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Effects of levetiracetam on generalized discharges monitored with ambulatory EEG in epileptic patients

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ABSTRACT

Purpose: Quantitative analysis of epileptiform discharges (EDs) before and after the initiation of an antiepileptic treatment is a useful tool to objectively documentate the efficacy of an antiepileptic drug (AED). Aim of this study was to evaluate the effect of levetiracetam (LEV) on EDs, monitored with ambulatory EEG (A/EEG), in a limited series of patients with generalized epilepsy.
Methods: We performed 24 h A/EEG recording in basal condition and at follow-up after LEV therapy in 21 adult epileptic patients. Eleven received LEV as monotherapy and 10 as add-on. For each patient we quantified total epileptic activity considering the following parameters: total number, total duration, maximal duration and median duration of EDs. Self-reported information on the effect of LEV on clinical seizures was also collected, to determine the electro-clinical correlation.
Results: A high variability of the response to LEV was observed in the monotherapy group, without statistical differences for all the parameters investigated. A significant reduction of the total number of seizures (113.6 vs. 41.2; $p = .01$) was observed in patients in add-on therapy. The modifications of epileptiform EEG abnormalities did not necessarily correlate with the self-reported clinical impressions.
Discussion: The quantification of EDs monitored by A/EEG provides a useful objective support for evaluating the neurophysiologic profile and the real efficacy of an antiepileptic treatment. In our patients LEV was able to significantly reduce the EDs only in add-on therapy. Further larger studies are necessary to clarify the effects of LEV on electro-clinical features of generalized epilepsy.

1. Introduction

Levetiracetam (LEV) is a new antiepileptic drug (AED) that has a favorable safety profile and no significant interaction with other AEDs or other drugs.[1–4] The efficacy and tolerability of LEV as adjunctive therapy or monotherapy have been demonstrated in patients with epileptic partial-onset seizures, with or without secondary generalization.[5–7] Recently, the efficacy of LEV in generalized idiopathic epilepsy has also been reported.[8–13] Some open-label studies indeed observed that LEV, in monotherapy or add-on, reduces the frequency of myoclonic seizures in patients with generalized epilepsy[14] and may be effective and well tolerated in resistant cases of juvenile myoclonic epilepsy.[8,15] Moreover, Berkovic et al.[16] demonstrated, in a randomized placebo-controlled study, that LEV is effective as adjunctive therapy also for treating generalized tonic–clonic seizures in patients with idiopathic epilepsies.

Despite the several evidences of LEV efficacy in the treatment of generalized epilepsy, little information is reported in literature regarding the effects of LEV on epileptiform discharges evaluated objectively with EEG quantification. Some experimental studies showed that LEV attenuates spike and wave discharges in rats with different genetic models of epilepsy with absences.[17–19] Few case reports and preliminary studies with long-term EEG recordings conducted in patients affected by partial and generalized epilepsy have also reported the efficacy of LEV in the reduction of interictal epileptiform discharges.[20–23]

Long-term EEG recording provides a reliable and objective documentation of the efficacy of an antiepileptic treatment, through the quantitative evaluation of the epileptic activity. However, there is often a discrepancy between the patient self-reported impressions and the objective neurophysiological evaluation of the response to the treatment. In particular, in generalized epilepsy with absence seizures, it may be possible

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that the self-reporting of seizures actually underestimates the real frequency of the ictal episodes. Ambulatory EEG (A/EEG) is a simple available tool in routine clinical practice to perform long-term monitoring in outpatients.

Aim of this study was to evaluate the objective effect of LEV on epileptiform discharges in patients with generalized epilepsy, monitored with ambulatory EEG (A/EEG). The quantification of epileptiform discharges before and after LEV administration has been also correlated with the self-reported clinical informations on seizures frequency during the treatment.

