Case Report

Ictal Generalized EEG Attenuation (IGEA) and hypopnea in a child with occipital type 1 cortical dysplasia – Is it a biomarker for SUDEP?

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Abstract

An interesting association of ictal hypopnea and ictal generalized EEG attenuation (IGEA) as possible marker of sudden unexpected death in epilepsy (SUDEP) is reported. We describe a 5-years-old girl with left focal seizures with secondary generalization due to right occipital cortical dysplasia presenting with ictal hypopnea and IGEA. She had repeated episodes of the ictal apnoea in the past requiring ventilator support and intensive care unit (ICU) admission during episodes of status epilepticus. The IGEA lasted for 0.26-4.68 seconds coinciding with the ictal hypopnea during which both clinical seizure and electrical epileptic activity stopped. Review of literature showed correlation between post-ictal apnoea and post ictal generalized EEG suppression and increased risk for SUDEP. The report adds to the growing body of literature on peri-ictal apnea, about its association with IGEA might be considered as a marker for SUDEP. She is seizure free for 4 months following surgery.

Key Words

Ictal hypopnea, ictal generalized EEG attenuation, occipital lobe epilepsy, status epilepticus, sudden unexpected death in epilepsy, SUDEP

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Introduction

Occurrence of sudden unexpected death in epilepsy (SUDEP) is rare in children with a prevalence of 0.11-0.43/1000 person-years compared to adults (1.1-5.9/1000 person-years) with chronic refractory epilepsy.[1,2] The proposed mechanisms for SUDEP might be related to a combined cardiac, respiratory, and autonomic dysfunction during the peri-ictal period. Abnormalities of cardiac rhythms or respiration like bradypnea, hypopnea and apnea during the ictus have been observed. Post-ictal generalized EEG suppression (PGES) and burst suppression, noted in electroencephalography (EEG) of patients with drug resistant epilepsy, have been identified as high risk for SUDEP.[3] Terminal cessation and diffuse suppression of EEG activity before any cardiac or respiratory changes akin to central nervous system (CNS) shutdown has also been reported.[4]

We discuss clinical-EEG profile of a child with localization related occipital epilepsy due to cortical dysplasia manifesting with multiple episodes of ictal generalized EEG attenuation (IGEA) and hypopnea during a prolonged focal motor seizure while undergoing video-EEG recording.

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Case Report

This 5-year girl developed fever and seizures at 6 months of age, four hours after Diptheria Pertussis and Tetanus (DPT) vaccination. Subsequent seizures were non-febrile and occurred once/2-3 months for the initial 2 years. The seizure frequency increased to four seizures/week and so did the seizure duration lasting often upto 30-45 minutes. During last 3 years, on four occasions, the prolonged seizures were associated with ictal apnea requiring lifesaving ventilator support. Seizures were characterized by confusion, subdued response, with or without vomiting, left focal motor seizures, deviation of eyes to the left and left hemi-generalized tonic-clonic movements. Occasionally, she would also have a clockwise gyratory movement for 3-4 circles with secondary

generalized seizures. There was no history of post-ictal weakness, visual phenomenon, myoclonus, or regression of milestones. She was born by caesarean section at full term gestation. The developmental milestones were appropriate. Despite protracted seizure and several emergency admissions, she had relatively well preserved cognition. However, frequent seizures prevented her to go to school. There was no neurological deficit. Brain magnetic resonance imaging (MRI) (1.5T) was normal.

She received phenobarbitone (60 mg/day), carbamazepine (700 mg/day), valproate (600 mg/day), levetiracetam (600 mg/day), and clobazam (15 mg/day) without much success. She developed skin rash to lamotrigine. By the time of evaluation at our centre, she was already receiving lacosamide 100 mg/day, clobazam 15 mg/day, zonisamide 100 mg/day, and phenytoin 150 mg/day.

Routine EEG showed frequent spike and wave discharges the right posterior quadrant. During the video-EEG recording, she had left focal with secondary generalized seizures that progressed to status epilepticus (SE) lasting for >2 hours, requiring termination of recording, and urgent intervention. She woke up from sleep in a confused state not responding to questions, had bouts of cough and ictal vomiting. There was a relative immobility of the left side of the body. Then there was left facial twitching and tonic-clonic movements of the left side of the body and limbs. Subsequently, she had short periods (total of 45 episodes, duration ranging from 260-4684 ms) where the convulsions would stop and she would have a shallow breathing possibly "hypopnea". Seizure continued despite administering intravenous lorazepam (2 mg). She was shifted to ICU and administered intravenous valproate (250 mg) followed by levetiracetam (250 mg) for seizure control. The total seizure duration was nearly 90 minutes.

