of fMRI paradigms was not possible because of language regression. Due to her disability of reading, the fMRI could only be done with auditory presentation of stimuli. She showed left-sided activation pattern. At 10.9 years in a third fMRI, the paradigm of *silent generation of simple sentences* was applied twice. Bilateral activation patterns were seen with a more dominant left-sided activation. At 11.2 years, both sentence generation tasks showed a bilateral activation pattern. At 11.4 years activation pattern was still bilateral. At 11.8 years the activation pattern switched to the right hemisphere. The last fMRI was performed at 14.5 years. The activation pattern was again left-sided.

4.3. Course of neuropsychological performance

Detailed results of neuropsychological assessments are provided in supplementary Tables 2a-d. Results of the first neuropsychological testing at 8.8 years showed age appropriate intelligence (WISC-IV, CPM). Perceptional reasoning, working memory, processing speed and verbal comprehension in total, as well as reading

were within normal limits. Solely, vocabulary and orthographic writing in her second language were slightly below the norm.

To have a deeper insight into expressive language, a specific language test (P-ITPA) was assessed at 9.1 years. A reduced general level of expressive and receptive language was detected: Deductive verbal reasoning, oral expression, listening comprehension (spoken analogies), word knowledge, word recognition and semantics (spoken vocabulary) were clearly impaired. Also phonological perception, acoustic sound differentiation (Mottier-test) were below average, while normal scores for verbal learning and memory (VLMT) as well as visuo-spatial memory (ROCF) were observed.

At 9.5 years signs of regression, such as problems of understanding instructions at school, were reported in the neuropediatric consultation. Therefore, corticosteroid treatment was initiated. Shortly thereafter, parents saw a very clear improvement in attention and comprehension in every-day life at school and at home and the neuropsychological testing at 9.8 years revealed age appropriate intelligence and development (IDS); verbal learning and memory (VLMT) were in average. Her acoustic sound differentiation was still substantially reduced (Mottier).

At 10.8 years the girl and her parents reported good school performance and a high compliance for comleting her homework. While working on language tasks she seemed strained and depressed, showed word finding problems in spontaneous speech.

Still, expressive language (P-ITPA) as well as sound differentiation (Mottier test) were below average. Phonological Awareness (P-ITPA), reading and spelling were slightly below average (P-ITPA). The impairment of auditory memory was even more evident in the specific language test (repeating sentences and rhyme sequence of P-ITPA). Scores of selective attention and concentration (d2-R), visuo-spatial (Rey-figure) and verbal memory (VLMT) were stable and within the norm.

Four months later, at 11.2 years a regression period with new school problems was again reported by the parents in the medical follow-up, comparable to what was reported in the previous medical examination at 9.5 years. In the test session, processing speed and working memory continued to decrease (WISC-IV). Beside this, selective attention (d2-R) was within the norms and verbal learning and memory (VLMT) above average.

The testing at 11.8 years was not fully completed due to poor compliance of the girl. Perceptual reasoning (WISC-IV), writing (P-ITPA), visuo-perceptual memory (ROCF) were within the norms and verbal learning and memory (VLMT) was again above average.

The last neuropsychological examination at 14.5 years was again stopped after a few subtests because of poor compliance by the patient. The subtests block design, picture concepts and similarities were within normal range and digit span was reduced.

5. Discussion

Our longitudinal study delineates the time course of epilepsy in a girl with a history of an atypical fluctuating course of an epilepsy within the epilepsy-aphasia spectrum with two episodes with developmental regression and final recovery. Here, we show the temporal relationship between the epilepsy, total as well as focal SWI, overnight change of slope of SW, language reorganisation measured by fMRI and neuropsychological outcome.

Nocturnal SWI, overnight change of slope of SW and cognition

The present case study demonstrates the following temporal relationship between total as well as focal SWI, alterations of overnight SW slope change and behaviour twice: Clinical deterioration was accompanied by a deterioration of EEG with synchronous bilateral ESES, high focal and total SWI, and deterioration of overnight change of slope of SW. Clinical improvement occurred already, when focal and total SWI as well as the overnight slope change still worsened. An improvement in the slope change, i.e. reaching values within range of healthy age matched children, and SWI was seen only with a certain time lag.

During the first "regression phase" (arrow in Fig. 1), when rapid deterioration of school performance, attention and behaviour were reported, no neuropsychological assessment was performed. But expressive language and phonological processing were reduced over the prior 2 months. Initially asynchronous right hemispheric ESES became bilateral synchronous and may be responsible for language deterioration [6]. In parallel to this regression, the overnight change of slope started to deteriorate, even more after starting corticosteroids, when improvement in attention and mood was noted, already.

