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Case Report

Seizure disorder as cause of sudden death in pregnancy: A case report

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Abstract

Maternal mortality has long been associated with a handful of well-known causes, but sudden unexpected death in epilepsy has not typically been one of them. We describe a 16-year-old at 21 weeks gestational age whose sudden unexpected death was precipitated by her pre-existing seizure disorder potentially complicated by pre-eclampsia diagnosed by post-mortem evidence. Physiologic changes in pregnancy cause not only hemodynamic burden for mother but also changes in normal metabolism. The use of antiepileptic drugs in pregnancy has been a matter of concern for teratogenicity and decreased serum levels due to metabolic changes. These changes have the potential for breakthrough seizures in pregnancy, leading to death. More effective patient monitoring and education for pregnant patients with pre-existing epilepsy is needed, as is awareness for increased risk of preeclampsia and screening of pre-eclampsia in these patients.

Key Words:

SUDEP, sudden death, epilepsy, seizure, antiepileptic, pregnancy, pre-eclampsia

Introduction

Due to physiologic changes that occur during pregnancy, women are at increased risk of morbidity and mortality. In the United States the mortality ratio in 2010 was 16.0 per 100,000 live births [1]. More commonly known causes of maternal death in pregnancy, such as hemorrhage, amniotic fluid embolism (AFE), thromboembolism, hypertensive disorders, and cardiovascular disease, are well studied, and many, if caught soon enough, are treatable. A less common cause of sudden maternal death in pregnancy is seizure disorder. Sudden unexpected death in epilepsy (SUDEP) is defined as: "Sudden, unexpected, witnessed or unwitnessed, non-traumatic and nondrowning death in a patient with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus, where the autopsy examination does not reveal a toxicological or anatomical cause of death" [2]. With the added difficulty due to physiologic changes, seizure control and predictability in pregnancy becomes a challenge for physicians. In this report, we present the case of a pregnant teen whose seizure disorder led to her sudden demise with subsequent death. Clinical evaluation, laboratory evidence, and autopsy findings failed to reveal a definitive cause of death; however, placental examination revealed changes suggestive of pre-eclampsia. The death was due to a pre-existing seizure disorder, complicated by pre-eclampsia.

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Case Presentation

A 16-year-old, gravida 1, para 0, black female at 21 weeks gestation was found unresponsive at home. The patient had a confirmed history of epilepsy treated with Lamotrigine (150 mg BID), and had been seizure-free for the pre-

vious two years. According to family, she had potentially missed her doses the day prior to and/or the morning she was found. She was healthy and had been receiving prenatal care. Emesis was noted in her hair with no loss of bladder or bowel control. Emergency medical services was called and cardiopulmonary resuscitation started. Pulseless electrical activity was present and was unshockable. During this time, a weak pulse was regained. The patient remained unresponsive and was intubated in the field. Upon arrival to a local hospital the patient remained unresponsive with no movements, or spontaneous breathing. Hypothermia protocol was initiated and an ultrasound was obtained that showed no fetal cardiac activity. She was then transferred to a referral hospital more equipped to stabilize her. She was afebrile with a temperature of 32˚C, a blood pressure of 69/42mmHg, a pulse of 123 beats per minute, and respirations count of 14 per minute on a ventilator with no breathing above respirator. Her pupils were fixed at 6 mm and nonreactive. Her Glasgow coma scale was 3. The patient was noted to have bloody output from her nasogastric tube and venipuncture sites. Her laboratory values on admission to the referral hospital are shown in Table 1. An electrocardiogram (ECG) demonstrated sinus tachycardia with a rate of 103 and prolonged corrected QT (QTc) of 503. A commuted tomography scan of the head showed diffuse anoxic brain injury. A transthoracic echocardiogram demonstrated normal cardiac size, anatomy, and an ejection fraction of 64.3%. The chest X-ray from the original facility was unremarkable, however on repeat chest X-ray a right upper lobe infiltrate developed. Urine toxicology screens were negative for drugs of abuse. Based on these findings, a diagnosis of disseminated intravascular coagulation (DIC) was rendered, with presumptive underlying AFE. Supportive treatment included mechanical ventilation, fluid resuscitation, cooling protocol, Levophed pressures, treatment for hyperkalemia, platelets, cryoprecipitate, packed red blood cells, fresh frozen plasma, factor VIIa, and tranexamic acid. The fetus was delivered by cesarean section in hopes to correct the DIC. The placenta and amniotic fluid appeared normal. The patient's pressures stabilized, international normalized ratio (INR) decreased to 1.2, aPTT to 77 seconds, and the white blood cell count (WBC) decreased to 8.0x 103/mm3. With time the patient's bleeding ceased. Despite this, brain death was confirmed by radionuclide cerebral flow study. The patient's family decided to withdraw care and the patient passed away 17 hours after admission to the referral hospital, and 19 hours after being found unresponsive. As the case represented a sudden, unexpected death, it was referred to the coroner, who took jurisdiction and ordered an autopsy. At autopsy there was no evidence of trauma. The cerebral hemispheres demonstrated diffuse edema with blurring of the grey-white junction on sectioning, but no other abnormality. The pituitary gland was unremarkable. There was no evidence of pulmonary thromboembolism, and no evidence of catastrophic hemorrhage in any vessel or organ. The heart had rare foci of mottling of a papillary muscle and the left ventricular free wall. The spleen was dark red and demonstrated areas of red discoloration indicative of infarct. Microscopic exam demonstrated focal cardiac coagulation necrosis with contraction bands, splenic infarcts, and markedly congested lung vasculature. Extensive evaluation of the lungs showed no evidence of amniotic fluid embolism, even with use of special stains (trichrome, mucicarmine, alcian blue, and cytokeratin immunoperoxidase (IPX) stain). Chronic bronchial inflammation was evident, as was early hyaline membrane formation. All other organs were microscopically unremarkable other than changes consistent with DIC. Retrospective review of the placenta pathology revealed the presence of hypertrophic vasculopathy, suggestive of pre-eclampsia. A postmortem blood Lamotrigine level was less than 0.9 mcg/mL. Clinical blood culture results were negative after 5 days. Based on the autopsy findings, placental pathology, and the history of the patient, the cause of death was ruled as complications of seizure disorder exacerbated by pre-eclampsia. The manner of death was considered natural.

