Postictal generalized EEG suppression

An inconsistent finding in people with multiple seizures

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ABSTRACT

Objective: To determine the consistency and facilitating cofactors of postictal generalized EEG suppression (PGES) of >20 seconds after convulsive seizures (CS), a suggested predictor of sudden unexpected death in epilepsy risk.

Methods: We retrospectively reviewed video-EEG data of people with ≥2 recorded CS. Presence and duration of PGES were assessed by 2 independent observers blinded to patient status. Intraindividual consistency of PGES >20 seconds was determined and correlations with clinical characteristics were analyzed after correction for individual effects and the varying number of seizures.

Results: One hundred fifty-four seizures in 59 people were analyzed. PGES >20 seconds was found in 37 individuals (63%) and 57 (37%) of CS. The proportion of persons in whom PGES occurred consistently (presence or absence of PGES >20 seconds in all CS) was lower in those with more CS. PGES of >20 seconds was more frequent in seizures arising from sleep (odds ratio 3.29, 95% confidence interval 1.21–8.96) and when antiepileptic medication was tapered (odds ratio 4.80, 95% confidence interval 1.27–18.14).

Conclusion: Apparent PGES consistency was less frequent in people with more CS recorded, suggesting that PGES is an inconsistent finding in any one individual. Thus, we believe that PGES >20 seconds is not a reliable predictor of sudden unexpected death in epilepsy. Sleep and antiepileptic drug reduction appear to facilitate the occurrence of PGES. *Neurology*® 2013;81:1252-1256

GLOSSARY

AED = antiepileptic drug; **CI** = confidence interval; **CS** = convulsive seizures; **HR** = heart rate; **OR** = odds ratio; **PGES** = postictal generalized EEG suppression; **SUDEP** = sudden unexpected death in epilepsy.

Sudden unexpected death in epilepsy (SUDEP) is the most important epilepsy-related cause of premature death.[1–3] In most ictal recordings of SUDEP, postictal generalized EEG suppression (PGES), followed by apnea and asystole, appears to be an EEG hallmark.[2]

The mechanism of PGES is not well understood.[2] PGES occurs more frequently after convulsive seizures (CS),[4,5] and is associated with more severe peri-ictal hypoxemia and postictal coma.[6–9] Seizure duration is not related to PGES,[4,5,7,9–11] but a longer duration of the tonic phase has been suggested to facilitate PGES.[9] We found that PGES occurs more frequently after CS arising from sleep.[11] Nocturnal CS increase SUDEP risk,[12] thus adding to the evidence that PGES may be a biomarker for SUDEP. PGES was associated with older age at seizure onset[11]; this might be explained by differences in epilepsy etiology, but requires further study.[13] Antiepileptic drug (AED) changes may affect occurrence of PGES: introduction of levetiracetam after AED withdrawal reduced severity of postictal EEG suppression and coma.[14]

It remains unclear whether PGES is a predictor of SUDEP. PGES >20 seconds after CS was associated with higher SUDEP risk, which increased proportionally with PGES duration.[4] These findings, however, could not be replicated in a larger study.[5] High intraindividual variability of PGES >20 seconds may explain these conflicting results. We addressed PGES consistency in

people with multiple CS and analyzed cofactors that facilitate occurrence of PGES >20 seconds, including state of wakefulness, age of seizure onset, and AED tapering.

METHODS **Sample selection.** We reviewed reports of digital video-EEGs from 2 tertiary epilepsy referral centers (Bonn and Heemstede) from the period 2003 to 2011 and selected people 15 years and older who had 2 or more CS recorded on long-term monitoring. The study size was determined by the number of available video-EEGs. We identified 170 CS in 64 individuals. EEG recordings with less than 1-minute postictal recording time (n = 13) and those of insufficient quality because of lead disconnection (n = 3) were discarded, leaving 59 people with 154 CS (19 with 47 seizures from Heemstede and 40 with 107 seizures from Bonn). The median number of monitoring days was 5 (range 1–13).