In "focal" electrodes the slope even increased over night - a finding also observed in earlier studies [26,30,25]. This local emphasis of impaired homeostasis of slope might be a reason for the more pronounced deficits in language and is in accordance with the observation that epileptic focus is related to the mode of deficits, such as for example in Landau Kleffner Syndrome [41,42]. Moreover, the increase of SW across the night cannot be fully explained by an impairment of the physiological decrease. Spike waves during sleep may hypothetically potentiate synapses within epileptic networks, thereby counteracting synaptic homeostasis locally. This would result in an increase in network synchrony and thus SW slope. Such spike-dependent potentiation was proposed earlier [12,43] and there exists some evidence for consolidation of seizure-activated networks in post-ictal sleep [44].

The introduction of corticosteroids was followed by a "remission period" by rapid improvement of attention and mood. Overnight change of slope of SW and SWI and language only improved between 3 and 6 months of steroid treatment.

During the second period of regression, clinically reported deficits in expressive language were more subtle compared to the first. We suspected that the reorganization processes of expressive language localized to the right hemisphere and seen on fMRI were initiated to preserve language function. However, a clear-cut relation to the laterality of the SWI was not evident. With clinical improvement and stabilisation of the overnight change of slope, language laterality switched back to the left hemisphere again. We hypothesised that a low SWI on the left hemisphere (compared to the right) may have facilitated this switch.

After termination of pulse dose corticosteroids administration the course was generally stable. However, around the age of 14 years, the SWI increased again, although without cognitive deterioration. A reason might be that epileptic activity remained unilaterally pronounced and no bilateral synchrony occurred. This is in agreement with previous work, where bilateral activity was found to be a prerequisite for the development of neuropsychological deficits [6]. Interestingly, at this time the overnight slope change was comparable to healthy, which is in congruence with stable cognitive performance.

Effects of corticosteroids

Looking at the general effect of corticosteroids on SWI and the overnight change of slope of SW, it varied between the application form (continuous vs. pulsatile). Under treatment with continuous use of corticosteroids, improvement of overnight change in slope of SW and SWI only occurred with a certain delay and after initial worsening. We hypothesise that there was ongoing deterioration which was at the base of spike-waves and disturbed overnight change of the slope of SW – may need some time to be reversed.

A more pronounced delay was observed under pulse dose administration of corticosteroids, and with dose reduction, a deterioration of the slope of SW (though only the focal one) and SWI (though only locally) occurred. A reason for this less pronounced effect most probably is due to pulsatile instead of continuous use.

Early recovery of frontal dysfunctions including executive skills and attention is a known phenomenon in non-lesional encephalopathy with CSWS under efficacious treatment [10]; bifrontal dysfunction during a critical developmental window under widespread neuronal networks by CSWS seems to be more rapidly reversible [10]; therefore most probably attention and mood improved before the measured electrophysiological parameters in our patient. Whereas other neuropsychological aspects as e.g. acoustic sound differentiation were still substantially reduced when SWI and slope already started to improve.

Interestingly, there exists evidence that corticosteroid treatment leads to an overall reduction of the slope of SW [27,45] and it was hypothesised that this reduction of slope would indicate a reduction of network synchrony and thus may be an explanation for the therapeutic effect in hypersynchronous states, i.e. epileptic networks. The effect on the overnight change of SW slope though was not investigated, yet. The patient reported in this study was treated not only with corticosteroids but also – without success - with the anti-seizure medication sulthiame, levetiracetam and clobazam, which also may have affected the sleep EEG [46,47].

Limitations

A main limitation is the single case report, which makes generalizability on other self-limited focal epilepsies and epilepsy in general difficult. Also, due to the aphasia and disability to read during the first regression period, language paradigm in fMRI at that time had to be presented auditorily instead of visually. Therefore, it is not entirely comparable to the other fMRI assessments. Overnight EEGs were not always performed with 21 electrodes which reduced comparability between EEG features.

Another drawback was that neuropsychological testing, geared to clinical needs. It followed in short time intervals, why we had to use a broad battery of tests. An additional problem was, that during most pronounced regression phase, neuropsychological testing was not possible. Unfortunately, we could not conclusively examine the linguistic skills.

