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Pulmonary edema following generalized tonic clonic seizures is directly associated with seizure duration

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ABSTRACT

Purpose: Postictal pulmonary edema (PPE) is almost invariably present in human and animal cases of sudden unexpected death in epilepsy (SUDEP) coming to autopsy. PPE may be a contributing factor in SUDEP. The incidence of postictal PPE is unknown. We retrospectively investigated PPE following generalized tonic clonic seizures (GTCS) in the epilepsy monitoring unit.
Method: Chest X-rays (CXR) following each GTCS were obtained in 24 consecutive patients. Relationship of CXR abnormality to seizure duration, ictal/postictal oxygen desaturation (SpO2), apnea and presence of postictal generalized EEG suppression (PGES) was investigated using logistic regression.
Results: Eleven of 24 patients had CXR abnormalities following a GTCS. In these 11 patients, 22 CXR were obtained and abnormalities were present in 15 CXR. Abnormalities included PPE in 7 patients, of which 2 also had focal infiltrates. In 4 patients focal infiltrates were present without PPE. There was no significant difference in mean time to CXR (225 min) following GTCS in the abnormal CXR group versus the normal group of patients (196 min).

Mean preceding seizure duration was longer ($p = 0.002$) in GTCS with abnormal CXR (259.7 s) versus GTCS with normal CXR (101.2 s). Odds-ratio for CXR abnormality was 20.46 ($p = 0.006$) with seizure duration greater than 100 s versus less than 100 s. On multivariable analysis, only the seizure duration was a significant predictor of CXR abnormality ($p = 0.015$).
Conclusion: Radiographic abnormalities are not uncommon following GTCS. The presence of CXR abnormality is significantly associated with the duration of the preceding GTCS. Severe, untreated PPE may be relevant to the pathophysiology of SUDEP.

1. Introduction

Postictal pulmonary edema (PPE) may be one factor leading to sudden unexpected death in epilepsy (SUDEP) [1]. The relevance of PPE to SUDEP remains controversial and insufficiently investigated. Case reports indicate that PPE occurs in a subset of individuals following convulsions, and may recur with subsequent convulsions and lead to SUDEP [2–7]. In an autopsy study of 74 cases of SUDEP, 52 had microscopic examinations of the lungs that showed moderate to marked pulmonary congestion and edema in all 52 cases [8]. In epileptic primates PPE is likely a factor in the pathophysiology of SUDEP [9]. Autopsies of 48 epileptic baboons that died suddenly were compared with 78 non-epileptic baboons. Almost all epileptic baboons that died suddenly without apparent cause had PPE without other pathology and about half had bloody frothy sputum [9].

Despite these observations, recent reviews of SUDEP pathophysiology concluded that PPE following seizures is mild, uncommon and not likely an etiological factor resulting in death [10–12]. This notion may be based in part on two studies [13,14]. A retrospective review of 45 patients who had chest radiographs (CXR) obtained in an emergency department following presumed generalized tonic clonic seizures (GTCS) demonstrated that only one had PPE [13]. In CXRs obtained following electroconvulsive therapy only 1 of 12 patients had radiographic evidence of subclinical PPE [14].

The incidence of postictal PPE is unknown given that CXRs are infrequently obtained after GTCS. Given the discrepancy in prior

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studies regarding the occurrence of PPE, we sought to determine the incidence and extent of pulmonary abnormalities following GTCS and evaluate patient and seizure characteristics in patients undergoing video-EEG telemetry (VET) in the epilepsy monitoring unit (EMU).

2. Methods

We retrospectively examined CXRs in consecutive patients who had GTCS while undergoing VET in the University of California, Davis Medical Center EMU. All patients undergoing VET in this EMU have concurrent synchronized recording of nasal airflow, abdominal excursions, digital pulse oximetry, end-tidal CO2 (ETCO2), and 3-channel electrocardiogram. Details of the methodology have been previously published [15]. By protocol portable bedside CXRs are ordered immediately following all GTCS in patients admitted to the EMU. The practice of obtaining CXR after GTCS was instituted in the EMU once we became aware of human autopsy findings and animal data indicating pulmonary edema in SUDEP. Antiepileptic drugs were reduced or had been withdrawn in the EMU at the discretion of the attending epileptologist.

