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Original Article

Long-Term Response to High-Dose Diazepam Treatment in Continuous Spikes and Waves During Sleep

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ABSTRACT

BACKGROUND: This study evaluated whether the reduction in epileptiform activity after treatment with high-dose diazepam in continuous spikes and waves during sleep persists over time. **PATIENTS:** Patients aged 1 to 21 years with continuous spikes and waves during sleep who received high-dose nocturnal diazepam and who had electroencephalogram follow-up were included. Twenty-nine patients met the inclusion criteria and underwent a total of 48 high-dose diazepam treatment cycles. **RESULTS:** An overnight reduction of the spike wave percentage of at least 25% (i.e., 75-50%) occurred in 29 cycles (20 patients), and persisted within 6 months in 16 of 29 cycles (12 patients), but returned to baseline in three of 29 cycles (three patients). An overnight reduction of at least 50% (i.e., 75-25%) occurred in 15 cycles (13 patients), and persisted within 6 months in eight of 15 cycles (eight patients), but returned to baseline in three cycles (three patients). Twenty of 29 cycles that responded in the short term had persistent response on follow-up. Thirteen cycles of treatment were associated with mild side effects that did not recur with repeated treatment cycles. **CONCLUSIONS:** Treatment with high-dose diazepam reduced epileptiform activity in continuous spikes and waves during sleep in the short term, and improvement persisted for several months in most cycles. Short-term response predicted persistence of this effect on subsequent follow-up.

See related article on page 147.

Introduction

Interictal epileptiform activity can be sleep potentiated and tends to become more generalized during nonrapid eye movement sleep.[1,2] The most dramatic sleep potentiation of epileptiform activity is observed during electrical status epilepticus in sleep. In electrical status epilepticus in sleep marked potentiation of epileptiform activity in the transition from wakefulness to sleep results in an electroencephalographic pattern of near-continuous spikes and waves that occupy a significant proportion of the nonrapid eye movement sleep electroencephalographic tracing.[3-5] Frequent and prolonged interictal epileptiform activity is thought to cause a disruption of normal cognitive processes.[6-9] Patients with continuous spikes and waves during sleep present with electrical status epilepticus in sleep patterns on electroencephalogram in association with a severe and global regression on most aspects of development.[4,5] Consequently, several authors assume that successfully treating the electrical status epilepticus in sleep patterns on the

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electroencephalogram may also improve the neurocognitive prognosis of patients with continuous spikes and waves during sleep,[5,9-17] although this aspect remains to be proven.[6,18] To date, there is a lack of detailed studies characterizing this assumed beneficial effect of reduction of epileptiform activity on cognition. A major limitation when studying this correlation is the scarce data on the influence of antiepileptic treatment on epileptiform activity. Short-term reduction of epileptiform activity following treatment with high-dose diazepam was described in several series.[11,19-21] However, specific studies outlining follow-up of the interictal epileptiform activity after treatment are not available, and therefore it is still unclear whether reduction in epileptiform activity persists over time.

The aim of this study was to address this gap. This article presents a consecutive series of patients with continuous spikes and waves during sleep defined based on electroencephalographic assessment of the spike wave percentage and on regression or stagnation in at least two domains of development who underwent treatment with high-dose diazepam and had available long-term follow-up. The specific objectives were (1) to evaluate whether reduction of epileptiform activity persists over time and (2) to describe the reported clinical changes to this treatment.

Patients and Methods

This study was approved by the institutional review board of Boston Children's Hospital. This is a case series.

Patients were included during 8 consecutive years. Included patients were aged 1 to 21 years with the electrical status epilepticus in sleep pattern on electroencephalogram (≥50% of spike waves during nonrapid eye movement sleep). They had received the high-dose nocturnal diazepam treatment protocol and had epileptiform activity evaluated the night before and after the initiation of high-dose diazepam treatment. The patients had at least one follow-up electroencephalogram that included sleep. Patients were excluded when they had a lack of information on the indication for high-dose diazepam treatment, or had treatment with high-dose diazepam protocol without the electrical status epilepticus in sleep pattern on electroencephalogram, or had no regression or stagnation associated with the electrical status epilepticus in sleep pattern, or had mild regression or stagnation in only one aspect of development that could not be differentiated from normal fluctuations in the natural course of their disease.

High-dose diazepam treatment protocol

A treatment cycle with the high-dose nocturnal diazepam treatment protocol consisted of oral administration of 1 mg/kg of diazepam (maximum of 40 mg) before sleep on the first night, 0.5 mg/kg (maximum of 20 mg) before sleep each night during the following month(s), and subsequent medication weaning to avoid withdrawal symptoms. The protocol used was based on a previously described rectal diazepam treatment protocol[19] and variants.[11,20] Changes in the dose and duration of administration of diazepam were made based on the clinical response and treatment tolerability in each individual patient.

Electroencephalogram analysis

All patients underwent continuous overnight electroencephalographic monitoring to study the electroencephalogram pattern of electrical status epilepticus in sleep. Scalp electroencephalographic recordings were placed according to the 10-20 international system. Electroencephalographic recordings were continuously monitored throughout the day and night by dedicated electroencephalogram technologists. For the purposes of this study, a patient was considered to exhibit electrical status epilepticus in sleep in the electroencephalogram when the spike percentage during nonrapid eye movement sleep was 50% or more. The epileptiform activity was quantified using the first minutes of nonrapid eye movement sleep. For the purposes of quantification, focal and generalized discharges were considered equivalent. The percentage of epileptiform activity was calculated as the percentage of 1-second bins with at least one spike wave in them, as in the series by Aeby et al.[22] and reproduced by our group.[23] This was evaluated during the night prior to initiation of high-dose diazepam treatment, during the night after treatment initiation, and on the follow-up electroencephalograms with sleep.

Analysis of clinical data

Demographic and clinical variables were extracted by retrospective chart review, including age at occurrence of the main clinical events[23] and age at the use of high-dose diazepam treatment. Information was also collected on the different domains of development such as cognitive, motor, language or behavioral developmental delay, stagnation, or regression. Information on other comorbidities was also collected and included autistic spectrum disorders, attention-deficit/hyperactivity disorder, and learning and memory deficits. The assessment of development was based on the information recorded by the primary provider in the clinical charts. The use of concomitant antiepileptic treatments was also documented. Descriptive statistics were performed where appropriate and the clinical course was graphically documented for each patient.

We performed descriptive statistical analysis using SPSS 19 (SPSS Inc, Chicago, IL).

Results

Patients

This retrospective review identified 29 patients meeting inclusion criteria. All patients presented with the electrical status epilepticus in sleep pattern on electroencephalogram and had regression or stagnation in at least two domains of development, therefore they met continuous spikes and waves during sleep diagnosis and were treated with the high-dose diazepam protocol (Fig 1).