Conclusions

In the qualitative analysis of this longitudinal case study, clinical cognitive regression was paralleled by a reduction of the decline in overnight change of the slope of SW and bilateral synchrony of spike-waves. In combination with qualitative EEG analysis, the course of the overnight change of slope of SW may serve as a quantitative and objective indicator for neuropsychological impairment in children with epilepsies within the epilepsy-aphasia spectrum. Further, corticosteroids led to an improvement of cognitive function and the homeostasis of the slope of SW. To be able to generalize results and find causal relations between behavioral and electrophysiological parameters, larger longitudinal and ideally prospective studies with standardized treatment approaches and testing, are needed.

Authors affirm that the work described is consistent with the Journal's guidelines for ethical publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We thank the patient and her family for participating.

Bigna K. Bölsterli was funded by EMDO Foundation, Anna Müller Grocholski Foundation, Starr International Foundation and the Children's Research Center of the University Children's Hospital Zurich.

Nadine Oser was funded by Anna Müller Grocholski Foundation and Hirt-Martin Foundation. Martina Hubacher was funded by Hirt-Martin Foundation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2021.100488.

References

[1] Lesca G et al. Update on the genetics of the epilepsy-aphasia spectrum and role of GRIN2A mutations. Epileptic Disord 2019;21(S1):41–7.
[2] Lesca G et al. GRIN2A mutations in acquired epileptic aphasia and related childhood focal epilepsies and encephalopathies with speech and language dysfunction. Nat Genet 2013;45(9):1061–6.
[3] Carvill GL et al. GRIN2A mutations cause epilepsy-aphasia spectrum disorders. Nat Genet 2013;45(9):1073–6.
[4] Fejerman N. Atypical rolandic epilepsy. Epilepsia 2009;50(Suppl 7):9–12.
[5] Verrotti A et al. Typical and atypical rolandic epilepsy in childhood: a follow-up study. Pediatr Neurol 2002;26(1):26–9.
[6] Massa R et al. EEG criteria predictive of complicated evolution in idiopathic rolandic epilepsy. Neurology 2001;57(6):1071–9.
[7] Deonna T. Rolandic epilepsy: neuropsychology of the active epilepsy phase. Epileptic Disord 2000;2(Suppl 1):S59–61.
[8] Deonna T et al. The spectrum of acquired cognitive disturbances in children with partial epilepsy and continuous spike-waves during sleep. A 4-year follow-up case study with prolonged reversible learning arrest and dysfluency. Eur J Paediatr Neurol 1997;1(1):19–29.
[9] Deonna T et al. Benign partial epilepsy of childhood: a longitudinal neuropsychological and EEG study of cognitive function. Dev Med Child Neurol 2000;42(9):595–603.
[10] Seegmuller C et al. Long-term outcome after cognitive and behavioral regression in nonlesional epilepsy with continuous spike-waves during slow-wave sleep. Epilepsia 2012;53(6):1067–76.
[11] Tassinari CA, Rubboli G. Encephalopathy related to Status Epilepticus during slow Sleep: current concepts and future directions. Epileptic Disord 2019;21 (S1):82–7.
[12] Holmes GL, Lenck-Santini PP. Role of interictal epileptiform abnormalities in cognitive impairment. Epilepsy Behav 2006;8(3):504–15.
[13] Holmes M et al. Resting state functional connectivity of the hippocampus associated with neurocognitive function in left temporal lobe epilepsy. Hum Brain Mapp 2014;35(3):735–44.
[14] Datta AN et al. Cognitive impairment and cortical reorganization in children with benign epilepsy with centrotemporal spikes. Epilepsia 2013;54 (3):487–94.
[15] Lillywhite LM et al. Neuropsychological and functional MRI studies provide converging evidence of anterior language dysfunction in BECTS. Epilepsia 2009;50(10):2276–84.
[16] Datta AN et al. BECTS evolving to Landau-Kleffner Syndrome and back by subsequent recovery: a longitudinal language reorganization case study using fMRI, source EEG, and neuropsychological testing. Epilepsy Behav 2013;27 (1):107–14.
[17] Diekelmann S, Born J. The memory function of sleep. Nat Rev Neurosci 2010;11 (2):114–26.
[18] Huber R, Born J. Sleep, synaptic connectivity, and hippocampal memory during early development. Trends Cogn Sci 2014;18(3):141–52.
[19] Tononi G, Cirelli C. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron 2014;81 (1):12–34.
[20] Frank MG. Sleep and synaptic plasticity in the developing and adult brain. Curr Top Behav Neurosci 2015;25:123–49.
[21] Cirelli C, Tononi G. Cortical development, electroencephalogram rhythms, and the sleep/wake cycle. Biol Psychiatry 2015;77(12):1071–8.
[22] Vyazovskiy VV et al. Triggering slow waves during NREM sleep in the rat by intracortical electrical stimulation: effects of sleep/wake history and background activity. J Neurophysiol 2009;101(4):1921–31.
[23] Steriade M, Contreras D. Relations between cortical and thalamic cellular events during transition from sleep patterns to paroxysmal activity. J Neurosci 1995;15(1 Pt 2):623–42.
[24] Frauscher B et al. Facilitation of epileptic activity during sleep is mediated by high amplitude slow waves. Brain 2015;138(Pt 6):1629–41.