VEEG revealed a normal background activity. Inter-ictally, there were frequent spike and sharp wave discharges from right posterior quadrant (T6-O2) [Figure 1a]. Prior to clinical seizure, there was build-up of spikes and sharp waves in the right temporo-occipital leads (T6, O2) [Figure 1B] which lasted for a very long period, later spreading to the right hemisphere before becoming generalized. During the apparent periods of hypopnea there was cessation of the clinical seizure, and EEG showed absence of epileptiform activity and generalized attenuation of the cerebral electrical activity (right > left) [Figure 1c] lasting for 260-4682 msec with mean amplitude of 20 ± 10 μV, compared to the average background amplitude of 175.55 ± 19.11μV. Interestingly on some occasions, IGEA would be followed by either generalized seizure activity or seizure onset building up again in the right occipital region [Figure 1g]. Ictal tachycardia was noted (125-135 bpm). Simultaneous chest lead electrocardiography (ECG) showed tachycardia with ST segment inversion during the IGEA periods which was not noted during the baseline ECG recording. However, during the seizure the ECG was marred by movement artifacts. Four hours later, she was conscious and interacting with her parents.

Evaluation with plasma ammonia, lactate, tandem mass spectroscopy (TMS) profile, abnormal urine metabolites was unremarkable. Cardio-pulmonary evaluation was unremarkable. A 3-Tesla brain MRI revealed focal loss of grey-white matter differentiation on T2W imaging with subtle cortical hyperintensity on 3D-Flair involving the right lateral superior temporo-occipital gyrus, suggesting cortical dysplasia [Figure 2a]. Inter-ictal positron emission tomography (PET) scan revealed right temporo-occipital hypometabolism [Figure 2b]. Magnetoencephalography (MEG) revealed dipole clusters from the right occipital

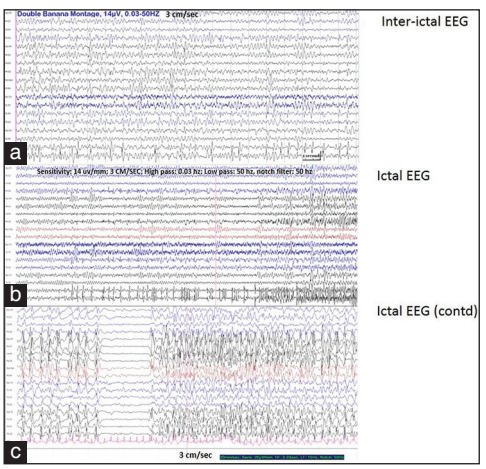

Figure 1: (a) Inter-ictal EEG shows right occipital discharges with normal symmetrical background activity and posterior dominant alpha waves; (b) Ictal onset was in the right occipital region; (c) IGEA noted during the seizure the mean amplitude was 62.40 ± 15.1 μV. During this period the ECG was normal but with decreased chest excursions