Demographic characteristics and clinical features

Overall, 12 (41%) patients had abnormal development prior to regression or stagnation. Twenty-six (90%) patients were enrolled in special education at last follow-up. Details on the demographic data and clinical events are presented in Table 1, Fig 2, and Supplementary Fig 1.

Treatment with other antiepileptic drugs

The treatment strategies in this patient population are presented in Fig 2 and Supplementary Fig 1. This overview demonstrates that polypharmacy is used more frequently than monotherapy for continuous spikes and waves during sleep and that treatment with high-dose diazepam frequently results in acute reduction of epileptiform activity that persists in time in most instances.

Response of epileptiform electroencephalogram activity to high-dose diazepam treatment

The 29 patients underwent a total of 48 cycles of treatment with high-dose diazepam. Fourteen patients underwent only one cycle of treatment, 11 patients underwent two cycles of treatment, and four patients underwent three cycles of treatment. The need for several treatment

cycles in some patients derived from relapse over time, but not because of treatment failure. The median (P25-P75) duration of the treatment during the acute phase was 4 weeks (3.25-8 weeks) and the median (P25-P75) duration of the taper period was 4 weeks (4-8 weeks) (Supplementary Fig 2). An overnight reduction of at least 25% (i.e., 75-50%) occurred in 29 cycles (20 patients) and persisted within 6 months in 16 of 29 cycles (12 patients), while the spike wave percentage returned to baseline in three of 29 cycles (three patients). Within this 6-month follow-up period, the median (P25-P75) duration of follow-up was 13 weeks (6-20 weeks). Follow-up data within 6 months were not available for 10 cycles. An overnight reduction of at least 50% (i.e., 75-25%) occurred in 15 cycles (13 patients), persisted within 6 months in eight of 15 cycles (eight patients), and returned to baseline in three of 15 cycles (three patients). There was no information on the follow-up within 6 months for four cycles. Individual patient information on the clinical features, domains of development, and response to treatment can be found in Table 2 and Supplementary Table 1.

Relationship between short-term and follow-up electroencephalographic responses

Of the 29 cycles (20 patients) that responded (at least 25% reduction in epileptiform activity) to treatment in the first 24 hours, 20 cycles (14 patients) had persistent response (at least 25% reduction in epileptiform activity as compared to pretreatment baseline) on follow-up, six cycles (six patients) did not have persistent responses on follow-up (returned to baseline), and three cycles (three patients) did not have follow-up. No response (<25% reduction in epileptiform activity) to treatment in the first 24 hours occurred in 19 cycles (17 patients). Of those, 12 cycles (10 patients) did not respond on subsequent follow-up, five cycles (five patients) responded (at least 25% reduction in epileptiform activity as compared to pretreatment baseline) on subsequent follow-up, and two cycles (two patients) did not have follow-up (Table 2). Although the period of follow-up varied among different patients, there was a significant correlation between the absolute spike wave percentage 24 hours after treatment in relationship to the spike wave percentage at last follow-up (Spearman correlation coefficient of 0.332; $P = 0.03$). However, the reduction in spike wave percentage after the first 24 hours of treatment (difference in spike wave percentage from baseline to 24 hours after treatment) did not correlate with the spike wave percentage reduction at last follow-up (difference in spike percentage from baseline to last follow-up), but there was a tendency toward a negative correlation that did not achieve statistical significance (Spearman correlation coefficient of −0.278; $P = 0.071$).

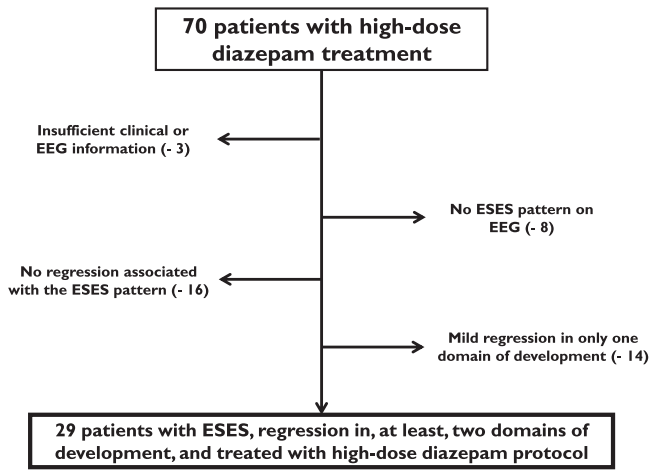

Figure 1. Flowchart of included and excluded patients in our study, demonstrating the steps for inclusion and exclusion of patients. Patients were excluded due to insufficient clinical information, lack of EEG features meeting diagnostic criteria of electrical status epilepticus in sleep or lack of regression or developmental stagnation. EEG, electroencephalogram; ESES, electrical status epilepticus in sleep.

Modification of the clinical features in response to high-dose diazepam treatment

Based on clinical assessment, most patients who presented with an improvement in epileptiform activity also had a concomitant improvement in developmental features (Table 2 and Supplementary Table 1).

Adverse events

Side effects occurred in 13 cycles of treatment (13 patients) and included agitation (five cycles), sedation (three cycles), ataxia (three cycles), hallucinations (two cycles), and emotional lability (one cycle). In one treatment cycle, agitation and hallucinations appeared together. Adverse events were mild in most cases and led to shortening or interruption of the protocol in three cycles (6.25% of the cycles). After an adverse event during one treatment cycle, seven patients were treated with at least one other cycle of high-dose diazepam (at the same weight-adjusted doses as in the initial treatment). During this repeat treatment neither the previously noted side effects nor different adverse events were seen. Therefore, no adverse events occurred upon repeated treatment after a first adverse event (Table 2 and Supplementary Table 1).

Discussion

This series shows that high-dose diazepam treatment reduces epileptiform activity in the short term for most patients with continuous spikes and waves during sleep, and this reduction lasts for several months in a majority of patients.