[25] Boly M et al. Altered sleep homeostasis correlates with cognitive impairment in patients with focal epilepsy. Brain 2017;140(4):1026–40.
[26] Bolsterli BK et al. Impaired slow wave sleep downscaling in encephalopathy with status epilepticus during sleep (ESES). Clin Neurophysiol 2011;122 (9):1779–87.
[27] Fattinger S et al. Impaired slow wave sleep downscaling in patients with infantile spasms. Eur J Paediatr Neurol 2015;19(2):134–42.
[28] Fattinger S et al. Overnight changes in the slope of sleep slow waves during infancy. Sleep 2014;37(2):245–53.
[29] van den Munckhof B et al. Sleep slow-wave homeostasis and cognitive functioning in children with electrical status epilepticus in sleep. Sleep 2020;43(11).
[30] Bolsterli Heinzle BK et al. Spike wave location and density disturb sleep slow waves in patients with CSWS (continuous spike waves during sleep). Epilepsia 2014;55(4):584–91.
[31] Bolsterli BK et al. Remission of encephalopathy with status epilepticus (ESES) during sleep renormalizes regulation of slow wave sleep. Epilepsia 2017;58 (11):1892–901.
[32] Tassinari CA, Rubboli G. Cognition and paroxysmal EEG activities: from a single spike to electrical status epilepticus during sleep. Epilepsia 2006;47 (Suppl 2):40–3.
[33] Galer S et al. Impaired sleep-related consolidation of declarative memories in idiopathic focal epilepsies of childhood. Epilepsy Behav 2015;43:16–23.
[34] Storz S et al. Sleep-dependent memory consolidation in children with self-limited focal epilepsies. Epilepsy Behav 2020;113:107513.
[35] Riedner BA et al. Sleep homeostasis and cortical synchronization: III. A high-density EEG study of sleep slow waves in humans. Sleep 2007;30 (12):1643–57.
[36] Kurth S et al. Mapping of cortical activity in the first two decades of life: a high-density sleep electroencephalogram study. J Neurosci 2010;30 (40):13211–9.
[37] Wehrle FM et al. Sleep EEG maps the functional neuroanatomy of executive processes in adolescents born very preterm. Cortex 2017;86:11–21.
[38] Ashburner J, Friston K. Multimodal image coregistration and partitioning–a unified framework. Neuroimage 1997;6(3):209–17.
[39] Wilke M, Lidzba K. LI-tool: a new toolbox to assess lateralization in functional MR-data. J Neurosci Methods 2007;163(1):128–36.
[40] Helmstaedter C, Durwen HF, The Verbal Learning and Retention Test. A useful and differentiated tool in evaluating verbal memory performance. Schweiz Arch Neurol Psychiatr 1985; 1990;41(1):21–30.
[41] Landau WM, Kleffner FR. Syndrome of acquired aphasia with convulsive disorder in children. Neurology 1957;7(8):523–30.
[42] Roulet Perez E et al. Mental and behavioural deterioration of children with epilepsy and CSWS: acquired epileptic frontal syndrome. Dev Med Child Neurol 1993;35(8):661–74.
[43] Buzsaki G. Two-stage model of memory trace formation: a role for "noisy" brain states. Neuroscience 1989;31(3):551–70.
[44] Bower MR et al. Evidence for consolidation of neuronal assemblies after seizures in humans. J Neurosci 2015;35(3):999–1010.
[45] Heinrich B et al. Disparate effects of hormones and vigabatrin on sleep slow waves in patients with West syndrome - An indication of their mode of action? J Sleep Res 2021;30(3):e13137.
[46] Jain SV, Glauser TA. Effects of epilepsy treatments on sleep architecture and daytime sleepiness: an evidence-based review of objective sleep metrics. Epilepsia 2014;55(1):26–37.
[47] Bast T et al. Efficacy and tolerability of methylprednisolone pulse therapy in childhood epilepsies other than infantile spasms. Neuropediatrics 2014;45 (6):378–85.