Collection of variables. We collected the following data: sex, age, presence of mental retardation (yes/no), epilepsy classification (symptomatic or cryptogenic/idiopathic), lesion on MRI (yes/no), age at onset, duration of epilepsy, frequency of CS, AED regimen (before admission and for each subsequent monitoring day), state of wakefulness before seizure onset (awake/asleep), sleep stage before seizure onset (rapid eye movement, non–rapid eye movement 1–3), localization of EEG seizure onset (temporal/extratemporal), and duration of the tonic and tonic-clonic phase as well as entire seizure duration. Tapering was defined as any reduction of the total AED load during the recording period, compared with the regimen before admission.

The overall drug load (before admission and each subsequent monitoring day) was estimated as the sum of the prescribed daily dose/defined daily dose ratios for each AED.[15] Heart rate (HR) was measured during the last minute before seizure onset and the first minute after seizure end.

Standard protocol approvals, registrations, and patient consents. This study was approved by the ethics committees at both sites; because of its observational nature, informed consent was not required at either site.

Evaluation of PGES >20 seconds and duration of the tonic phase. Conventional scalp EEG recordings (International 10–20 System) (Stellate Harmonie, Stellate Systems, Montreal, Canada; Schwarzer GmbH/Natus, Germany) were performed at a sampling rate of 200 Hz. A modified lead-I ECG (Stellate Harmonie; Schwarzer GmbH/Natus) (adhesive electrode[s] placed below the clavicle) was simultaneously recorded. Random numbers were assigned to all individual seizures to blind patient status. Two board-certified clinical neurophysiologists (A.G., R.D.T.) independently analyzed the presence or absence of PGES >20 seconds and duration of the tonic phase in all CS.

PGES was defined as the immediate postictal (within 30 seconds), generalized absence of EEG activity >10 μV in amplitude, allowing for muscle, movement, breathing, and electrode artifacts.[4] Only PGES of >20 seconds after CS were scored because these were previously associated with increased SUDEP risk.[4] Because of privacy rules, video-recordings from Bonn could not be evaluated off-site; thus, PGES was only assessed using EEG recordings in this

Table 1	Characteristics of people with a mixture of CS with and without PGES >20 seconds, and those in whom PGES >20 seconds was either consistently present or absent		
Variables	CS ± PGES >20 s (n = 25)	All CS + PGES >20 s (n = 12)	All CS − PGES >20 s (n = 22)
No. of recorded CS (%)			
2	11 (44)	9 (75)	15 (68)
>2	14 (56)	3 (25)	7 (32)
Sex, n (%)			
Male	17 (68)	6 (50)	11 (50)
Female	8 (32)	6 (50)	11 (50)
Age at time of EEG, y, median (range)	29 (16-63)	29 (15-49)	26 (16-57)
Duration of epilepsy, y, median (range)	16 (1-44)	14 (1-47)	17 (0-53)
Epilepsy classification, n (%)			
Symptomatic	11 (44)	8 (67)	16 (73)
Cryptogenic	14 (56)	4 (33)	6 (27)
Lesion on MRI, n (%)[a]			
Yes	11 (44)	7 (64)	16 (73)
No	14 (56)	4 (36)	6 (27)
Frequency of CS, n (%)			
1-2 CS/y	7 (28)	6 (50)	13 (59)
≥3 CS/y	18 (72)	6 (50)	9 (41)
Mental retardation, n (%)			
Yes	2 (8)	1 (8)	2 (9)
No	23 (92)	11 (92)	20 (91)

Abbreviations: CS = convulsive seizures; PGES = postictal generalized EEG suppression.
[a] In one person with symptomatic generalized epilepsy, no MRI was performed.

site, but in Heemstede, EEG and video were assessed. In 2 CS from Bonn, PGES based on EEG alone could not be scored because of uncertainty about the presence of movement artifacts, so a third clinical neurophysiologist (R.S.) analyzed both EEG and video for a final decision. In the remaining 152 CS, PGES was evaluated by 2 examiners; in case of disagreement, the examiners discussed to reach consensus. Interobserver agreement on PGES >20 seconds was good: Cohen κ = 0.77.