Note on the use of terminology

The use of terminology in the literature on electrical status epilepticus in sleep and continuous spikes and waves during sleep is heterogeneous.[24] For the purposes of this study, the term *electrical status epilepticus in sleep* was used to refer to the electroencephalographic pattern only and the term *continuous spikes and waves during sleep* was used to refer to the clinical syndrome of severe cognitive regression that occurs with the electroencephalographic pattern.[4] A subgroup of patients with developmental regression or stagnation in at least two different aspects of development (continuous spikes and waves during sleep) was selected in

Table 1. Demographic characteristics and clinical events in this study population

Sex (n, %)	Male: 18 (62%) Female: 11 (38%)
Age at seizure onset (yr)	Mean (SD): 4.4 (2) Median (P25-P75): 4.5 (3.5-5.2) Range: 0.07-10.17
Baseline development before regression/stagnation (n, %)	Normal: 17 (59%) Abnormal: 12 (41%)
Age at regression/stagnation (yr)	Mean (SD): 5.1 (2) Median (P25-P75): 4.8 (4.5-5.8) Range: 1-10.3
Age at recognition of the ESES pattern (yr)	Mean (SD): 6 (2) Median (P25-P75): 5.4 (4.6-6.9) Range: 3.2-11.8
Age at disappearance of the ESES pattern (data from 14 patients with resolution of the ESES pattern at last follow-up, 15 patients did not have resolution of the ESES pattern at last follow-up) (yr)	Mean (SD): 10.6 (4.1) Median (P25-P75): 9.6 (8.2-12.1) Range: 6.3-22.8
Age at last follow-up (yr)	Mean (SD): 13.1 (4.1) Median (P25-P75): 13.4 (10.7-15.7) Range: 5.2-22.8
Age at seizure freedom (data from 14 patients with seizure freedom at last follow-up, 15 patients did not have resolution of seizures at last follow-up) (yr)	Mean (SD): 8.4 (2.2) Median (P25-P75): 8.6 (6.3-10.4) Range: 4.8-11.5
Type of education at last follow-up (n, %)	Mainstream education: 3 (10%) Special education: 26 (90%)

Abbreviations:
ESES = Electrical status epilepticus in sleep
P25 = Twenty-fifth percentile
P75 = Seventy-fifth percentile
SD = Standard deviation

order to have information on the evolution of the developmental features.

Demographic characteristics and clinical features

Subgroups of this patient population have been already described in previous studies[21,23,25,26] and presented with similar demographic findings to those in series from other groups.[10,11,27-37] We noticed a delay of around 1 year between neurocognitive regression or stagnation that occurred around age 5 years and recognition of the electrical status epilepticus in sleep pattern that clustered around age 6 years. This difference suggests that patients with epilepsy who regress should have an electroencephalogram with sleep to evaluate for the possibility of electrical status epilepticus in sleep.

Treatment options in continuous spikes and waves during sleep

Treatment strategies in continuous spikes and waves during sleep are mostly based on case reports and small uncontrolled series.[13,38] The comparison of therapeutic strategies used in different studies is challenging because of heterogeneous patient populations, different drug doses, frequent polytherapy, variable durations of treatment, different measures of outcome, and naturally occurring fluctuations in severity over time. Therefore, available studies in the literature do not allow detailed evidence-based comparisons among different treatment options. However, this study provided information on results that can be similar to those in other series. In a study of 44 patients with electrical status epilepticus in sleep and different clinical presentations, corticosteroids normalized the electroencephalogram in 48% of patients.[39] In a series of 18 patients with electrical status epilepticus in sleep and different clinical presentations, levetiracetam reduced the epileptiform activity, although the use of a different method for quantification prevented direct comparison with other results.[40] Neuropsychological outcomes are generally more heterogeneously described and, therefore, more difficult to compare.[39,41] One treatment approach that has been reproduced at several centers includes the use of high-dose benzodiazepines for treatment of the epileptiform activity.[11,19-21] The short-term decrease in epileptiform activity following treatment with high-dose benzodiazepines is well documented both qualitatively[11,19,20] and quantitatively.[21] However, the response of epileptiform activity to treatment in these patients has not been followed up over a longer time period. This series shows that those patients whose epileptiform activity responds to high-dose diazepam in the short term have a persistent reduction for several months.

Modification of clinical features following treatment of the epileptiform activity

Improvement of interictal epileptiform activity in continuous spikes and waves during sleep may also be accompanied by improvement in the clinical features.[7,9,42] However, published data are contradictory,[6] and the correlation of interictal epileptiform activity with cognitive features is not always consistent.[18,20,22,43] This series

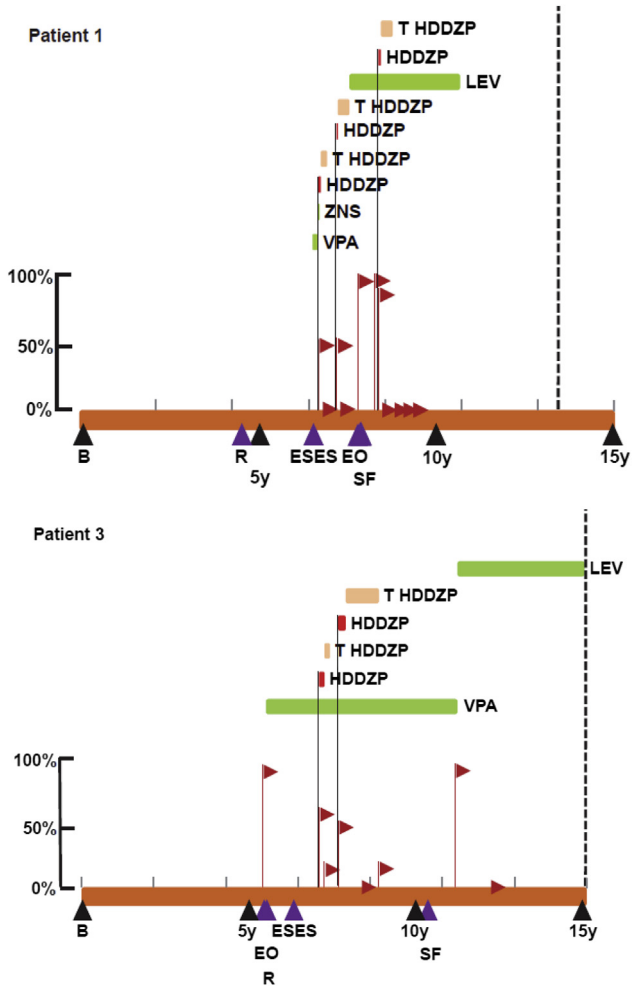

Figure 2. Graphical representation of the clinical and EEG evolution in two representative patients in our population. Information on patients 1 and 3 is presented in this figure. (The information in the entire patient population can be found in Supplementary Fig 1.) The y axis displays spike wave percentage on EEG and the x axis displays the timing of clinical events, including different stages of the condition (as marked by abbreviations for epilepsy onset [EO], electrical status epilepticus in sleep [ESES], regression [R], and seizure freedom [SF] on the bottom of each figure), spike wave percentage as demonstrated by *red flags*, and antiepileptic treatment choices and respective duration displayed as *horizontal bars* on top of each figure. The different clinical events are displayed as *triangles* in the orange timeline. The *vertical dotted line* represents the time of last follow-up. Treatment with high-dose diazepam reduces epileptiform activity even when it is very elevated and this reduction persists for a period of several months in most cases. B, birth; EO, epilepsy onset; HDDZP, high-dose diazepam; LEV, levetiracetam; T HDDZP, taper high-dose diazepam; VPA, valproate; ZNS zonisamide.

provides long-term follow-up of the epileptiform activity in patients with continuous spikes and waves during sleep. Although the retrospective approach did not allow detailed statistical analysis of clinical improvement, information in the clinical charts suggested an improvement in their developmental features that mirrored the improvement in epileptiform activity.