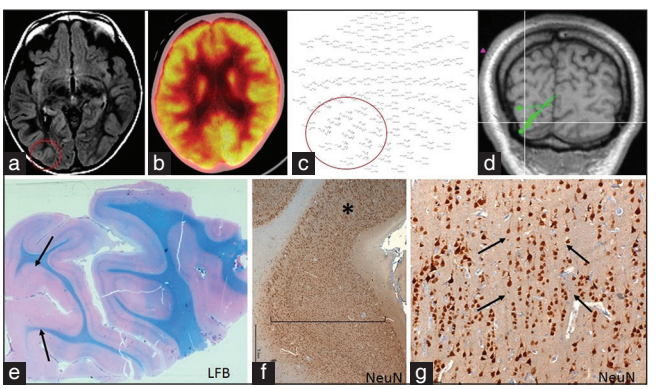

Figure 2: (a-g): (A): 3TMRI Brain FLAIR–axial sequence showing subtle cortical hyperintensity of the right lateral superior (temporo) occipital gyrus with poor grey white matter differentiation; (b) Interictal FDG - PET with CT axial, showed hypometabolism in the right posterior quadrant, predominantly the occipital and posterior temporal regions; (c,d) MEG showing spikes and dipole clusters predominantly from the right occipital regions propagating anteriorly; E-G: Histopathological examination of the occipital lobe revealed focal widening of the cortical ribbon (Figure 1e, arrows) highlighted on Luxol Fast Blue stain (Figure 1e, bracket) and NeuNimmuno labeling compared to adjacent cortex of normal thickness (Figure 1e, asterix). Radial dyslamination and microcolumnar organization of neurons is seen on NeuNimmunolabeling in these zones [Figure 1f, g) corresponding to focal cortical dysplasia type 1a. [e: LFB×8, f,g: neuNimmunostaining; magnification=scale bar]

region [Figure 2c,d]. The case was in the pre-surgical meet as possible surgical candidate for better seizure control, to avoid SE and ictal apnea. In view of concordant EEG, MRI, Video-EEG, PET and MEG findings, she underwent right occipital lobectomy under electrocorticographic (ECoG) guidance. Intra-operative ECoG revealed almost continuous spikes over the temporo-occipital region and extending to neocortical posterior temporal lobe. Based on ECoG findings, resection of posterior temporal cortex, and then hippocampus and amygdala through the temporal horn were performed. Histo-pathological examination revealed focal widening of the cortical ribbon [Figure 2e]. NeuNimmuno labeling revealed radial dyslamination in these zones with micro-columnar organization of neurons [Figure 2f,g] corresponding to focal cortical dysplasia type 1a in the occipital neocortex. Similar findings were also noted in the posterior temporal neocortex. Four months after surgery, the patient is seizure free.

Discussion

We highlight the possible association of IGEA as cause of hypopnea in a young girl with drug resistant occipital epilepsy due to cortical dysplasia, which might be a marker for SUDEP. Earlier, she did have ictal apnea requiring mechanical ventilatory support.

SUDEP is defined as sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus (seizure duration > 30 min or seizures without recovery in between), in which postmortem examination does not reveal a cause of death.[1] Although, epilepsy-related mortality and SUDEP have been recognized, its patho-physiology remains to be ascertained.[3] The underlying mechanisms vary from being unknown to ictal/post-ictal arrhythmia, dysautonomia, pulmonary edema, post ictal generalized EEG suppression and central apnea.[2-6] (Table 1 [3,14-28]).

Table 1: It shows review of various underlying mechanisms of SUDEP

Mechanisms	Causes of SUDEP	Study	Level of evidence
Related to seizure type and frequency	History of and Frequent seizures 1·4 times higher in male than in female 1·7 times higher in those with onset of epilepsy before the age of 16 years than in those with onset between 16 years and 60 years, and twice as high in those who had had epilepsy for longer than 15 yrs.	Shorvon & Tomson (2011)[3], Tellez Zenteno *et al.*[14] (2005), Tomson *et al.*[15] (2005), So *et al.* (2006)[16] Nilsson *et al.* (1999), [17] Walczak *et al.* (2001),[18] Hitiris *et al.* (2007),[19] Langan *et al.* (2005)[20]	Case control studies
Antiepileptic drugs (AEDs)	Sub-therapeutic AED levels can indirectly	Tellez-Zenteno *et al.*[14] (2005), Tomson *et al.*[15] (2005), So *et al.* (2006)[16]	Case control studies
	Carbamazepine, phenytoin and lamotrigine are rarely associated with atrioventricular block by sodium channel blockade causing decreased HRV and prolonged QT interval.	Persson *et al.* (2003)[21]	Case control study
	Lamotrigine in idiopathic generalized epilepsy is associated with increased risk for SUDEP	Aurlien *et al.* (2007)[22]	Case series
	Polytherapy increases risk for SUDEP	Nilsson *et al.* (1999), [17] Walczak *et al.* (2001),[18]	Case control and cohort studies
	Absence of AEDs has increased risk of SUDEP by 21.7% as compared with those taking 1 or 2 AEDs.	Langan *et al.* (2005)[20]	Case control
Respiratory	In an animal study, 5/13 sheep died within 5 min of the onset of seizures due to increased peak left atrial and pulmonary artery pressures and in extravascular lung water although the pulmonary oedema was not severe enough to be the primary cause of death.	Johnston *et al.* (1995)[23]	Animal experiments done on sheep
	Obstructive apnea due to increased airway secretions due to elevated parasympathetic activity	Hotta *et al.* (2009)[24]	Animal experiments in rats
Cardiac arrhythmia	Ictal bradyarrhythmia has been recorded in cerebral stimulation and ictal recordings, both clinically and in animals, in the insular, orbital frontal, and anterior temporal lobe regions	Oppenheimer *et al.* (1992)[25]	Prospective interventional study
	Ictalasystole is estimated to occur in 0·27-0·40% of patients who have seizures on video-EEG monitoring units	Rocamora *et al.* (2003)[26]	Retrospective descriptive study
Autonomic dysfunction	A decreased heart rate variability with fall in total power and reduction in both low frequency and low frequency/ high frequency powers have been reported. A predominant dysfunction of parasympathetic systems are associated with poorer outcomes.	Tomson *et al.*[15] (2005), Ronkainen *et al.* (2005)[27] Persson *et al.* (2007)[28]	Prospective analytical study and case control study