Postictal CXRs obtained within 24 h following a GTCS were evaluated for possible abnormality. Additionally, if available, a baseline CXR obtained within 3 days prior to the first GTCS and delayed CXRs obtained within 3 days following the immediate postictal CXR were also evaluated. CXRs initially underwent routine clinical interpretation by board-certified radiologists at the University of California, Davis Medical Center. Subsequently, CXRs were also independently reviewed by one of the authors (KAH), a board-certified pulmonologist, without knowledge of the radiologist's findings or of the clinical state of the patient. Cohen's kappa [16], a measure of agreement between the two sets of interpretations for CXR findings was performed.

CXRs interpreted as showing PPE were subsequently assessed by the pulmonologist using a clinical chest radiographic scoring system that has been validated against direct measurements of pulmonary edema [17]. Using this system, each lung on the radiograph was divided into two quadrants by a horizontal line through the center of the hilum. For each quadrant, a score between 0 and 4 was assigned with 0 representing no edema, 1 representing edema in 0–25% of the quadrant, 2 representing edema in 25–50% of the quadrant, 3 representing edema in 50–75% of the quadrant, and 4 representing edema in >75% of the quadrant [17]. A total score was generated for each CXR.

The following seizure-associated variables were recorded: interval from the end of the GTCS to acquisition of the CXR, seizure duration, duration of ictal/postictal apnea, duration of oxygen desaturation (SpO2 < 90%), duration of hypercapnia (ETCO2 > 45 mm Hg), periictal SpO2 nadir, peak ETCO2, ictal peak heart rate, baseline and peak respiratory rate and presence of any postictal generalized EEG suppression (PGES). The study was approved by the UC Davis Institutional Review Board.

2.1. Statistical analysis

Seizure associated variables and patient age and gender were treated as independent variables, and the relationship of these to CXR abnormality was determined. Logistic regression was used to study the relationship between the presence or absence of chest radiographic abnormalities and the independent variable in each case. A multivariable logistic regression analysis was performed in which the independent variables were selected based on a stepwise selection procedure with the criterion of significance level (<0.2) for entering independent variables (predictors) and significance level (>0.25) for removing independent variables.

P-values <0.05 were considered significant. Summary data are presented as mean ± standard deviation (median, range). All analyses were performed with SAS v9.2 (SAS Inc., Cary, NC)

3. Results

Descriptive statistics are summarized in Table 1. There were 24 consecutive patients (19 females) admitted to the EMU who had at least one GTCS and a CXR within 24 h of the end of the GTCS. A total of 42 GTCS were recorded in these patients. There was close agreement regarding CXR findings between the two reviewers. The kappa coefficient was 0.8799 ± 0.0669 (95% CI: 0.7488–1.0) ($p < 0.0001$). The blinded CXR interpretations were used for statistical analysis.

Thirteen patients had no CXR abnormalities following 21 GTCS. Eleven patients had at least 1 abnormal CXR following a GTCS. In these 11 patients a total of 22 GTCS were recorded of which 14 GTCS were associated with an abnormal CXR. One GTCS was excluded from analysis as seizure end time could not be

Table 1
Summary statistics.