Relationship between short-term and follow-up responses

Of 29 cycles that responded acutely, 20 (69%) cycles had a persistent response on follow-up. Of 19 cycles that did not respond acutely, 12 (63%) did not respond on follow-up. Therefore, the response to high-dose diazepam during the first night was suggestive of the response on follow-up (Table 2 and Supplementary Table 1). Based on these data, it is reasonable to recommend continuation of treatment in patients who respond during the first night because their probability of a relatively prolonged response is high. In those patients who do not respond during the first night, continuation of treatment should be based on best clinical judgment and, even if chances of success are low, a short trial to assess delayed response may be reasonable if clinically indicated.

Adverse events

In concordance with previous studies, adverse events were relatively infrequent, mild, and led to discontinuation of the treatment in a minority of individuals.[11,19-21] Interestingly, this series confirms and expands on these findings by showing that in 54% of patients who presented with an adverse event during the first cycle did not have this side effect during subsequent diazepam treatment trials.

Strengths and weaknesses

Data need to be interpreted in the clinical context of the data acquisition. The decision to exclude patients with mild regression or stagnation in only one developmental domain may have led to selection of a subpopulation of patients with a more severe condition. However, this criterion was necessary to evaluate the clinical response to treatment and to exclude patients in whom normal fluctuations of their baseline condition may be confounded with regression or stagnation.

The approach in this study is limited in that it relies on the quantification of epileptiform activity and evaluation of clinical response as recorded in the clinical records. The intervals and timeline of follow-up were different for every patient, which jeopardized comparability. Because of the heterogeneous intervals of electroencephalogram assessment, the duration of the response cannot be summarized in a consistent way, but only be described for every individual patient.

Ideally, patients treated with high-dose diazepam should be compared with similar patients who did not undergo this treatment approach. However, the heterogeneity in the patient population and the natural fluctuations of the disease make this approach difficult. This study compared the epileptiform activity before and after treatment in each patient.

Only a prospective approach with standardized neuropsychological evaluation and standardized evaluation of epileptiform activity before and after treatment will conclusively answer the question of whether treatment of interictal epileptiform activity is associated with improvement in neurocognitive features. However, this retrospective series suggests that the evaluation of the response of epileptiform activity and neurocognitive function to high-dose benzodiazepine treatment is worth studying prospectively.

Table 2. Detailed clinical information and response to treatment in the individual patients

Patient (Cycle)	Age (y)	Domains of Development in Which There Was Regression or Stagnation During the Acute Period of Worsening	Acute Epileptiform Activity Change (SWP)	First Follow-Up (w: SWP)	Second Follow-Up (w: SWP)	Third Follow-Up (w: SWP)	Clinical and Developmental Response	Adverse Events
1 (1)	6.8	A, C, L	50%→0%	5: 0%			Improved language	No
1 (2)	7.3		50%→40%	3: 0%	31: 90%	55: 90%	No clinical change	No
1 (3)	8.4		80%→30%	4: 0%	22: 0%	35: 0%	No clinical change	No
2 (1)	5.5	A, B, C, L*	90%→30%	3: 0%	8: 0%	12: 0%	Improved language for 1 week	No
2 (2)	7.1		85%→50%	4: 50%	9: 0%	16: 0%	Improved language	No
3 (1)	7.1	AU, C*	60%→20%	8: 20%			Improved behavior and language	No
3 (2)	7.7		50%→10%	35: 0%	63: 20%	183: 85%	Improved behavior and language	No
4 (1)	6.7	C, L	60%→0%	24: 0%			Improved language	No
4 (2)	7.7		60%→30%	14: 0%	53: 0%	226: 25%	No clinical change	No
5 (1)	9	AU, B, C	95%→90%	9: 90%			Improved cognitive	No
5 (2)	10.3		95%→95%	92: 95%			Improved cognitive	No
6 (1)	3.2	B, C*, L	80%→36%	4: 30%	10: 20%	24: 60%	Improved language, and behavior	No
6 (2)	4.8		60%→10%	10: 0%	13: 0%	33: 0%	Improved language	Ataxia
6 (3)	6.3		80%→50%	3: 0%	76: 0%	161: 0%	Improved language	No
7 (1)	7.9	B*, C, L	80%→40%	19: 80%	26: 80%	29: 0%	Improved cognitive	Agitation and hallucinations
8 (1)	4.2	AU, L	85%→40%	160: 30%			Improved language	No
8 (2)	6.8		90%→35%	No follow-up			Improved language	No
9 (1)	9.8	C*, L, M	85%→20%	20: 0%	46:60%	100: 60%	Improved language	No
10 (1)	9.2	B, C	80%→40%	10: 30%			No clinical change	Sedation
10 (2)	9.5		50%→20%	No follow-up			No clinical change	No
10 (3)	10.1		90%→90%	29: 50%			No clinical change	No
11 (1)	10	B, C	50%→20%	155: 50%			Worsening of behavior and cognitive	Agitation
11 (2)	12.9		100%→100%	No follow-up			No response	No
12 (1)	8.4	B, L	60%→60%	11: 95%	15: 90%	27: 90%	Improved cognitive	Sedation
12 (2)	10.1		100%→100%	12: 100%	176: 20%	250: 95%	Improved language	No
13 (1)	6.3	AU, B, C	70%→60%	14: 60%	42: 33%	115: 22%	Improved language	No
14 (1)	5.3	B, C, L	88%→28%	5: 91%	18: 95%	25: 86%	Improved language	No
15 (1)	5.8	B, C	99%→94%	14: 85%	17: 100%		No clinical change	No
16 (1)	8	B, C*, L	65%→27%	35: 25%	56:0%	106: 20%	No clinical change	Hallucinations
17 (1)	11.8	B, C, L	85%→80%	11: 80%	35: 50%	66: 60%	Improved cognitive	Sedation
18 (1)	4.6	B, C, L	95%→90%	21: 85%	66: 86%	84:4%	Improved cognitive	No
19 (1)	4.9	C, L, M	82%→24%	4: 0%	26: 0%	64: 65%	Improved cognitive and language	Ataxia
19 (2)	8.1		95%→90%	5 : 90%	28: 80%	54: 76%	No clinical change	No
20 (1)	5.9	AU, B, C*, L*	70%→25%	7: 75%			Improved language and behavior	No
20 (2)	6.2		50%→45%	4 : 60%	44 : 20%	162: 0%	Improved language and behavior	No
21 (1)	5.2	B, C*, L	100%→50%	67: 90%	84: 70%	186: 85%	Improved cognitive	Agitation
22 (1)	6.6	AU, B, C, L	80%→40%	6: 35%			Improved cognitive, and language	No
23 (1)	8.1	B, C, L	75%→5%	4: 0%			Improved cognitive	Emotional lability
23 (2)	8.4		70%→20%	No follow-up			No clinical change	No
23 (3)	8.7		85%→85%	No follow-up			No clinical change	No
24 (1)	6.1	AU, B, L	85%→85%	8: 60%	202: 20%	222: 70%	Improved cognitive	No
25 (1)	5.3	B, C, L	85%→85%	13: 90%			No clinical change	Agitation
25 (2)	6		90%→20%	14: 30%	20: 40%	57: 90%	No clinical change	No
26 (1)	6.8	B, C*, L	50%→50%	32: 45%	36: 45%	85: 80%	No clinical change	Ataxia
27 (1)	10.6	C, M	95%→95%	56: 0%	69: 0%	166: 0%	No clinical change	No
28 (1)	5.5	B, C, L*	90%→20%	6: 0%			Improved language, and behavior	No
28 (2)	5.9		80%→80%	11: 0%			Improved language, and behavior	No
29 (1)	4.4	B, C, L	90%→10%	75: 80%	87: 50%	292: 75%	Improved cognitive	Agitation