Discussion

Women with a history of epilepsy have an increased maternal risk of morbidity and mortality in comparison to women of the general population [3], and epilepsy is a frequently encountered disorder affecting 1 in 200 pregnant women, [4]. Causes for increased risk of sudden death due to epilepsy in pregnancy may be related to decreased use of antiepileptic drugs (AED) due to concerns of teratogenicity and changes in clearance of drugs resulting in decreased serum levels [2]. In existing cases of seizure disorder prior to pregnancy, medication goals are to find the lowest effective dose using monotherapy to control seizure behavior based on seizure type. This predetermined dose, however, may not be as effective during the course of pregnancy. In some pa

Table 1. Patient Clinical Laboratory Values

White Blood Cell Count (WBC)	41.0 x 10^3/mm^3
Hematocrit	35.5%
Platelets	161 K/uL
INR	2.0
Prothrombin time (PT)	23.3 seconds
Activated Partial Thromboplastin time (aPTT)	114.3 seconds
Fibrinogen	158.0 mg/dL
Fibrin degradation products (FDP)	>20 ug/mL
D-dimer	>20 ug/mL
Potassium	7.2 mmol/L
CO2	7.2 mmol/L
Anion Gap (AGAP)	33 mmol/L
Creatinine	1.1 mg/dL
BUN	10 mg/dL
Calcium	7.7 mg/dL
Lactic Acid	9.2 mmol/L
Aspartate aminotransferase (AST)	1896 IU/L
Alanine aminotransferase (ALT)	1267 IU/L
Total Protein	6.0 gm/dL
Albumin	3.2 gm/dL
Urine protein	100 mg/dL