	CXR Group	Mean	SD	Median	MIN	MAX	*p*-value
Age (years)	Normal	31.9	13.2	29	17	58	
	Abnormal	32.9	12.1	29	19	49	0.87
Seizure duration (s)	Normal	101.2	42.9	88.5	50	239	
	Abnormal	249.7	180.7	216.0	74	786	0.002
Apnea duration (s)	Normal	71.7	27.1	70	26	120	
	Abnormal	71.6	31.7	61	30	133	0.99
SpO2 nadir (%)	Normal	76.0	7.5	75	60	91	
	Abnormal	74.8	6.9	74	66	86	0.62
Desaturation duration (s)	Normal	82.3	55.2	66	14	183	
	Abnormal	100.2	51.4	101	12	182	0.34
ETCO2 peak (mm Hg)	Normal	64.5	16.8	58.5	44	98	
	Abnormal	60.20	21.0	57.0	38	95	0.63
ETCO2 increase duration (s)	Normal	310.6	325.7	140	8	826	
	Abnormal	381.0	502.1	381	26	736	0.78
Peak heart rate (beats/min)	Normal	142.6	17.2	146	108	174	
	Abnormal	142.9	24.8	136	108	180	0.97
Baseline respiratory rate (breaths/min)	Normal	16.4	3.6	15	11	22	
	Abnormal	17.5	4.7	18	10	26	0.42
Peak respiratory rate (breaths/min)	Normal	27	7.6	25	19	50	
	Abnormal	30	9.6	27	19	50	0.29

determined. In the group with PPE, the mean 4-quadrant pulmonary edema score was 4.55 ± 3.30 (4, range 2–14, IQR 2).

The mean interval from end of GTCS to CXR acquisition was 202.9 ± 257.5 min (103, 6.2–1197). There was no significant difference in the time to CXR following GTCS in the group of normal versus abnormal CXRs ($p = 0.312$). The mean delay to CXR in the group of normal CXRs was 196 ± 282 min (100, 6–1197). The mean delay to CXR after GTCS in the group with abnormal CXRs was 225 ± 217 min (145, 30–678). All except 1 CXR were obtained within 12 h of the end of the seizure.

In the 11 patients with at least 1 abnormal postictal CXR, 7 CXRs following GTCS were normal, 14 CXRs were abnormal (Fig. 1) and 1 CXR could not be classified as normal or abnormal. Seven patients had evidence for PPE on at least 1 CXR and 4 patients had focal infiltrates or atelectasis alone without PPE (Fig. 2). Two of the 7 patients with PPE also had CXR evidence for focal CXR abnormality. Finally, 2 of the 7 patients with PPE also had CXR evidence for cardiomegaly.

3.1. Patient characteristics

Comparing the group of patients with no CXR abnormalities after any GTCS to the group of patients with at least 1 CXR abnormality following a GTCS, there were no significant differences in age ($p = 0.87$) or gender ($p = 0.21$). Details of the patients' epilepsy and relevant comorbities are in Table 2.

3.2. Seizure characteristics

The duration of ictal/postictal apnea, duration of oxygen desaturation, SpO2 nadir, duration of hypercapnia, peak ETCO2, baseline and peak respiratory rate, or ictal peak heart rate were not significantly different in GTCS with or without CXR abnormality (Table 1). There was no difference in CXR abnormality associated with the presence or absence of PGES ($p = 0.89$).

The duration of the preceding seizure was significantly longer ($p = 0.002$) in the group of GTCS with any postictal CXR abnormalities compared with in the group with normal CXRs. The mean seizure duration was 249.7 ± 181 s (216, 74–786) in the group with CXR abnormalities and 101.2 ± 42.9 s (88.5, 50–239) in the group with normal CXRs (Table 1).

We then analyzed CXRs after excluding CXRs with only focal abnormalities. In this second analysis the duration of the seizure remained significantly longer ($p = 0.002$) in the group of GTCS with PPE than in the group of GTCS with normal CXRs. The estimated probability of CXR abnormality for a given seizure duration is shown in Fig. 1. On multivariable analysis only the seizure duration was a significant predictor of chest CXR abnormality ($p = 0.015$) when seizure duration, SpO2 nadir, desaturation duration, peak ETCO2, peak ictal/postictal heart rate and peak respiratory rate were included as possible predictors.

The odds-ratio for the presence of a CXR abnormality was 20.46 (95% C.L. 2.39–175.29) ($p = 0.006$) when seizure duration was greater than 100 s compared with seizures less than or equal to 100 s. The odds-ratio for CXR abnormality was 171.0 comparing seizure duration >200 s with seizures ≤100 s ($p = 0.002$).