Abbreviations:
A = Attention
Age = Age at the diazepam cycle in years
AU = Autistic features
B = Behavioral
C = Cognitive
L = Language
SWP = Spike wave percentage
W = Weeks

Epileptiform activity change: Percentage of epileptiform activity found during the night before diazepam and during the night after treatment. First follow-up: Weeks after initiation of treatment and percentage of epileptiform activity. Second follow-up: Weeks after initiation of treatment and percentage of epileptiform activity. Third follow-up: Weeks after initiation of treatment and percentage of epileptiform activity.

* The domains of development that are marked with an asterisk did not clearly regressed but stagnated, that is, did not progress as expected per age.

Conclusion

This series shows that treatment with high-dose diazepam for continuous spikes and waves during sleep reduces epileptiform activity in the short term. This reduction persists for several months in most patients, and the presence of acute response correlates with persistence of this effect on subsequent follow-up. This series also suggests safety with mild adverse events that led to discontinuation in a minority of patients and did not recur with repeated high-dose diazepam administration cycles.

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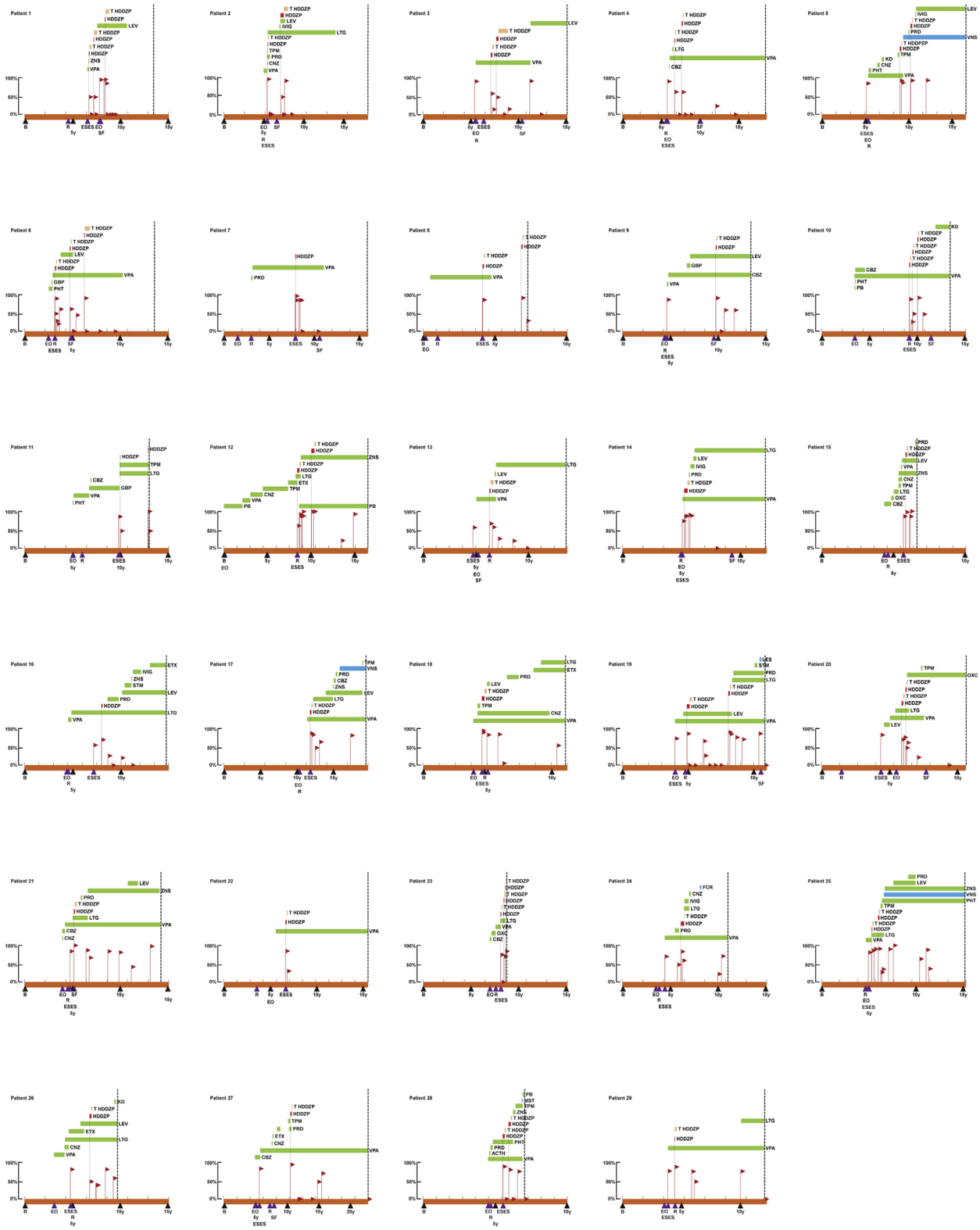
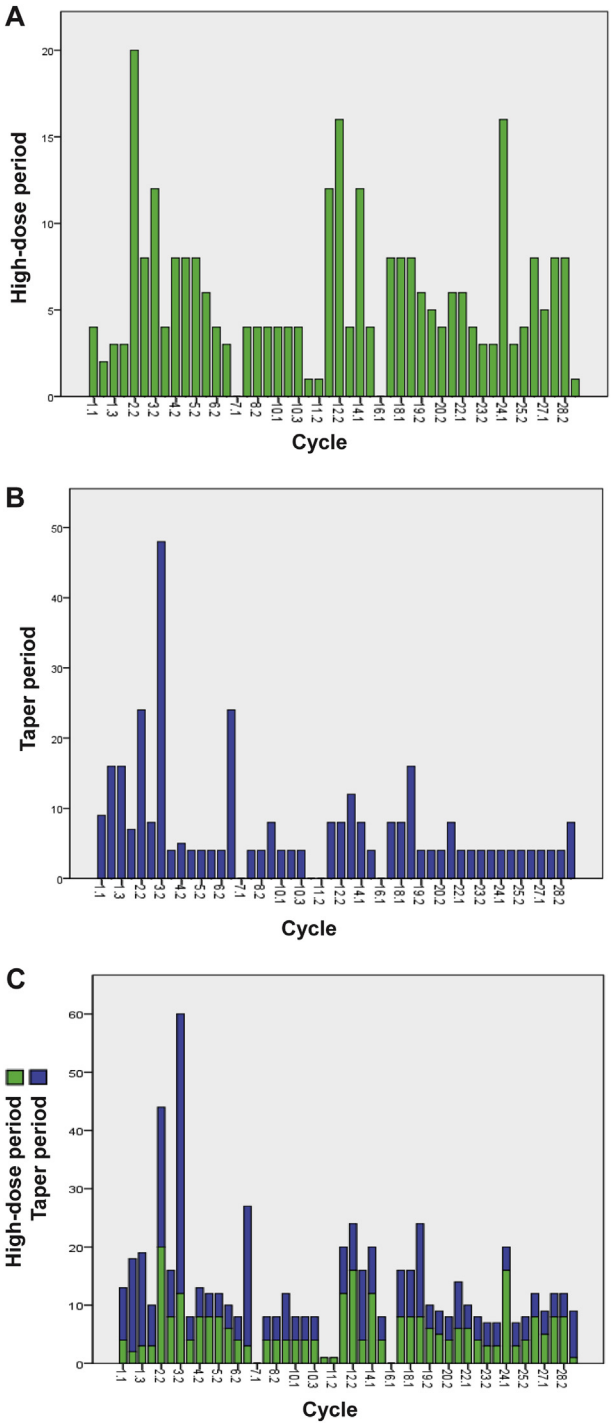
References

