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Ictal laryngospasm monitored by video-EEG and polygraphy: a potential SUDEP mechanism

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ABSTRACT – A 56-year-old man with refractory bitemporal epilepsy was monitored in the Epilepsy Monitoring Unit (EMU). In a video-EEG captured seizure, brief oroalimentary automatisms were followed by increased inspiratory effort, accompanied by prominent, visible tracheal movements and audible inspiratory stridor. The patient's oxygen saturation rapidly declined to 62%; persistent severe hypoxemia ended with spontaneous effective respiration commencing at seizure end. Subsequent seizures necessitated intensive care unit admission for respiratory distress, and ventilator support. This case suggests that ictal laryngospasm, a rare seizure manifestation, may represent another potential mechanism of sudden unexpected death in epilepsy (SUDEP).
[*Published with video sequence on www.epilepticdisorders.com*].

Key words: SUDEP, breathing, laryngospasm, airway obstruction, apnea

Individuals with intractable epilepsy have an approximately 0.5-1% annual risk of sudden unexpected death in epilepsy (Devinsky *et al*., 2016). SUDEP's precise agonal mechanisms are unknown, although recent evidence from the Mortality in Epilepsy Monitoring Units Study (MORTEMUS) points to combined respiratory and cardiovascular collapse driving the fatal event (Ryvlin *et al*., 2013). However, heterogeneity in SUDEP phenomenology is also described (Lhatoo *et al*., 2016), and documented, near fatal, postictal laryngospasm after a generalized tonic-clonic seizure (GTCS) in one patient has been suggested as a potential mechanism of death (Tavee and Morris, 2008). Laryngospasm has been linked to sudden infant death syndrome (SIDS) and sudden unexplained death in childhood (SUDC), and a recent study in an adult Sprague-Dawley urethane/kainite rat seizure model recorded severe laryngospasm, ST segment elevation, bradycardia, and death (Nakase *et al*., 2016). Electromyographic (EMG) artifact evidence of increased inspiratory effort in laryngospasm and shortened R-R intervals during the same periods were subsequently noted by the authors in a re-evaluation of MORTEMUS patients, and proposed as potential SUDEP biomarkers (Stewart *et al*., 2017). We report a

VIDEO ONLINE

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monitored case of severe ictal (rather than postictal) laryngospasm and hypoxemia, in the absence of a generalized tonic-clonic seizure, eventually requiring intubation and intensive care ventilation because of respiratory decompensation.

Case study

The patient was a 56-year-old, right-handed male with intractable epilepsy, and a consented participant in the NINDS Center for SUDEP Research's Autonomic and Imaging Biomarkers of SUDEP Project (U01-NS090407). As one of 126 patients in a seizure and breathing dysfunction study, polygraphic physiological responses were analyzed in the Epilepsy Monitoring Unit, including video electroencephalogram (VEEG), electrocardiogram (EKG), peripheral capillary oxygen saturation (SpO_2), and abdominal and thoracic inductance plethysmography for breathing. The patient was known to have Wolf Parkinson White syndrome (status post ablation), and was on treatment with metoprolol and isosorbide mononitrate.