3.2.1. Pre-GTCS and delayed post-GTCS CXRs

Five of the 11 patients with abnormal CXRs also had a CXR prior to the first GTCS in the EMU and all pre-GTCS CXRs were normal. Five of these 11 patients with an abnormal GTCS-associated CXR also had a delayed CXR within 3 days after the last GTCS. Three of the delayed follow up CXRs were normal, one patient with marked PPE required a diuretic and follow up CXR showed persistent but improved PPE (Fig. 2) and one patient showed improvement in previously present right lung opacity.

3.2.2. Seizure frequency and PPE

Four patients had PPE following the first seizure with no other seizures in the preceding 24 h. In the other 3 patients PPE was not present with the first seizure and PPE developed only when the patient had more than one seizure in the preceding 24 h. Six patients had more than one seizure in any 24 h period preceding a CXR without developing PPE.

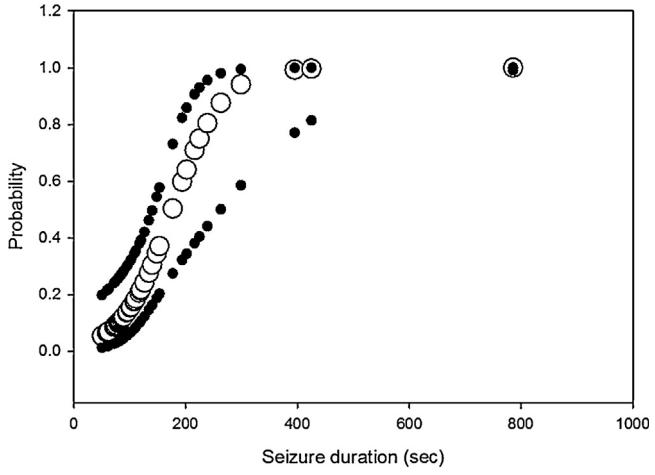

Fig. 1. Probability of CXR abnormality versus seizure duration. The large circles are the estimated probability for CXR abnormality for a given seizure duration. The small filled circles are the upper and lower point-wise 95% confidence intervals versus seizure duration time.

4. Discussion

In contrast to previous studies, we have shown that radiographic abnormalities are often present in patients following a GTCS and the presence of PPE is significantly associated with the duration of the preceding GTCS. Evidence for PPE was present in 7 of 24 patients with GTCS during admission to the EMU.

Clinical evidence for PPE, such as dyspnea, may be difficult to discern in the EMU in patients who are confused for minutes to hours following a GTCS [18] and the main clinical focus is assessment of the patient's seizure. PPE when present may be transient in most patients in the EMU, however we have seen marked PPE requiring diuretics. PPE may not necessarily be the direct cause of death in SUDEP and an argument can be made that PPE is an epiphenomenon of little or no clinical relevance. However the occurrence of PPE in about 29% of monitored patients suggests that postictal PPE is not uncommon and may be relevant to SUDEP pathophysiology. Focal infiltrates and atelectasis, contributing to seizure-related morbidity, occurred in 6 of 24 patients following GTCS. Aspiration pneumonia occurs in patients with seizures both in the outpatient setting and in patients undergoing VET [19]. The incidence of aspiration pneumonia is more common in institutionalized patients and was reported to occur in 17 of 95 patients after a generalized seizure [19]. In an epilepsy monitoring unit, 5.6% of seizures occurred while the patients were eating or drinking, most patients received oral suctioning and only one suspected aspiration occurred [20].

Previous animal studies support our finding that seizure-related PPE requires prolonged convulsive seizures. In a sheep model of generalized convulsive seizures and status epilepticus it was shown that pulmonary microvascular pressures were elevated in proportion to the duration of seizure stimulus [21]. Longer duration seizures were associated with a higher rise in left atrium and pulmonary artery pressures and pulmonary microvascular