2. Methods

Patients with idiopathic and cryptogenic generalized epilepsy were enrolled in the study, according to the following inclusion criteria: (a) recurrence of generalized seizures (absence, myoclonic and/or tonic–clonic seizures) in the previously 3 months; (b) presence on basal standard EEG (S/EEG) of generalized epileptiform discharges, evaluated before the onset of LEV treatment; (c) normal cerebral MR imaging; (d) no evidence of relevant medical and neuropsychiatric diseases.

At baseline, S/EEG tracings were recorded for 30 min, at rest and during photostimulation and hyperventilation, with a digital apparatus (Micromed, Italy) and sampled at a rate of 256 s^{-1}. According to the International 10-20 System, the following scalp electrodes were applied: Fp2, Fp1, F8, F7, F4, F3, C4, C3, T4, T3, T6, T5, P4, P3, O2 and O1. During EEG recordings, heart and breathing rates were continuously monitored. The baseline S/EEG was used for the characterization of epileptic generalized discharges (bursts of spikes, polyspikes, spike-and-wave complexes).

After the baseline S/EEG, each patient was submitted to ambulatory EEG (A/EEG) recording, performed by a Brain Spy MS-40 Ambulatory Recorder (Micromed). The following conventional chloride disc electrodes, according to the International 10-20 System, were applied on the scalp with EC2 (Grass-Telefactor) adesive paste: Fp2, Fp1, T4, T3, C4, C3, O2 and O1. A/EEG lasted for 24 h, starting between 9:00 and 10:00 a.m., thus including active and quiet awake and nocturnal sleep at home.

After the baseline S/EEG and A/EEG recordings, LEV was administered at the dosage of 1000–1500 mg/day, starting with 500 mg/day and increasing of 500 mg/day every 5th day. At inclusion, 11 patients started LEV as monotherapy, being totally untreated or drug-free since the past 3 months, and 10 patients started LEV as add-on therapy, being already under other AED treatment and pharmacoresistant (Table 1). All patients and their relatives were instructed to keep a detailed diary of seizures and of normal activity of the daily living. The second A/EEG was performed after a 4–6 months follow-up, during treatment with LEV. A/EEG recordings were evaluated offline by two experts neurophysiologists blinded to the treatment. Well-structured, organized and well identifiable epileptiform pattern lasting at least 1 s were considered for the inspective quantification of epileptic activity. Single spikes or sharp waves or the bursts of duration of less than 1 s have not been considered for the quantification.

The epileptic activity, evaluated for each A/EEG before and during LEV treatment, was quantified according to the following parameters: 1, total number of discharges in 24 h (TN); 2, total duration in seconds of all registered discharges in 24 h (TD); 3, maximal duration (MaxD) and median duration (MedD) in seconds of discharges. At follow-up, patients were required to return their clinical diary with the self-evaluation of the efficacy of therapy on seizures control and the occurrence of adverse effects. On the basis of these self-reported clinical information, patients were classified as: (a) patients seizure-free; (b) patients improved (reduction in seizures $\geq$50%); (c) patients with seizure frequency substantially unchanged; (d) patients with worsening of seizures.

The study was approved by the local Ethical Committee and all subjects gave their written informed consent.

3. Statistical analysis

Data were collected on an Excel datasheet and SPSS13 for Macintosh was used to perform statistical analysis. Student's paired *t*-test and Wilcoxon signed rank test were used to determine mean differences among the groups. Statistical significance was considered for $p < .05$.

Table 1
Patients characteristics.