1. Loddenkemper T, Lockley SW, Kaleyias J, Kothare SV. Chronobiology of epilepsy: diagnostic and therapeutic implications of chrono-epileptology. *J Clin Neurophysiol*. 2011;28:146-153.
2. Quigg M. Circadian rhythms: interactions with seizures and epilepsy. *Epilepsy Res*. 2000;42:43-55.
3. Loddenkemper T, Sánchez Fernández I, Peters JM. Continuous spike and waves during sleep and electrical status epilepticus in sleep. *J Clin Neurophysiol*. 2011;28:154-164.
4. Sánchez Fernández I, Loddenkemper T, Peters JM, Kothare SV. Electrical status epilepticus in sleep: clinical presentation and pathophysiology. *Pediatr Neurol*. 2012;47:390-410.
5. Tassinari CA, Rubboli G, Volpi L, et al. Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the acquired aphasia. *Clin Neurophysiol*. 2000;111(suppl 2):S94-S102.
6. Aldenkamp AP, Arends J. Effects of epileptiform EEG discharges on cognitive function: is the concept of "transient cognitive impairment" still valid? *Epilepsy Behav*. 2004;5(suppl 1):S25-S34.
7. Bolsterli BK, Schmitt B, Bast T, et al. Impaired slow wave sleep downscaling in encephalopathy with status epilepticus during sleep (ESES). *Clin Neurophysiol*. 2011;122:1779-1787.
8. Holmes GL, Lenck-Santini PP. Role of interictal epileptiform abnormalities in cognitive impairment. *Epilepsy Behav*. 2006;8:504-515.
9. Tassinari CA, Cantalupo G, Rios-Pohl L, Giustina ED, Rubboli G. Encephalopathy with status epilepticus during slow sleep: "the Penelope syndrome.". *Epilepsia*. 2009;50(suppl 7):4-8.
10. Caraballo RH, Bongiorni L, Cersosimo R, et al. Epileptic encephalopathy with continuous spikes and waves during sleep in children with shunted hydrocephalus: a study of nine cases. *Epilepsia*. 2008;49:1520-1527.
11. Inutsuka M, Kobayashi K, Oka M, Hattori J, Ohtsuka Y. Treatment of epilepsy with electrical status epilepticus during slow sleep and its related disorders. *Brain Dev*. 2006;28:281-286.
12. Liukkonen E, Kantola-Sorsa E, Paetau R, et al. Long-term outcome of 32 children with encephalopathy with status epilepticus during sleep, or ESES syndrome. *Epilepsia*. 2010;51:2023-2032.
13. Nickels K, Wirrell E. Electrical status epilepticus in sleep. *Semin Pediatr Neurol*. 2008;15:50-60.
14. Nieuwenhuis L, Nicolai J. The pathophysiological mechanisms of cognitive and behavioral disturbances in children with Landau-Kleffner syndrome or epilepsy with continuous spike-and-waves during slow-wave sleep. *Seizure*. 2006;15:249-258.
15. Robinson RO, Baird G, Robinson G, Simonoff E. Landau-Kleffner syndrome: course and correlates with outcome. *Dev Med Child Neurol*. 2001;43:243-247.
16. Rossi PG, Parmeggiani A, Posar A, et al. Landau-Kleffner syndrome (LKS): long-term follow-up and links with electrical status epilepticus during sleep (ESES). *Brain Dev*. 1999;21:90-98.
17. Sinclair DB, Snyder TJ. Corticosteroids for the treatment of Landau-Kleffner syndrome and continuous spike-wave discharge during sleep. *Pediatr Neurol*. 2005;32:300-306.
18. Holmes GL, McKeever M, Saunders Z. Epileptiform activity in aphasia of childhood: an epiphenomenon? *Epilepsia*. 1981;22:631-639.
19. De Negri M, Baglietto MG, Battaglia FM, et al. Treatment of electrical status epilepticus by short diazepam (DZP) cycles after DZP rectal bolus test. *Brain Dev*. 1995;17:330-333.
20. Kramer U, Sagi L, Goldberg-Stern H, et al. Clinical spectrum and medical treatment of children with electrical status epilepticus in sleep (ESES). *Epilepsia*. 2009;50:1517-1524.
21. Sánchez Fernández I, Hadjiloizou S, Eksioglu Y, et al. Short-term response of sleep-potentiated spiking to high-dose diazepam in electric status epilepticus during sleep. *Pediatr Neurol*. 2012;46:312-318.
22. Aeby A, Poznanski N, Verheulpen D, Wetzburger C, Van Bogaert P. Levetiracetam efficacy in epileptic syndromes with continuous spikes and waves during slow sleep: experience in 12 cases. *Epilepsia*. 2005;46:1937-1942.
23. Sánchez Fernández I, Peters JM, Hadjiloizou S, et al. Clinical staging and electroencephalographic evolution of continuous spikes and waves during sleep. *Epilepsia*. 2012;53:1185-1195.
24. Sánchez Fernández I, Chapman KE, Peters JM, et al. The tower of Babel: survey on concepts and terminology in electrical status epilepticus in sleep and continuous spikes and waves during sleep in North America. *Epilepsia*. 2013;54:741-750.
25. Sánchez Fernández I, Peters J, Takeoka M, et al. Patients with electrical status epilepticus in sleep share similar clinical features regardless of their focal or generalized sleep potentiation of epileptiform activity. *J Child Neurol*. 2013;28:83-89.
26. Sánchez Fernández I, Takeoka M, Tas E, et al. Early thalamic lesions in patients with sleep-potentiated epileptiform activity. *Neurology*. 2012;78:1721-1727.
27. Bureau M. Outstanding cases of CSWS and LKS: analysis of the data sheets provided by the participants. In: Beaumanoir A, Bureau M, Deonna L, Mira L, Tassinari CA, eds. *Continuous spikes and waves during slow sleep*. London:: John Libbey; 1995:213-216.
28. Bureau M. "Continuous spikes and waves during slow sleep" (CSWS): definition of the syndrome. In: Beaumanoir A, Bureau M, Deonna L, Mira L, Tassinari CA, eds. *Continuous spikes and waves during slow sleep*. London:: John Libbey; 1995:17-26.
29. Galanopoulou AS, Bojko A, Lado F, Moshe SL. The spectrum of neuropsychiatric abnormalities associated with electrical status epilepticus in sleep. *Brain Dev*. 2000;22:279-295.
30. Guzzetta F, Battaglia D, Veredice C, et al. Early thalamic injury associated with epilepsy and continuous spike-wave during slow sleep. *Epilepsia*. 2005;46:889-900.
31. Morikawa T, Seino M, Watanabe M. Long-term outcome of CSWS syndrome. In: Beaumanoir A, Bureau M, Deonna L, Mira L, Tassinari CA, eds. *Continuous spikes and waves during slow sleep*. London:: John Libbey; 1995:27-36.
32. Peltola ME, Liukkonen E, Granstrom ML, et al. The effect of surgery in encephalopathy with electrical status epilepticus during sleep. *Epilepsia*. 2011;52:602-609.