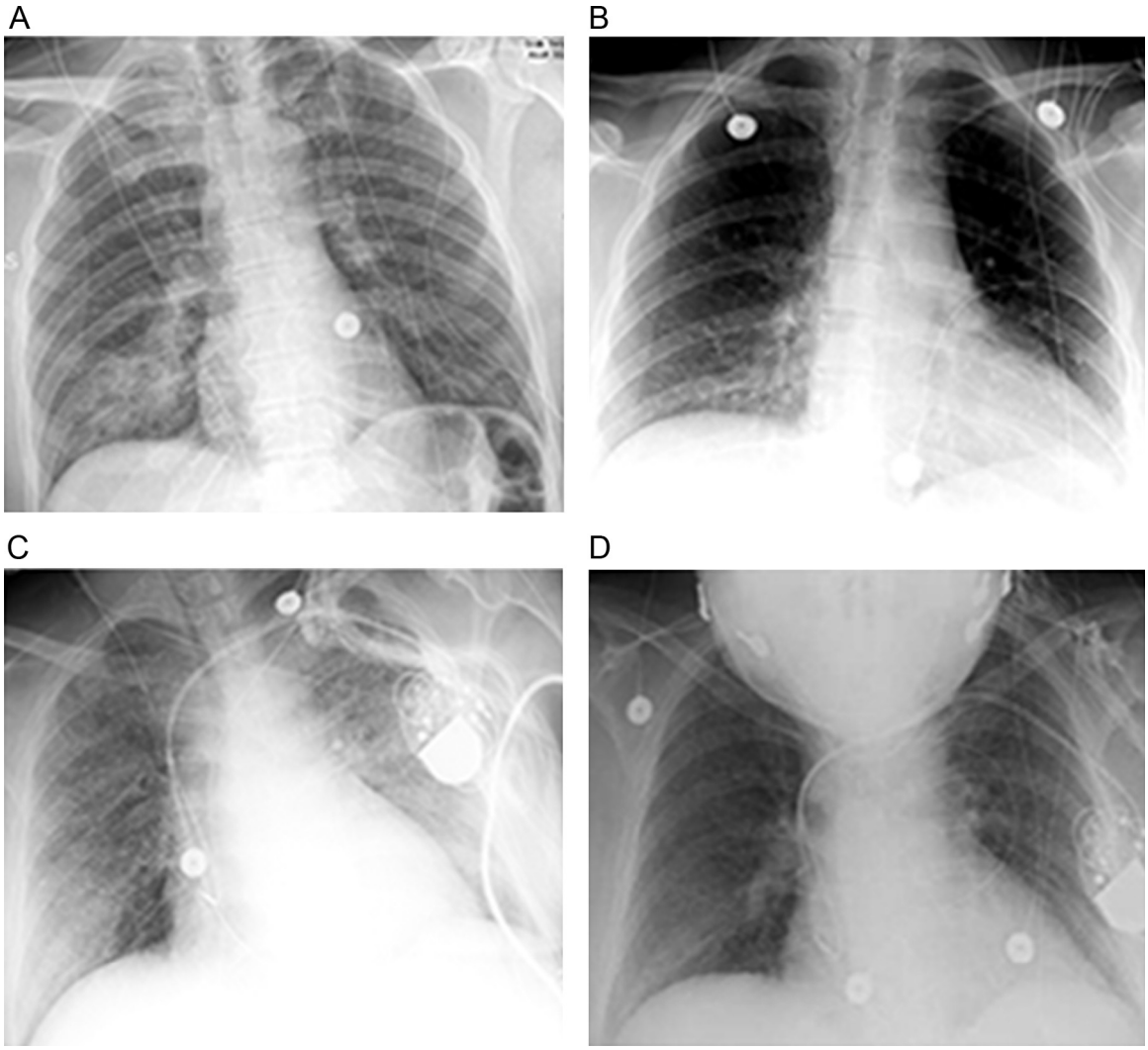

Fig. 2. CXR in 3 patients demonstrating varying degrees of pulmonary edema. (A) 38-year-old male, 299 second right hemisphere onset seizure with secondary generalization. CXR obtained 39 min after end of seizure. (B) 47-year-old female, 263 second left frontal seizure with secondary generalization. CXR obtained 143 min after end of seizure. (C) 54-year-old woman, 202 second right frontal seizure with secondary generalization. CXR obtained 30 min after end of seizure. The patient had 2 other GTCS in the 3 h prior this seizure and no CXR was obtained. A routine CXR earlier that day preceding the GTCS had shown no evidence of pulmonary edema. The patient had a seizure-related takotsubo dilated cardiomyopathy and had a cardiac pacemaker implanted. (D) Repeat CXR in patient (C) obtained the next day showing improving pulmonary edema.