Pts	Age (years)	Gender	Seizure type	AEDs at first A/EEG	AEDs at second A/EEG	Follow-up (months)	LEV (mg/die)
Monotherapy							
1	57	F	Absence, myoclonic	–	LEV	4	1500
2	17	F	Myoclonic, GTCS	–	LEV	6	1000
3	25	M	Absence, GTCS	–	LEV	6	1000
4	16	F	Absence, GTCS	–	LEV	4	1000
5	18	F	Absence	–	LEV	5	1500
6	39	F	Absence, GTCS	–	LEV	5	1500
7	21	M	Absence	–	LEV	5	1000
8	22	M	Absence	–	LEV	6	1000
9	29	M	Myoclonic, GTCS	–	LEV	5	1500
10	24	F	Absence, GTCS	–	LEV	5	1500
11	32	F	Absence, GTCS	–	LEV	6	1500
Add-on							
12	65	F	Myoclonic, GTCS	VPA	LEV + VPA	6	1500
13	24	F	Absence, GTCS	VPA	LEV + VPA	4	1000
14	20	M	Absence, GTCS	ETS	LEV + ETS	6	1000
15	60	M	Absence, GTCS	VPA + PB	LEV + VPA + PB	4	1500
16	27	F	Absence, GTCS	VPA + PB + LTG	LEV + VPA + PB + LTG	5	1500
17	23	F	Myoclonic, GTCS	VPA	LEV + VPA	4	1000
18	30	F	Absence, GTCS	LTG + TPM	LEV + LTG + TPM	4	1000
19	25	M	Absence, GTCS	VPA	LEV + VPA	5	1500
20	35	F	Myoclonic, GTCS	VPA + LTG	LEV + VPA + LTG	5	1500
21	45	M	Absence, GTCS	PB	LEV + PB	6	1500

GTCS (generalized tonic–clonic seizures); LEV (levetiracetam), VPA (valproic acid), ETS (ethosuximide), PB (phenobarbital), LTG (lamotrigine), TPM (topiramate).

Table 2
Total number (TN), total duration (TD, s), maximal duration (MaxD, s) and median duration (MedD, s) of epileptic discharges at A/EEG before and after LEV therapy in all patients, in patients in monotherapy and in patients in add-on therapy (mean ± S.D.).

	Total number		Total duration		Maximal duration		Median duration	
	Basal	Follow-up	Basal	Follow-up	Basal	Follow-up	Basal	Follow-up
All patients	170.8 ± 159.5	130.6 ± 161.1	472.3 ± 439.4	409.5 ± 490.7	8.5 ± 8.3	11.3 ± 11.2	2.5 ± 1	2.5 ± 1.5
Monotherapy	222.8 ± 193.5	212 ± 190.3	534.7 ± 470.5	598.2 ± 600.9	6.1 ± 6.3	6.9 ± 8	2.3 ± 0.9	2.2 ± 1.2
Add-on	113.6 ± 89.5	41.2 ± 21.7*	381.7 ± 407	202 ± 206.4	11.1 ± 9.8	16.2 ± 31.3	2.7 ± 1.1	2.9 ± 1.7

* $p = .01$ in respect to basal condition.

4. Results

Twenty-one patients (8 men and 13 women, mean age 31.1 ± 14.3 years) were included in this prospective study. The patients were affected by idiopathic (n. 16) and cryptogenic (n. 5) generalized epilepsy.

Out of the 21 patients enrolled, 11 were treated with LEV in monotherapy and 10 in add-on therapy. Mean follow-up period was 5 months. The detailed patients characteristics are shown in Table 1. All patients completed the treatment period and no relevant adverse event has been reported.

4.1. Quantification of epileptic discharges

Considering all patients together (those treated with LEV in monotherapy and those in add-on), we did not observe significant differences for each of the objective EEG parameters investigated at follow-up after LEV treatment.

Considering the two groups separately, no statistical difference was observed within the group of patients treated in monotherapy with LEV for the EEG parameters. Only in the group of patients treated with LEV in add-on therapy, a significant reduction of the total number of epileptform discharges was observed at follow-up (Table 2 and Fig. 1).