Epilepsy duration was 12 years, and seizure frequency was one to two partial seizures per month, with at least one GTCS per year. He typically had automotor seizures without aura, sometimes followed by secondary generalization. He was on valproic acid 1,000 mg/day and levetiracetam 2,000 mg/day. Physical examination and epilepsy protocol MRI brain scans were normal. He was admitted to the EMU, where a single seizure was recorded. At the time of the seizure, the patient was on the same dose of valproic acid and levetiracetam. A nocturnal habitual automotor seizure, arising from the left deep sphenoidal electrode (Sp1), was recorded. Careful scrutiny of breathing revealed a preceding central apnea of six seconds, followed by arousal, brief oroalimentary automatisms, and continuing apnea. Oxygen saturation dropped 40 seconds after respiratory movements ceased, from 95% to a nadir of 62%, with a total hypoxia duration of 90 seconds. When automatisms ceased, tracheal tug movements were evident, synchronous with abdominal respiratory belt excursions (*see video sequence*). Inspiratory effort became increasingly prominent, accompanied by prominent tracheal movements and inspiratory stridor, also evidenced by increasing EMG artifact in EEG and EKG channels (*figure 1*). There was baseline sinus rhythm with ventricular preexcitation at an average rate of 66 beats per minute (bpm). At clinical seizure onset, sinus rhythm increased to 90 bpm for 36 seconds, and then decreased to baseline for 10 seconds. When inspiratory effort became evident, sinus rate decreased to 46 bpm with junctional escape rhythm at the same rate (iso-rhythmic dissociation) (*figure 1 and video sequence*). EEG showed bitemporal rhythmic theta activity several seconds prior to laryngospasm onset. Attempts to improve ventilation by repositioning the patient did not improve respiration; emergency code was called and oxygen was administered 15 seconds before seizure end, and the patient began spontaneous effective respiration. Review of a previous EMU admission revealed an identical seizure with a SpO2 nadir of 47%, suggesting this ictal laryngospasm was not an isolated event. The patient was discharged after medication adjustment, and remained seizure-free until a year later, when he was readmitted with breakthrough seizures because of medication noncompliance. While in the emergency room, he had a further GTCS, and Ativan 2 mg was intravenously administrated. Prominent stridor was noted, resulting in intubation and admission to the neurological intensive care unit. EEG monitoring was not performed. The patient then made an uneventful recovery and was discharged to outpatient follow-up.

Discussion

The occurrence of laryngospasm in this case, one of 126 patients (0.8%) in our larger study of breathing dysfunction, suggests that this is an either rare, or under scrutinized phenomenon. Postictal laryngospasm causing near-SUDEP after a GTCS has been reported in only a single adult patient (Tavee and Morris, 2008), and ictal laryngospasm reported also in only one adult patient (Murray *et al*., 2010). The latter had right frontal opercular seizures consisting of choking and inability to speak. After stereotactic EEG evaluation (SEEG) and subsequent epilepsy surgery, he was seizure-free at six months. In the absence of polygraphy and oxygen measurements, laryngospasm was an inferred explanation for choking. Ictal laryngospasm may be more frequent in children, although only eight cases appear in the literature (Ravindran, 1981; Amir *et al*., 1983; Cohen *et al*., 2000; Wyder-Westh *et al*., 2005), based on clinical symptoms of increased inspiratory effort, and inspiratory stridor. Since diagnosis in these cases was based on interictal epileptiform EEG findings rather than video-EEG monitoring, it may be more appropriate to refer to these cases as peri-ictal laryngospasm (*table 1*).

Postictal laryngospasm is postulated to be a primitive protective airway reflex against aspiration (Stewart *et al*., 2017). Ictal laryngospasm on the other hand, may either be driven by tonic seizure discharge spread to cortical areas governing laryngeal motor control (perisylvian motor homunculus and anterior insula), or a profound increase in vagal tone (Subramani and Paul, 2005), both of which can drive recurrent laryngeal nerve mediated laryngospasm. The marked bradycardia and junctional escape rhythm during increased inspiratory effort support significant