The onset of the tonic phase was defined as the occurrence of bilateral, symmetrical or asymmetrical, continuous muscle activity obscuring EEG background activity. Muscle activity was evaluated in the frontotemporal regions using a bipolar montage. The end of the tonic and onset of the clonic phase was defined by a sustained pattern of bilateral and synchronous bursts of muscle artifact with burst intervals ≥150 milliseconds, and absence of muscle activity between bursts.

Statistical analysis. The proportion of people in whom PGES consistently occurred (presence or absence of PGES >20 seconds in all CS) was calculated and related to the number of recorded CS. Associations between PGES >20 seconds and person- or seizure-specific variables were assessed with Fisher exact probability test, χ^2, or Mann-Whitney U tests, where appropriate. A mixed linear regression model was used to determine which variables were independently associated with PGES >20 seconds after correction for individual effects and the varying number of seizures contributed by each person. Only those variables with $p < 0.05$ at univariate analysis were entered, and adjustments for multiple comparisons were made using the Holms-Bonferroni method. Statistical analysis was performed with SPSS version 17 software (SPSS Inc., Chicago, IL) and STATA 12 software (StataCorp LP, College Station, TX).

RESULTS Prevalence and intraindividual consistency of PGES >20 seconds. PGES >20 seconds occurred in 63% of individuals (37/59) and in 37% of CS (57/154) (tables 1 and 2). Presence or absence of PGES >20 seconds was a consistent finding in 34 of 59 individuals (presence 12/59; absence 22/59), whereas 25 of 59 individuals had a mixture of CS with and without PGES >20 seconds (figure 1). The number of people with "consistent" results decreased as the number of CS recorded increased (table 1, figure 1).

Factors that facilitate the occurrence of PGES >20 seconds. In univariate analysis, PGES >20 seconds was more frequently found after CS that started from sleep (odds ratio [OR] 2.5, 95% confidence interval [CI] 1.3–5.0) and in CS where medication was tapered (OR 3.7, 95% CI 1.4–9.7). Other person- or seizure-related variables did not differ between groups (tables 1 and 2). In multivariate analysis, the variables "sleep" and "AED reduction" remained independent risk factors for PGES >20 seconds after introduction into a mixed linear regression model: sleep OR 3.29, 95% CI 1.21–8.96; AED reduction OR 4.80, 95% CI 1.27–18.14.

DISCUSSION We addressed the intraindividual variability of PGES >20 seconds in people with multiple CS and found that PGES consistency depended on the number of seizures recorded per person. Prevalence of PGES was higher in those CS that started from sleep or when medication had been reduced. PGES >20 seconds had limited consistency in people with multiple recorded CS. High intraindividual variability may explain the discrepancy between studies as to the value of PGES as a risk marker for SUDEP.[4,5] Interestingly, intraindividual consistency was lower in the study where no link between PGES and SUDEP was found.[5] Overall, these findings emphasize that the occurrence of PGES is critically dependent on the number of seizures recorded and therefore unlikely to be a reliable factor to assess SUDEP risk. A link between duration of the tonic phase and PGES has recently been suggested,[9] but this was not seen in our study. These conflicting results may be explained by differing seizure selection. In the former study, 18.5% of CS lacked a tonic phase compared with none in our sample.[9] Presence of a tonic phase was strongly associated with PGES: OR 180.[9] Therefore, the reported link between tonic duration and PGES may predominantly rely on the contrast between seizures with and without a tonic phase. Therefore, we believe that a difference in seizure types rather than a variation in length of the tonic phase may be responsible for the reported association between tonic duration and PGES. We did not find significant differences in peri-ictal HR change between CS with and without PGES >20 seconds, confirming our previous finding.[11] In contrast, others reported a lower postical HR in CS with PGES (119 vs 140 bpm).[9] Unfortunately, these cannot be easily compared because in their study no exact definition of HR measurement periods was given and all CS with PGES were included, even those of shorter duration.[9]