Profound cortical neuronal inhibition of abrupt onset, possibly with associated inhibition of brainstem respiratory centres and resultant postictal central apnea had been proposed as a mechanism for PGES resultant SUDEP.[4,7] Burst suppression and PGES have been reported in epilepsy and said to be one of the mechanisms of SUDEP. Steriade and colleagues have demonstrated that EEG burst phases were associated with excitatory activities in cortical neurons, while suppression phases were paralleled by absence of cortical network interactions.[8] Here, there was IGEA, which was characterized by a cessation of the ictal rhythm and a definitive attenuation of generalized EEG activity (right > left). Considering the occipito–temporal nature of the seizures, there is a possibility of seizure activity spreading from the temporal region to the midbrain. According to the network inhibition hypothesis, seizure activity often spreads from the temporal lobe to midline subcortical structures leading to depressed bilateral cortical activity leading to loss of consciousness, which has been implicated in both secondary generalization and suppression of respiratory centers.[9,10] The prolonged nature of seizures might have resulted in global neuronal exhaustion causing respiratory depression with simultaneous suppression of cerebral electrical activity resulting in IGEA and hypopnea. Conde *et al*. (2012) had reported ictal bradypnea/hyponea associated with a complete suppression of the EEG activity in two infants with occipital lobe seizures.[11] The association of these ictal changes with occipital lobe seizures is yet to be understood. Systematic evaluation of various mechanisms involved in the causation of occipital lobe seizures, focal cortical dysplasia (FCD), seizure termination/ electro-cerebral shut down, etc. and their possible overlap with respiratory mechanisms might unravel the clinico-electrical observation noted in this child.

Autonomic dysfunction as assessed by heart rate variability (HRV) during ongoing seizures have shown poor cardiac-autonomic reserve. Tachycardia as a manifestation of either of these mechanisms is known to occur in SE.[12] In a patient with near SUDEP, ventricular arrhythmia was noted at the end of secondary generalization which was reverted with defibrillation.[13]

It has been suggested that longer the duration of PGES, the higher the risk of SUDEP.[4] The child had ictal apnea during prolonged seizure on four occasions requiring ventilatory assistance. We hypothesize that the IGEA might be linked to seizure-associated respiratory dysfunction like apnea/ hypopnea and might result in SUDEP. Though uncommonly observed, timely planned surgical intervention provided seizure freedom, avoided frequent SE and possible apnea.

The drawback of this study was not being able to record the abdomino-thoracic excursion and end-tidal CO_2. This study highlighted a possible association of IGEA as cause of 'hypopnea' which might be a marker for SUDEP. Physicians need to educate the caregivers prompt medical attention to avoid any untowardly event(s).