Considering the individual response of each patient separately (Table 3), we observed a higher variability in the response to LEV within the monotherapy treated group: one patient (pt 7) showed the total disappearance of epileptiform discharges, two patients (pt 1, 8) showed a clear reduction of the discharges, five patients were substantially unchanged (pt 2, 3, 9–11), and three patients (pt 4–6) showed an increase of epileptiform discharges. In the group of patients treated with LEV in add-on therapy, the effects of LEV were more homogeneous and the total number of epileptiform discharges was significantly reduced, even though in none of them a total disappearance of epileptic discharges was observed (Table 3 and Fig. 1).

4.2. Clinical effects

Considering the self-reported clinical effects of LEV in all patients at follow-up (Table 3), 9/21 referred to be seizure-free, 2/21 reported a relevant decrease of seizures, 8/21 reported that the frequency of seizure was substantially unchanged and 2/21 reported a worsening of seizures.

In the monotherapy group, 2/11 patients referred the disappearance of seizures, 2/11 the decrease of frequency of seizure, 5/11 were unchanged and 2/11 referred a clinical worsening. In the add-on group, 7/10 patients referred the total disappearance of seizures, while 3/10 referred that the frequency of seizures was substantially unchanged.

4.3. Correlation of clinical effects with EEG quantification of epileptiform discharges

Considering all patients that reported to be seizure free or improved at follow-up after LEV (11/21), only in one patient LEV actually induced the disappearance of epileptiform discharges (pt 7); in 8 patients (pt 1, 8, 12, 16–18, 20, 21) epileptiform discharges were reduced in number and in total duration. Of the remaining 2 patients self-reporting as being seizure free at follow-up, patient 5

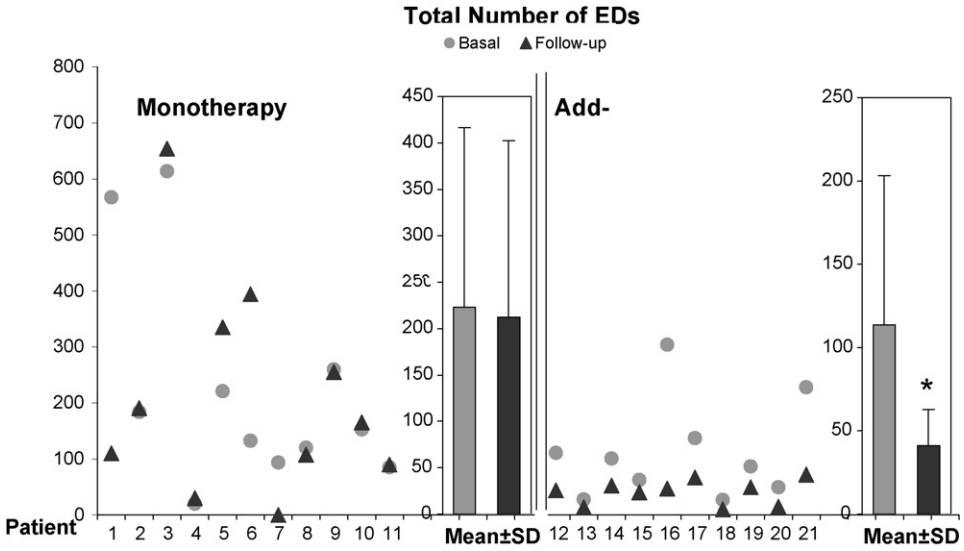

Fig. 1. Graphic representation of the total number of epileptic discharges modification after LEV therapy. The monotherapy group (left) shows a heterogeneous response, while the add-on group (right) shows a more homogeneous response with a significant reduction of the number of epileptic discharges.

Table 3
Total number (TN), total duration (TD, s), maximal duration (MaxD, s) and median duration (MedD, s) of spike-wave discharges at A/EEG at basal and follow-up after LEV therapy in the single subjects.