pressures rose well above the level of plasma oncotic pressure [21]. Pulmonary perfusion pressures above 30 Torr result in transcapillary movement of water and protein into the interstitial space and pressures of up to 75 Torr were observed in this study with longer seizures [21]. These high pulmonary pressures likely damaged the capillary-alveolar membrane allowing for leakage of RBCs and protein rich fluid creating delayed PPE [22].

Although the concept of neurogenic PPE has been around over 100 years, the pathophysiology remains incompletely understood. A neuro-hemodynamic mechanism also referred to as the "blast theory" postulates a sympathetic surge with increased hydrostatic pressure leading to alteration of Starling forces in the lungs resulting in increased pulmonary permeability [23]. Abrupt rises in intracranial pressure, result in intense sympathetic activation [24]. Intracranial pressure rises markedly and rapidly during generalized convulsions in humans [25,26]. Neurological disturbances resulting in acute increases in intracranial pressure are most likely to result in neurogenic PPE [22,27,28]. Spinal cord transection prevents the development of neurogenic PPE following convulsions, indicating that the effect is neurally mediated [21]. Seizure-related transient dilated cardiomyopathy (takotsubo cardiomyopathy) [29] resulting from intense sympathetic discharge [24] may also contribute to PPE [22]. In a series of 279 consecutive patients seen in an emergency department following seizures, 5 had takotsubo cardiomyopathy and none of these 5 patients reported any cardiac symptoms [30].

PPE can also result from excessive negative intrathoracic pressure. Negative pressure PPE (NPPE) develops after deep inspiratory effort against a closed glottis [31]. Marked and prolonged increases in negative pressure gradients result in a shift in fluid from capillaries to lung parenchyma and eventual damage to the capillary walls [31]. Postictal laryngospasm has been reported [32] and NPPE may thus be relevant in some cases of SUDEP. Severe hypoxemia may occur postictally [15,33]. Hypoxemia causes peripheral and pulmonary vasoconstriction with shunting of blood to pulmonary vasculature further compromising pulmonary hemodynamics. Hypoxemia also interferes with alveolar epithelial Na, K-ATPase active transport that is necessary for clearance of PPE fluid [34]. Disruption of the Na, K-ATPase mechanism is an important factor in acute hypoxemic respiratory failure [34] and likely relevant in PPE. The temporal characteristics of this mechanism in PPE remain to be determined. A complex

Table 2
Patient and seizure characteristics.