33. Saltik S, Uluduz D, Cokar O, Demirbilek V, Dervent A. A clinical and EEG study on idiopathic partial epilepsies with evolution into ESES spectrum disorders. *Epilepsia*. 2005;46:524-533.
34. Scholtes FB, Hendriks MP, Renier WO. Cognitive deterioration and electrical status epilepticus during slow sleep. *Epilepsy Behav*. 2005; 6:167-173.
35. Siniatchkin M, Groening K, Moehring J, et al. Neuronal networks in children with continuous spikes and waves during slow sleep. *Brain*. 2010;133:2798-2813.
36. Van Hirtum-Das M, Licht EA, Koh S, et al. Children with ESES: variability in the syndrome. *Epilepsy Res*. 2006;70(suppl 1): S248-S258.
37. Yan Liu X, Wong V. Spectrum of epileptic syndromes with electrical status epilepticus during sleep in children. *Pediatr Neurol*. 2000;22: 371-379.
38. Veggiotti P, Pera MC, Teutonico F, et al. Therapy of encephalopathy with status epilepticus during sleep (ESES/CSWS syndrome): an update. *Epileptic Disord*. 2012;14:1-11.
39. Buzatu M, Bulteau C, Altuzarra C, Dulac O, Van Bogaert P. Corticosteroids as treatment of epileptic syndromes with continuous spike-waves during slow-wave sleep. *Epilepsia*. 2009;50(suppl 7): 68-72.
40. Larsson PG, Bakke KA, Bjornaes H, et al. The effect of levetiracetam on focal nocturnal epileptiform activity during sleep—a placebo-controlled double-blind cross-over study. *Epilepsy Behav*. 2012;24: 44-48.
41. Bjornaes H, Bakke KA, Larsson PG, et al. Subclinical epileptiform activity in children with electrical status epilepticus during sleep: Effects on cognition and behavior before and after treatment with levetiracetam. *Epilepsy Behav*. 2013;27:40-48.
42. Majak K, Pitkanen A. Do seizures cause irreversible cognitive damage? Evidence from animal studies. *Epilepsy Behav*. 2004; 5(suppl 1)):S35-S44.
43. Bahi-Buisson N, Savini R, Eisermann M, et al. Misleading effects of clonazepam in symptomatic electrical status epilepticus during sleep syndrome. *Pediatr Neurol*. 2006;34:146-150.



Supplementary Figure 1. Graphical representation of the clinical, and EEG evolution of this patient population. Every figure visualizes care in each included patient. The y axis displays spike wave percentage on EEG and the x axis displays the timing of clinical events, including different stages of the condition (as marked by abbreviations for epilepsy onset [EO], electrical status epilepticus in sleep [ESES], regression [R], and seizure freedom [SF] on the bottom of each figure), spike wave percentage as demonstrated by *red flags*, and antiepileptic treatment choices and respective duration displayed as *horizontal bars* on top of each figure. The different clinical events are displayed as *triangles* in the orange timeline. The vertical dotted line represents the time of last follow-up. ACTH, adrenocorticotropic hormone; B, birth; CBZ, carbamazepine; CNZ, clonazepam; EEG, electroencephalogram; ETX, ethosuximide; GBP, gabapentin; HDDZP, high-dose diazepam; IVIG, intravenous immunoglobulin; KD, ketogenic diet; LEV, levetiracetam; LTG, lamotrigine; LES, lesionectomy; MST, multiple subpial transections; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PRD, prednisone; STM, sulthiame; T HDDZP, taper high-dose diazepam; TPM, topiramate; VPA, valproate, VNS, vagal nerve stimulator; ZNS, zonisamide.



Supplementary Figure 2. Histogram with the duration of the treatment. (A) Duration of the acute phase of the treatment. (B) Duration of the taper phase of the treatment. (C) Duration of the acute (green) plus the taper (blue) phases of the treatment. Both the acute phase and the taper phase clustered around 1 month of duration. x axis, treatment cycle; y axis, duration of the treatment (in weeks).