Pt	TN		TD		MaxD		MedD		Self-reported seizures
	Basal	Follow-up	Basal	Follow-up	Basal	Follow-up	Basal	Follow-up	
Monotherapy									
1	567	110	977	123	3	2	2	1	Decrease
2	184	191	401	585	5	8	2	3	Increase
3	614	654	1115	1420	7	12	2	2	Unchanged
4	20	30	34	50	3	4	2	1.5	Unchanged
5	221	335	1583	1914	25	29	5	4	Seizure-free
6	133	394	321	944	4	4	2	2	Unchanged
7	94	0	212	0	4	0	2	0	Seizure-free
8	120	108	310	285	4	2	2	1	Decrease
9	260	255	513	487	4	4	2	3	Unchanged
10	153	165	428	400	6	5	3	3	Unchanged
11	85	90	208	373	3	6	2	4	Increase
Add-on									
12	111	44	166	53	2	2	1	1	Seizure-free
13	28	14	105	37	7	7	3	2	Unchanged
14	101	53	179	219	5	11	1	4	Seizure-free
15	63	40	456	688	30	105	4	7	Unchanged
16	304	47	1405	138	27	10	4	2	Seizure-free
17	137	67	283	132	4	4	2	2	Seizure-free
18	27	10	67	28	8	5	2	2	Seizure-free
19	87	50	185	178	8	7	3	3	Unchanged
20	50	15	257	119	5	3	3	2	Seizure-free
21	228	72	715	428	15	8	4	4	Seizure-free

showed a paradoxical increase of the total number and total duration of discharges, but with a reduction of the median duration (4 s vs. 5 s) (Fig. 2); on the contrary, patient 14 showed a reduced number of the total discharges, but with a higher median duration (4 s vs. 1 s).

In the patients reporting no benefit after LEV (8/21), three patients (pt 13, 15, 19) showed a reduction of the number of discharges, two patients (pt 4, 6) showed an increase and three patients (pt 3, 9, 10) were substantially unchanged.

In the 2 patients self-reporting an increase of seizures (pt 2, 11), the total number of discharges was substantially unvaried, but with an effective increase of their maximal (pt 2: 8 s vs. 5 s, pt 11: 6 s vs. 3 s) and median (pt 2: 3 s vs. 2 s, pt 11: 4 s vs. 2 s) duration.

5. Discussion

LEV has an antiepileptic effect in a broad range of animal models that mimic generalized epilepsy in man, including different genetic models of absence epilepsy in rats.[17–19] In particular, the clinical benefit of LEV therapy observed in young rats with absence seizures seems to be correlated with a reduction of spike-and-wave discharges evaluated at EEG monitoring.[18]

Few human studies have been performed to investigate the effects of LEV on epileptiform EEG discharges and data are not comparable, due to the different methodological approaches applied. Nonetheless, even if evaluated through different parameters, an overall positive effect of LEV on interictal epileptiform activity has been reported in patients with idiopathic generalized epilepsy. Rocamora et al.[23] evaluated 8 patients treated with LEV (4 in mono- and 4 in add-on therapy) for refractory primary generalized epilepsy with long-term EEG recording. The parameters evaluated were the spike-wave median density (spike/h), the median spike-wave burst duration (s) and the maximum spike-wave burst duration (s), and they observed that LEV induces a consistent long-term reduction of interictal epileptiform activity, also correlated with a clinically relevant antiepileptic effect. All of the patients received previous AED drugs and, in 3 of the 4 patients in add-on therapy, the previous treatment was modified. Gallagher et al.[22] reported similar results evaluating spike-wave density and duration of interictal spike-wave complexes in 10 patients treated with LEV for idiopathic generalized epilepsy and monitored by continuous video/EEG monitoring. Only one study used A/EEG[24] but, even though an improvement after LEV treatment with a 60% reduction of EEG discharges or a total disappearance of ictal/interictal EEG abnormalities is reported, neither objective data nor the A/EEG quantification methods are provided.