Patient	Age (years)	Gender	Seizure onset	Seizure frequency	Epilepsy duration	MRI findings	Co-morbidities/VNS	Antiepileptic drugs
1.	17	M	BF, LF	1/2–3W	7 Y	Right frontal subcortical increased T2 signal	None	LCM, LEV
2.	17	M	RFT	2/M	3 Y	Abnormal morphology bilateral hippocampi. Hydrocephalus	Asthma	LEV, LTG, TPM
3.	18	F	LT	2/M	8 Y	Left MTS	None	OXC, LEV
4.	58	F	LT	2/W	4 Y	Irregular shaped left hippocampus	None	TPM, LTG
5.	19	F	RT	6–8/M	11 Y	Right temporal cavernous angioma	None	OXC
6.	19	F	RFT	1/M	6 Y	Moderate diffuse cerebral and cerebellar volume loss	None	OXC
7.	34	F	LT	3–4/M	22 Y	Normal	Asthma, Depression	LCM, TPM
8.	21	F	Gen.	20/Y	9 Y	JME. No MRI	Cerebral palsy	LEV, LTG
9.	28	M	LFT, LT	1/M	7 Y	Ovoid corpus callosum splenial lesion. No MTS	None	LEV, OXC
10.	49	F	LT	10/M	5 Y	Left MTS	Hypertension, Hypothyroidism	LEV, LCM
11.	44	M	RT	3/M	33 Y	Normal	Mild OSA (AHI = 11)	LEV, LCM
12.	29	F	L Hemi R Hemi	1/W	22 Y	Normal	Depression, VNS	LEV
13.	26	M	R Hemi	1/W	20 Y	Normal	Depression	LEV, LCM, ZNS
14.	34	F	Gen.	1/2 M	21 Y	Normal	Depression, Transient RBBB during convulsion, VNS	LTG, ZNS
15.	28	M	LT, BF	3/W	16 Y	Normal	Developmental delay, VNS	CBZ, LCM
16.	29	F	BFC	Many	8 Y	Normal	Developmental delay	CBZ, VPA
17.	54	F	RT	3/M	Unknown	CT head normal	Polysubstance abuse, chronic obstructive pulmonary disease, takotsubo cardiomyopathy	LEV
18.	20	M	RT	2/W	16 Y	Normal	Asperger syndrome	ZNS, LTG
19.	33	F	LT	6/W	7 Y	Normal	Bipolar disorder	LEV
20.	49	M	RT	2/Y	35 Y	Bifrontal encephalomalacia	None	OXC, PB
21.	21	F	RT	2–3/W	14 Y	Normal	Developmental delay	None
22.	41	F	LT	3/W	16 Y	Left MTS	Asthma	LTG
23.	47	F	LFC	3–4/W	5 Y	Left frontal arachnoid cyst – fenestration	Depression	OXC
24.	38	M	RT	Daily	30 Y	Right opercular cortical dysplasia	None	LEV, PHT

BF, bifrontal; LF, left frontal; BFC, bilateral frontocentral; RFT, right frontotemporal; LFT, left frontotemporal; L hemi, left hemisphere; R hemi, right hemisphere; LT, left temporal; RT, right temporal; LFC, left frontocentral; BFC, bilateral frontocentral; Gen, generalized; W, week; M, month; Y, year; MTS, mesial temporal sclerosis; JME, juvenile myoclonic epilepsy; VNS, vagus nerve stimulator; RBBB, right bundle branch block; OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; CBZ, carbamazepine; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; TPM, topiramate; VPA, valproate; ZNS, zonisamide.

interaction between the various mechanisms described above may account for the lack of a direct association between hypoxemia and PPE observed in this study.

Routine monitoring of respiratory parameters is not performed in most EMUs [10]. We had previously shown that there is a persistent postictal elevation of ETCO2 above preictal values for a mean duration in excess of 7 min despite persistent postictal tachypnea [15]. The postictal increase in ETCO2 occurs despite an increase in respiratory rate suggesting that the observed increase in ETCO2 may be a consequence of pulmonary dysfunction rather than a decrease in postictal ventilatory effort [15].

A study of CXR findings following electroconvulsive therapy showed subclinical PPE in only one of 12 patients [14]. The mean seizure duration in that study was 63 s. That finding lends support to the conclusions of our present study, indicating that postictal intrinsic pulmonary pathology is a direct function of seizure duration. Our data were insufficient to address whether the number of GTCS in a 24-h period influenced the development of PPE. Four of the 7 patients had PPE following the first GTCS with no other seizures in the preceding 24 h. On the other hand, 6 patients had more than one GTCS in a 24 h period without developing PPE. This suggests that perhaps the duration of a given GTCS, rather than the frequency of brief GTCS, may be more relevant in the development of PPE.

The high incidence of PPE found in this study may have been influenced by rapid withdrawal of antiepileptic drugs in the EMU and the resulting prolonged generalized convulsive seizures in some patients. The incidence of PPE may be lower in patients having focal or partial seizures as well as shorter breakthrough convulsions while on antiepileptic drugs.

PPE is not an infrequent occurrence in the EMU setting. Severe, untreated postictal PPE may be relevant in the pathophysiology of SUDEP particularly in patients with poorly controlled convulsive seizures or following abrupt or rapid cessation of antiepileptic drugs.

Conflict of interest statement

None.

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