tients taking Lamotrigine during pregnancy, seizure control is worsened in the second trimester in comparison to the first, with decreased serum levels [5]. These changes can partly be explained by the physiologic changes that occur during pregnancy such as increased volume of distribution, increased renal clearance, altered hepatic enzyme activity, and a decline in plasma protein concentration. This is especially pronounced in the renal elimination of Lamotrigine which increases throughout pregnancy [6]. The patient's postmortem level of Lamotrigine was subtherapeutic (0.9 mcg/mL) when compared to a normal therapeutic reference range of 3.0-15.0 mcg/mL. This may represent poor compliance or inadequate dosing in pregnancy leading to subtherapeutic levels and ultimately SUDEP. However, postmortem AED levels can be difficult to interpret. For reasons not completely understood, decreases in serum concentrations of commonly used AED levels occur postmortem; these decreases may be due to altered protein binding or tissue redistribution of the drug reflecting pH changes of the blood which occurs after death [7]. In attempting to determine the cause of death, the patient's history (including AED levels measured during life), clinical presentation, autopsy findings, and postmortem AED levels should be considered. With the potential for poor patient compliance and inadequate dosing leading to subtherapeutic concentrations, a breakthrough seizure likely occurred in the presented case, ultimately leading to cardiopulmonary failure and death. The patient in the current case presented with physical and lab findings consistent with DIC, which is often associated with AFE in pregnancy. However there was no microscopic evidence found of amniotic fluid debris within the maternal lungs at autopsy, a necessary finding for diagnosis of AFE [8]. A rare consequence of seizure is DIC [9]. Resuscitation following sudden cardiac arrest has also been shown to markedly activate blood coagulation without a balanced activation of fibrinolysis leading to DIC [10]. Besides the aforementioned definition of SUDEP further criteria for diagnosis of SUDEP is that largely of exclusion. As demonstrated by Nashef; the victim had epilepsy, died unexpectedly while in a reasonable state of health, the event occurred suddenly during normal activities, in or around bed at home, and no obvious cause of death was found at autopsy. A definite diagnosis of SUDEP meets all these criteria and includes postmortem examination. The patient in this case met all criteria for SUDEP [11]. In addition to the physiologic changes in pregnancy complicating seizure control, women with epilepsy have an increased risk of pregnancy induced hypertension and pre-eclampsia by 1.7 fold [12]. One must then consider pre-eclampsia as a contributing cause leading to this patient's demise. Pre-eclampsia is defined by new onset hypertension, with systolic pressure >140 mmHg, or diastolic pressure >90mmHg, taken on two separate occasions at least four hours apart, after 20 weeks gestation, and proteinuria > 0.3 grams in a 24 hour urine sample, or protein to creatinine ratio >0.3, or random dipstick of 1+ if a quantitative measurement is unavailable. It may be accompanied by a platelet count of less than 100,000/ microliter, creatinine >1.1 mg/dL or doubling serum creatinine, elevated liver enzymes at least doubling the normal concentration, pulmonary edema, cerebral or visual symptoms, and potentially DIC [13]. Nulliparity and age less than 18 years old are risk factors of for pre-eclampsia [14]. The patient in the presented case had the aforementioned risk factors, seizure activity, and DIC all of which can occur as parts of the eclampsia spectrum; however, the fact remains that the patient had a poorly controlled pre-existing seizure disorder which can also account for her presentation. We do know the patient had regular prenatal care and no history of the criteria which defines pre-eclampsia. With the potential for several of her laboratory values to be explained by either epilepsy related seizure or eclampsia, both must be considered as contributing factors in this patient's death. Ultimately, the placenta examination provided histologic evidence of hypertrophic vasculopathy, consistent with pre-eclampsia. Consequently, this case was considered a case of death related to underlying seizure disorder, complicated by new onset pre-eclampsia. When considering cases where seizure-activity is believed to play a role in death, many challenges exist for the certifying official, not the least of which deals with attempting to correlate various underlying potential explanations for the seizures. In certain instances, multiple potential sources for the seizure activity exist. In the case presented, two potential explanations for sudden unresponsiveness due to seizure activity existed: underlying epilepsy and eclampsia. As such, both were considered contributory to death. One final point deserves mention in this case. Although rare, pregnancy in some patients instigates first episodes of arrhythmias which are otherwise unknown [15]. The patient's history leads us to believe she had no other pre-existing health problems and autopsy confirmed a structurally normal heart. However, cardiac arrhythmias have been considered to play a role in some SUDEP [16]. Adrenaline released during seizure activity can cause a prolongation of the QTc.

Hypoxia and ischemia caused by seizures may lead not only to prolonged QTc but also arrhythmia and sudden death [16]. The finding of a prolonged QTc in this case might represent a pre-existing cardiac conduction abnormality versus persistence of changes induced by the presumed seizure activity that caused sudden unresponsiveness. While some cardiac conduction system abnormalities may be diagnosed in postmortem samples via molecular testing methods [17], such testing tends to be cost-prohibitive for many death investigation agencies and was not able to be performed in the current case. Ultimately, as the ECG findings in this case may be explained by underlying seizure activity, it is the opinion of the authors that, in this case, the history, clinical and autopsy findings, and the lack of any other credible explanation, death was due to complications of seizure disorder exacerbated by previously undiagnosed pre-eclampsia. This unfortunate case serves to remind the medical community that seizure disorder on its own is a risk for sudden unexpected death, let alone in the setting of new onset pre-eclampsia. With the added physiologic changes due to pregnancy, a patient with epilepsy needs more diligent, multi-disciplinary management of their seizure disorder. This should not only include better patient education about the potential risks for seizures in pregnancy, but proper compliance of medications, and closer monitoring of therapeutic AED levels throughout pregnancy. In addition to better seizure control, there should be a heightened sensitivity for the risks of developing pre-eclampsia in these patients. It is interesting to consider the implication for change in managing pregnant patients with epilepsy: should their management include not only seizure control, but also thorough screening for pre-eclampsia in hopes of preventing the potentially devastating consequences of each? Is there a correlation between poorly managed epilepsy and the risk of pre-eclampsia? Will adequately dosing AEDs in this patient population improve the risks of pre-eclampsia in pregnant women with underlying epilepsy? Can a multidisciplinary approach to monitoring these patients improve outcomes? More research should be considered in this area. With closer monitoring and more effective patient education, SUDEP in pregnancy may be prevented or at least reduced.

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Declaration of Interest
None

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