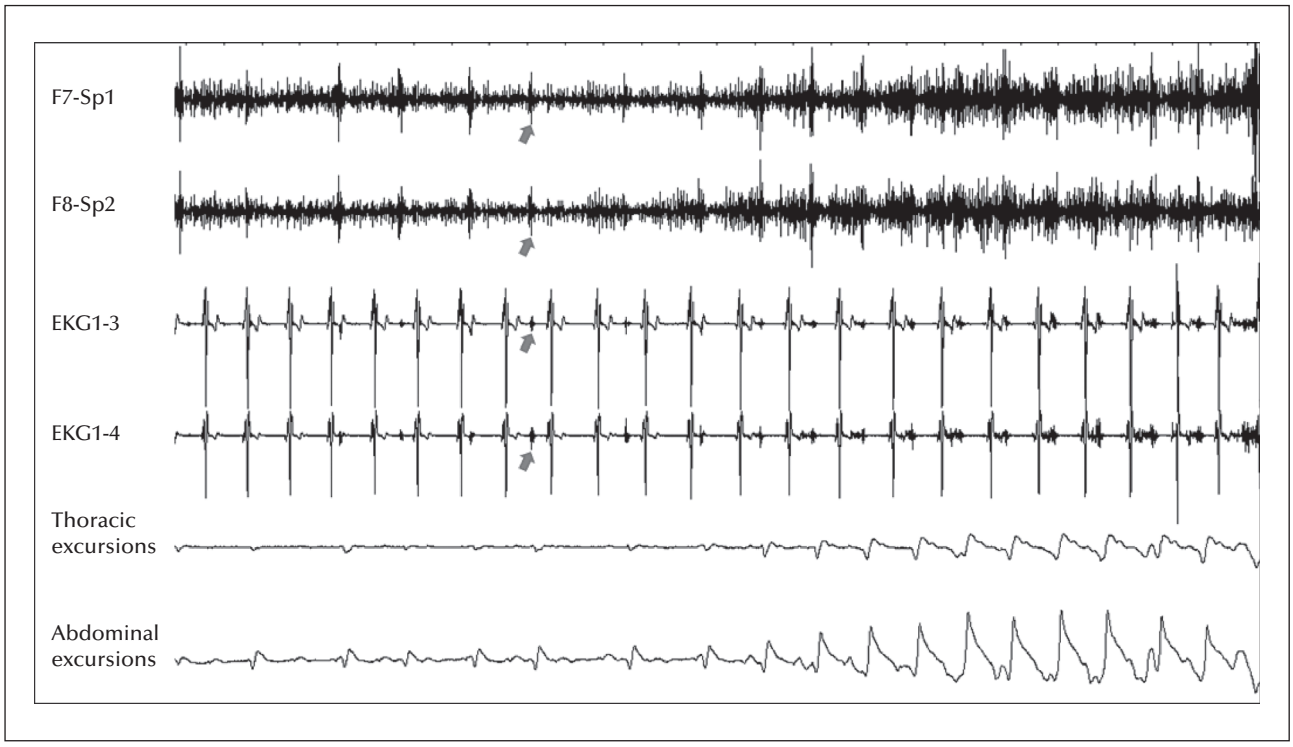

Figure 1. Thirty-second polygraphy recording during a focal seizure showing increasing abdominal respiratory effort amplitude, paradoxical abdomino-thoracic movements, concurrent increase in muscle artifact (arrows; also noted synchronously in EKG signal), and bradycardia with junctional rhythm during the period of laryngospasm and hypoxia.

vagotonia. In the absence of direct laryngoscopic examination, partial or complete laryngospasm is indicated by inspiratory stridor, or complete absence of air movement and breath sounds. Additional signs of airway obstruction, such as tracheal tug, paradoxical abdomino-thoracic movements, oxygen desaturation, bradycardia, and central cyanosis, may be present (Alalami *et al*., 2008). Our patient had evidence of progressively increasing respiratory effort, tracheal tug, and inspiratory stridor, in addition to progressive oxygen desaturation and bradycardia (*see video sequence*). The profound hypoxia recorded, and the audible stridor, suggest that airway obstruction was significant and severe.