In our experience, epileptiform pattern quantification with A/EEG before and after the initiation of an antiepileptic treatment is a very useful tool to evaluate the real antiepileptic effect of an AED. To obtain an objective, reliable and comparable measurement of the epileptic activity in the 24 h A/EEG recording, we evaluated the total number of discharges, their total duration in the 24 h, and the maximal and median discharge duration.

In the present study we have selected a small group of patients with idiopathic or cryptogenic generalized epilepsy, with well-structured and clearly identifiable generalized epileptic pattern at standard EEG, and treated with LEV both in monotherapy as well as in add-on therapy. Our main result is the consistent reduction of generalized epileptic activity only in the group of patients treated with LEV in add-on. The significant reduction of the total number of discharges was also correlated with the self-reported decreased incidence of clinical seizures in this group of patients.

Nonetheless, the effects of LEV monotherapy on epileptic discharges are heterogeneous, and also correspond to a high variability in the self-reported clinical efficacy. As a matter of fact, among the two patients referring to be seizure-free at follow-up, only one actually showed the disappearance of the epileptiform activity at A/EEG, while in the other patient epileptiform discharges were shorter, but paradoxically increased in number. Even if the latter reported a beneficial effect from AED therapy, it cannot be concluded in this case that the drug had itself a positive effect, since the patient probably did not perceive the seizures, because they were shorter. On the contrary, in the 2 patients reporting a clinical worsening, the number of discharges was unvaried, but with an increase of maximal and median duration of discharges. The lack of drug efficacy and statistical power in the