Supplementary Table 1. Detailed clinical information and response to treatment in the individual patients

Patient (Cycle)*	Age (y)	Domains of Development In Which There Was Regression or Stagnation During the Acute Period of Worsening	High Dose (w)	Taper Period (w)	Acute Epileptiform Activity Change (SWP)	First Follow-Up (w: SWP)	Second Follow-Up (w: SWP)	Third Follow-Up (w: SWP)	Clinical and Developmental Response	Adverse Events
1 (1)	6.8	A, C, L	4	9	50%→0%	5: 0%			Improved language	No
1 (2)	7.3		2	16	50%→40%	3: 0%	31: 90%	55: 90%	No clinical change	No
1 (3)	8.4		3	16	80%→30%	4: 0%	22: 0%	35: 0%	No clinical change	No
2 (1)	5.5	A, B, C, L†	3	7	90%→30%	3: 0%	8: 0%	12: 0%	Improved language for 1 week	No
2 (2)	7.1		20	24	85%→50%	4: 50%	9: 0%	16: 0%	Improved language	No
3 (1)	7.1	AU, C†,*	8	8	60%→20%	8: 20%			Improved behavior and language	No
3 (2)	7.7		12	48	50%→10%	35: 0%	63: 20%	183: 85%	Improved behavior and language	No
4 (1)	6.7	C, L	4	4	60%→0%	24: 0%			Improved language	No
4 (2)	7.7		8	5	60%→30%	14: 0%	53: 0%	226: 25%	No clinical change	No
5 (1)	9	AU, B, C	8	4	95%→90%	9: 90%			Improved cognitive	No
5 (2)	10.3		8	4	95%→95%	92: 95%			Improved cognitive	No
6 (1)	3.2	B, C†,*, L	6	4	80%→36%	4: 30%	10: 20%	24: 60%	Improved language, and behavior	No
6 (2)	4.8		4	4	60%→10%	10: 0%	13: 0%	33: 0%	Improved language	Ataxia
6 (3)	6.3		3	24	80%→50%	3: 0%	76: 0%	161: 0%	Improved language	No
7 (1)	7.9	B†, C, L	0	0	80%→40%	19: 80%	26: 80%	29: 0%	Improved cognitive	Agitation and hallucinations
8 (1)	4.2	AU, L	4	4	85%→40%	160: 30%			Improved language	No
8 (2)	6.8		4	4	90%→35%	No follow-up			Improved language	No
9 (1)	9.8	C†, L, M	4	8	85%→20%	20: 0%	46:60%	100: 60%	Improved language	No
10 (1)	9.2	B, C	4	4	80%→40%	10: 30%			No clinical change	Sedation
10 (2)	9.5		4	4	50%→20%	No follow-up			No clinical change	No
10 (3)	10.1		4	4	90%→90%	29: 50%			No clinical change	No
11 (1)	10	B, C	1	0	50%→20%	155: 50%			Worsening of behavior and cognitive	Agitation
11 (2)	12.9		1	0	100%→100%	No follow-up			No response	No
12 (1)	8.4	B, L	12	8	60%→60%	11: 95%	15: 90%	27: 90%	Improved cognitive	Sedation
12 (2)	10.1		16	8	100%→100%	12: 100%	176: 20%	250: 95%	Improved language	No
13 (1)	6.3	AU, B, C	4	12	70%→60%	14: 60%	42: 33%	115: 22%	Improved language	No
14 (1)	5.3	B, C, L	12	8	88%→28%	5: 91%	18: 95%	25: 86%	Improved language	No
15 (1)	5.8	B, C	4	4	99%→94%	14: 85%	17: 100%		No clinical change	No
16 (1)	8	B, C†, L	0	0	65%→27%	35: 25%	56:0%	106: 20%	No clinical change	Hallucinations
17 (1)	11.8	B, C, L	8	8	85%→80%	11: 80%	35: 50%	66: 60%	Improved cognitive	Sedation
18 (1)	4.6	B, C, L	8	8	95%→90%	21: 85%	66: 86%	84:4%	Improved cognitive	No
19 (1)	4.9	C, L, M	8	16	82%→24%	4: 0%	26: 0%	64: 65%	Improved cognitive and language	Ataxia
19 (2)	8.1		6	4	95%→90%	5 : 90%	28: 80%	54: 76%	No clinical change	No
20 (1)	5.9	AU, B, C†, L†	5	4	70%→25%	7: 75%			Improved language and behavior	No
20 (2)	6.2		4	4	50%→45%	4 : 60%	44 : 20%	162: 0%	Improved language and behavior	No
21 (1)	5.2	B, C†, L	6	8	100%→50%	67: 90%	84: 70%	186: 85%	Improved cognitive	Agitation
22 (1)	6.6	AU, B, C, L	6	4	80%→40%	6: 35%			Improved cognitive, and language	No
23 (1)	8.1	B, C, L	4	4	75%→5%	4: 0%			Improved cognitive	Emotional lability
23 (2)	8.4		3	4	70%→20%	No follow-up			No clinical change	No
23 (3)	8.7		3	4	85%→85%	No follow-up			No clinical change	No
24 (1)	6.1	AU, B, L	16	4	85%→85%	8: 60%	202: 20%	222: 70%	Improved cognitive	No
25 (1)	5.3	B, C, L	3	4	85%→85%	13: 90%			No clinical change	Agitation
25 (2)	6		4	4	90%→20%	14: 30%	20: 40%	57: 90%	No clinical change	No

(*continued on next page*)

Supplementary Table 1 (*continued*)

Patient (Cycle)*	Age (y)	Domains of Development In Which There Was Regression or Stagnation During the Acute Period of Worsening	High Dose (w)	Taper Period (w)	Acute Epileptiform Activity Change (SWP)	First Follow-Up (w: SWP)	Second Follow-Up (w: SWP)	Third Follow-Up (w: SWP)	Clinical and Developmental Response	Adverse Events
26 (1)	6.8	B, C†, L	8	4	50%→50%	32: 45%	36: 45%	85: 80%	No clinical change	Ataxia
27 (1)	10.6	C, M	5	4	95%→95%	56: 0%	69: 0%	166: 0%	No clinical change	No
28 (1)	5.5	B, C, L†	8	4	90%→20%	6: 0%			Improved language, and behavior	No
28 (2)	5.9		8	4	80%→80%	11: 0%			Improved language, and behavior	No
29 (1)	4.4	B, C, L	1	8	90%→10%	75: 80%	87: 50%	292: 75%	Improved cognitive	Agitation

Abbreviations:
A = Attention
Age = Age at the diazepam cycle in years
AU = Autistic features
B = Behavioral
C = Cognitive
L = Language
SWP = Spike wave percentage
W = Weeks

High dose: Duration of the high-dose treatment with diazepam in weeks (0 means not continued after the first 1-2 nights). Taper: Duration of the taper of treatment with diazepam in weeks (0 means not continued after the high-dose phase). Epileptiform activity change: Percentage of epileptiform activity found during the night before diazepam and during the night after treatment. First follow-up: Weeks after initiation of treatment and percentage of epileptiform activity. Second follow-up: Weeks after initiation of treatment and percentage of epileptiform activity. Third follow-up: Weeks after initiation of treatment and percentage of epileptiform activity.

* The cycles of treatment that did not respond acutely to treatment (<25% reduction in epileptiform activity during the first 24 hours) are displayed in red.

† The domains of development that did not clearly regress but stagnated, that is, did not progress as expected per age.