Laryngospasm as a SUDEP biomarker has recently been described in a rat model (Stewart *et al*., 2017), represented by high-frequency setting, electromyographic signal artifact, indicative of breathing attempts. Identical artifacts in EEG and EKG channels were visible in our case, with the same tendency to progressive increases in artifact size, consistent with increasing inspiratory effort (*figure 1 and video sequence*). As in our case, patients are reported to be agnostic to breathing distress (Ravindran, 1981; Amir *et al*., 1983). Thus, the importance of video-EEG monitoring and additional polygraphy in apparently intractable epilepsy cannot be understated since laryngospasm may be an under-recognized phenomenon in SUDEP series. A combination of obstructive apnea and bradycardia (typically seen in laryngospasm) have been postulated as a deleterious combination of signs in the SUDEP and near-SUDEP contexts (Nashef *et al*., 1996; Stewart *et al*., 2017). Recent evidence has been put forward to suggest that some MORTEMUS SUDEP cases may have suffered laryngospasm (Stewart *et al*., 2017). The animal evidence comes from studies in an adult Sprague-Dawley urethane/kainite rat seizure model, characterized by severe laryngospasm, increasing respiratory effort, ST segment elevation, bradycardia, and death (Nakase *et al*., 2016; Stewart *et al*., 2017). A typically seen EMG artifact representing increased inspiratory effort during endoscopically-proven laryngospasm in these animals (not seen in normal inspiration) was postulated as a potential SUDEP biomarker, and seen in MORTEMUS SUDEP patients, thereby raising laryngospasm as a significant concern in human seizures too. Thus, the observed seizure semiology and subsequent active resuscitation required in one seizure, suggests that SUDEP is a real concern in our patient. However, it should also be noted that the factors governing the occurrence of laryngospasm, and what drives fatal transformation, is unknown. The patient's seizures seem to be well controlled as long as medication compliance is observed; he has been seizure-free for the last six months. On the other hand, ictal or postictal central

Table 1. Cases reports and case series of peri-ictal laryngospasm.

Cases	Age	Symptoms	Laryngospasm diagnosis	EEG	Time	Awareness of episodes	Outcome after antiseizure treatment
Ravindran, 1981	15 y/o	"Vertigo" associated with loud, prolonged, noisy breathing and unresponsiveness	Clinical symptoms	Temporal spikes	Awake and sleep	No	Free of episodes (unknown duration) with carbamazepine 600 mg daily
Amir *et al.*, 1983	6y/o	Short cough followed by intensive inspiratory effort with severe air hunger without stridor	Clinical symptoms	Right parietal spikes	Sleep	No	Free of episodes (6-month follow-up period) with carbamazepine 400 mg daily
Cohen *et al.*, 2000	8-12 y/o (5)	All had severe air hunger, some with inspiratory stridor and/or cyanosis	Clinical symptoms	Fronto-temporal spikes (2), frontal (1) and temporal (2)	One episode during sleep, rest unknown	Unknown	Free of episodes, follow-up period of 15 months with carbamazepine
Wyder-Westh *et al.*, 2005	19 m/o	Dyspnea and sialorrhea	Clinical symptoms	Rhythmic right theta activity	Sleep	Unknown	Free of episodes, follow-up period of 12 months with carbamazepine
Tavee and Morris, 2008	42 y/o	Loud inspiratory stridor and marked cyanosis	Direct laryngoscopy	Left temporal spikes and seizures	Sleep	Unknown	Unknown
Murray *et al.*, 2010	34 y/o	Episodes of "choking"	Clinical symptoms	Epileptiform discharges and right opercular seizures	Sleep	Unknown	Free of episodes, follow-up period of 6 months after epilepsy surgery
The present case	56 y/o	Inspiratory stridor, intensive inspiratory effort, tracheal tug movements	Clinical symptoms and breathing polygraphy*	Left temporal seizures and bilateral temporal spikes	Sleep	No	Free of seizures, period of 6 months with levetiracetam and valproic acid.

y/o: years old; m/o: months old.
*Abdominal and thoracic movements using inductance inductance pletismograhy (belts) and peripheral capillary oxygen saturation (SpO2).

apnea in the absence of airway obstruction remain potential SUDEP mechanisms, and obstructive apnea due to laryngospasm may simply represent another example of SUDEP heterogeneity. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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Legend for video sequence

Video-EEG recording showing an automotor seizure, followed by laryngospasm and increasing breathing effort with audible inspiratory stridor. Polygraphy recording shows left temporal EEG seizure discharge with later spread to the right, increasing abdominal breathing excursion amplitudes with concurrent muscle artifact, and oxygen desaturation, consistent with significant airway obstruction.

Key words for video research on www.epilepticdisorders.com

Phenomenology: bradycardia
Localization: temporal lobe (left)
Syndrome: focal non-idiopathic temporal (TLE)
Aetiology: unknown

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TEST YOURSELF

(1) Can laryngospasm occur during seizures?

(2) How can we make the diagnosis of laryngospasm in the epilepsy monitoring unit in the absence of laryngoscopy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".