Figure 1 Intraindividual variability of PGES >20 seconds in people with multiple recorded CS
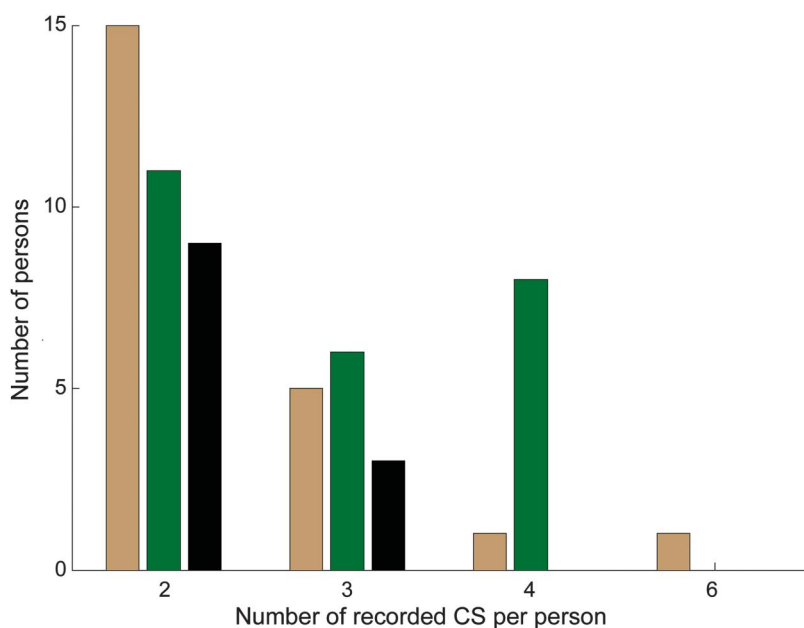
Most people (25 of 59) had a mixture of convulsive seizures (CS) with and without postictal generalized EEG suppression (PGES) >20 seconds (green bars). In 22 of 59 persons, PGES >20 seconds was consistently absent (tan bars), whereas in 12 of 59 persons, it was consistently present (black bars). Consistency of PGES >20 seconds seemed dependent on the number of recorded CS.

If PGES is associated with postictal HR deceleration, more pronounced HR changes would be expected in our study as we focused on CS with prolonged PGES. It therefore seems unlikely that PGES reflects a primary pathomechanism leading to asystole and SUDEP. Given the high intraindividual variation of PGES, especially when assessing multiple seizures per person, it is unlikely that a person-specific variable will predict PGES occurrence. This may explain why we did not find an association between age of seizure onset and PGES, unlike in our previous study where only one CS per person was analyzed.[11] PGES was scored differently in CS from Heemstede (EEG and video) and those from Bonn (EEG only), which may have introduced bias; we consider this unlikely because the prevalence of PGES >20 seconds was similar in both centers (table 2). All EEG studies were scored independently by 2 observers with good interobserver agreement. The effect of peri-ictal hypoxemia on PGES could not be analyzed because we lacked concurrent oximetry measurements. Underlying peri-ictal hypoxemia may possibly explain the link

between sleep and PGES. Currently, it remains unclear whether hypoxemia is more severe during CS arising from sleep. An earlier study of seizure-related respiratory dysfunction did not find a higher prevalence of ictal hypoxemia in nocturnal seizures, but mostly partial seizures were analyzed.[16] Similarly, underlying ictal hypoxemia may explain the association between AED reduction and PGES. This seems unlikely, however, because no link between AED withdrawal and ictal hypoxemia was found in a systematic analysis of seizure-related respiratory dysfunction.[16] Ideally, an analysis of AED withdrawal would take into account the amount and speed of AED reduction. In our study, however, because of its retrospective nature and the great variety of AEDs and withdrawal regimens, such an analysis was not feasible. There are several theories regarding PGES etiology. Neuronal exhaustion has been proposed as an underlying mechanism.[17] This explanation seems unlikely because seizure duration is not associated with PGES.[4,5,7,9–11] It has also been suggested that PGES triggers respiratory or cardiac dysfunction. However, PGES was not associated