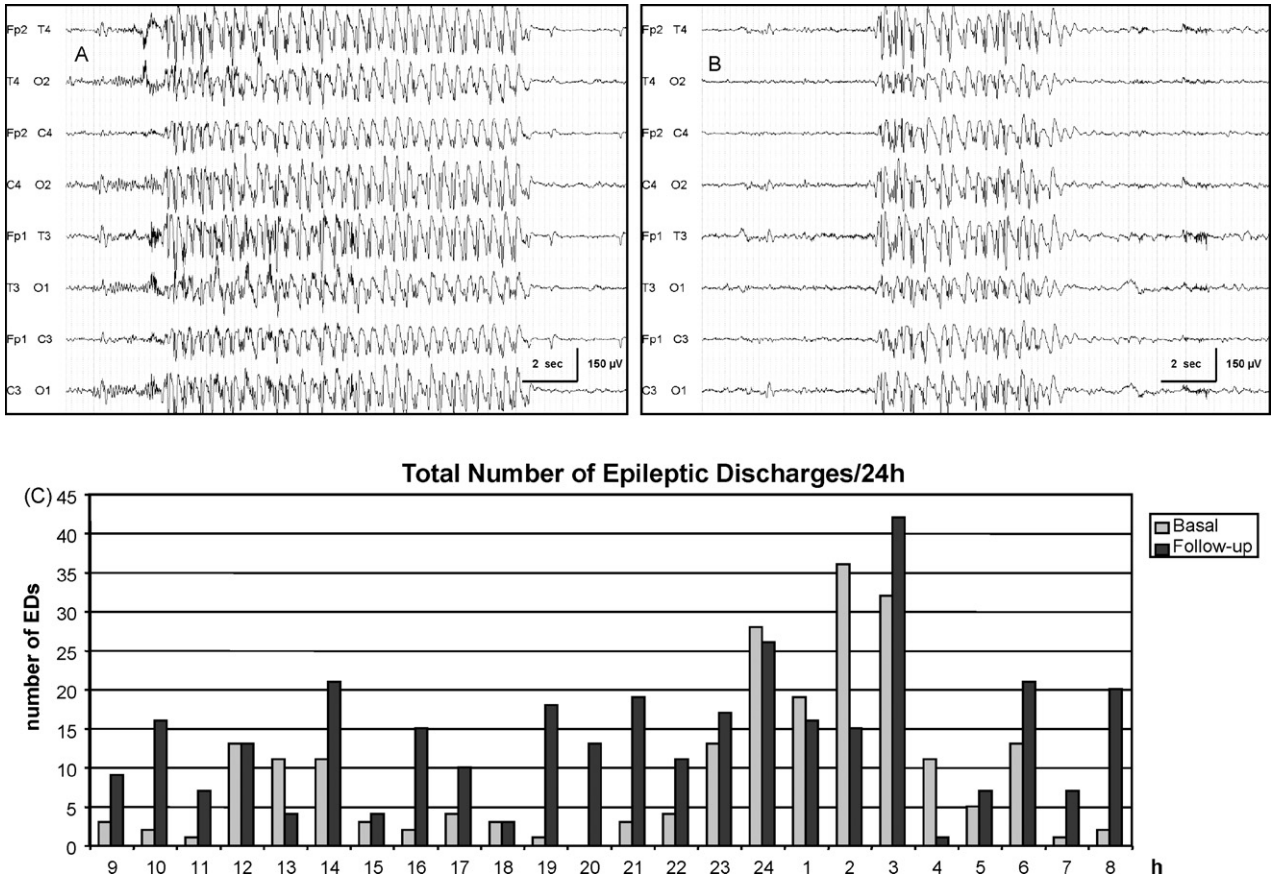

Fig. 2. Epileptic discharges at basal A/EEG (A) and at follow-up A/EEG (B) in patient no. 5, reporting the disappearance of absences after LEV therapy. Note the reduced duration of epileptic discharges duration at A/EEG, but the increased number of seizures at the 24 h^{-1} quantification (C).

LEV monotherapy group may then be related to such variability in the response and to the small number of patients included.

These data should however be considered cautiously, for the limitations of this study related to the small number of patients with a heterogeneous number of discharges before treatment, to the different disease history and to the short follow-up period.

Considering the clinical–electrophysiological correlation, it is though evident that, in our patients, self-reported clinical benefit does not necessarily correspond to a reduction of epileptiform activity. This reflects the fact that the distinction between interictal and ictal discharges is a confusing matter in generalized epilepsy: it is clear that the duration of a single discharge is a crucial point in determining the subjective perception of an absence, and that epileptic discharges shorter than 3 s are not able to determine periods of altered responsiveness. For these reasons, quantitative neurophysiological evaluation of both ictal and interictal epileptiform activity may be useful, together with the clinical self-reported impressions, to objectively assess the global effects of an antiepileptic drug.

Another point that has to be underlined is that the partial EEG response to LEV treatment in our patients might be related to the low dosages administered (1000–1500 mg/day). This was due to ethic reasons in the monotherapy treated group, in which LEV is not authorized alone for the treatment of generalized epilepsy, and to avoid sedative adverse effects in the add-on group. In these regards we could report that some patients (pt 3, 14, 15), treated with higher LEV dosages (2500 mg/die) after the end of the study, did not show an effective reduction of epileptiform discharges.

6. Conclusions

Our data show that the objective quantification of epileptiform discharges with A/EEG is a useful tool for the complete evaluation of the efficacy of an antiepileptic treatment. A/EEG is a modern system of continuous EEG monitoring, easily applicable in routine clinical practice with low costs and high sensitivity. The detailed quantification of the epileptic activity with A/EEG, easy to be performed, helps the definition of a neurophysiologic profile of an antiepileptic treatment that may be used for further follow-up analyses. The correlation of discharges quantification with the clinical self-reported impressions may also clearly identify those patients with an "electro-clinical dissociation", in which the drug induces a relevant clinical improvement, but only a decrease of the discharges duration without a significant modification of the total epileptic activity. We suggest that this method, with proper objective quantification, could be of help in monitoring clinical and electrophysiological responses to AEDs. Further studies on a larger number of patients will clarify the effects of LEV on epileptiform generalized discharges. In our patients with generalized epilepsy LEV seems to be more effective in add-on therapy than in monotherapy.

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