References

1. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia 2012; 53:227-33.
2. Milroy CM. Sudden unexpected death in epilepsy in childhood. Forensic Sci Med Pathol 2011;7:336-40.
3. Shorvon S, Tomson T. Sudden unexpected death in epilepsy. Lancet 2011;378:2028-38.
4. Seyal M, Hardin KA, Bateman LM. Postictal generalized EEG suppression is linked to seizure-associated respiratory dysfunction but not postictal apnea. Epilepsia 2012;53:825-31.
5. McLean BN, Wimalaratna S. Sudden death in epilepsy recorded in ambulatory EEG. J Neurol Neurosurg Psychiatry 2007;78:1395-7.
6. Tolstykh GP, Cavazos JE. Potential mechanisms of sudden unexpected death in epilepsy. Epilepsy Behav 2013;26:410-4.
7. Lhatoo SD, Faulkner HJ, Dembny K, Trippick K, Johnson C, Bird JM. An electroclinical case□control study of sudden unexpected death in epilepsy. Ann Neurol 2010;68:787-96.
8. Steriade M, Amzica F, Contreras D. Cortical and thalamic cellular correlates of electroencephalographic burst-suppression. Electroencephalogr Clin Neurophysiol 1994;90:1-16.
9. Seyal M, Bateman LM. Ictal apnea linked to contralateral spread of temporal lobe seizures: Intracranial EEG recordings in refractory temporal lobe epilepsy. Epilepsia 2009;50: 2557-62.
10. Blumenfeld H. Impaired consciousness in epilepsy. Lancet Neurol 2012;11:814-26.
11. Castro Conde JR, Gonzalez-Hernandez T, González Barrios D, González Campo C. Neonatal apneic seizure of occipital lobe origin: Continuous video-EEG recording. Pediatrics 2012;129:e1616-20.
12. Tomson T, Ericson M, Ihrman C, Lindblad LE. Heart rate variability in patients with epilepsy. Epilepsy Res 1998;30:77-83.
13. Espinosa PS, Lee JW, Tedrow UB, Bromfield EB, Dworetzky BA. Sudden unexpected near death in epilepsy: Malignant arrhythmia from a partial seizure. Neurology 2009;72:1702-3.
14. Tellez-Zenteno JF, Ronquillo LH, Wiebe S. Sudden unexpected death in epilepsy: Evidence-based analysis of incidence and risk factors. Epilepsy Res 2005;65:101-15.
15. Tomson T, Walczak T, Sillanpaa M, Sander JW. Sudden unexpected death in epilepsy: A review of incidence and risk factors. Epilepsia 2005;46 Suppl 11:54-61.
16. So EL. Demystifying sudden unexplained death in epilepsy — Are we close? Epilepsia 2006;47 Suppl 1:87-92.
17. Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: A case-control study. Lancet 1999;353:888-93.
18. Walczak TS, Leppik IE, D'Amelio M, Rarick J, So E, Ahman P, *et al*. Incidence and risk factors in sudden unexpected death in epilepsy: A prospective cohort study. Neurology 2001;56:519-25.
19. Hitiris N, Suratman S, Kelly K, Stephen LJ, Sills GJ, Brodie MJ. Sudden unexpected death in epilepsy: A search for risk factors. Epilepsy Behav 2007;10:138-41.
20. Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. Neurology 2005;64:1131-3.
21. Persson H, Ericson M, Tomson T. Carbamazepine affects autonomic cardiac control in patients with newly diagnosed epilepsy. Epilepsy Res 2003;57:69-75.
22. Aurlien D, Tauboll E, Gjerstad L. Lamotrigine in idiopathic epilepsy-increased risk of cardiac death? Acta Neurol Scand 2007;115:199-203.
23. Johnston SC, Horn JK, Valente J, Simon RP. The role of hypoventilation in a sheep model of epileptic sudden death. Ann Neurol 1995;37:531-7.
24. Hotta HK, Koizumi K, Stweart M. Cardiac sympathetic nerve acctivity during kainic cid — induced limbic coritical seizures in rats. Epilepsia 2009;50:923-7.
25. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology 1992;42:1727-32.
26. Rocamora R, Kurthen M, Lickfett L, Von Oertzen J, Elger CE. Cardiac asystole in epilepsy: Clinical and neurophysiologic

features. Epilepsia 2003;44:179-85.
27. Ronkainen E, Ansakorpi H, Huikuri HV, Myllylä VV, Isojärvi JI, Korpelainen JT. Suppressed circadian heart rate dynamics in temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 2005;76:1382-6.
28. Persson H, Kumlien E, Ericson M, Tomson T. Circadian variation in heart-rate variability in localization-related epilepsy. Epilepsia 2007;48:917-22.

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