Table 2	Characteristics of CS with PGES >20 seconds vs CS without PGES >20 seconds		
Variables	CS with PGES >20 s (n = 57)	CS without PGES >20 s (n = 97)	Test
Age at onset of epilepsy, y, median (range)	14 (0–55)	12 (0–55)	MW, p = 0.09
State of wakefulness, n (%)			χ^2, p = 0.009
Asleep	40 (70)	47 (48)	
Awake	17 (30)	50 (52)	
Sleeping stage, n (%)			NA
NREM 1	6 (15)	6 (13)	
NREM 2	25 (63)	31 (66)	
NREM 3	9 (22)	10 (21)	
AED reduction, n (%)			χ^2, p = 0.005
Yes	51 (89)	66 (68)	
No	6 (11)	29 (32)	
Location, n (%)			χ^2, p = 0.35
SEIN	20 (35)	27 (28)	
Bonn	37 (65)	70 (72)	
Ictal EEG onset, n (%)[a]			χ^2, p = 0.76
Temporal	32 (56)	52 (53)	
Extratemporal	25 (44)	45 (47)	
Time from seizure onset to generalization, s, median (range)	28 (2–367)	28 (0–121)	MW, p = 0.69
Duration of tonic phase, s, median (range)	32.5 (16–58)	31.5 (2–75)	MW, p = 0.59
Duration of tonic-clonic phase, s, median (range)	58 (22–118)	58.5 (11–138)	MW, p = 0.95
Total seizure duration, s, median (range)	92 (25–430)	91.5 (29–486)	MW, p = 0.85
Preictal HR, bpm, median (range)	73 (49–137)	73 (50–140)	MW, p = 0.91
Postictal HR, bpm, median (range)	132 (71–159)	136 (83–177)	MW, p = 0.16

Abbreviations: AED = anti-epileptic drugs; CS = convulsive seizures; HR = heart rate; MW = Mann-Whitney; NA = not applicable; NREM = non–rapid eye movement; PGES = postictal generalized EEG suppression.
[a] All people with symptomatic generalized epilepsy (n = 3) had focal-onset CS.

with postictal apnea, but with preceding seizure-induced oxygen desaturation.[7] Ictal hypoxia and PGES duration were shorter with earlier intervention after seizure onset.[8] CS with PGES are associated with a longer period of postictal immobility.[6,8,9] During this period of unconsciousness, the person may not be able to respond appropriately to seizure-induced hypoxemia (e.g., by changing body position), thus exacerbating the cerebral oxygen deficit. Others have proposed that PGES reflects increased activity of inhibitory neuronal networks in response to continuing seizure activity.[4] Because sleep is also related to inhibitory neuronal network activation, this may explain the relation between sleep and PGES.[18] This association further supports the link between sleep and SUDEP; most victims die during sleep and nocturnal CS are a risk factor for SUDEP.[2,12] The use of AEDs may modulate the seizure-related inhibitory neuronal network activation,[14] and AED reduction in the epilepsy monitoring unit can lead to an increase in seizure intensity and frequency.[19,20] It could be speculated that changes in these seizure characteristics may provoke an exaggerated termination response by inhibitory neuronal networks. A further exploration of the link between different AED withdrawal schedules, changes in seizure characteristics, and PGES would be of interest.

AUTHOR CONTRIBUTIONS

The study was conceived and designed by R.J.L., R.D.T., R.S., and J.W.S. Data were acquired by A.G., R.D.T., and R.J.L. Data analysis and interpretation by R.J.L., J.W.S., R.S., and R.D.T. The manuscript was drafted by R.J.L., J.W.S., R.S., and R.D.T. All revised and approved the submitted version. J.W.S. and C.E.E. are the guarantors.

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