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CASE REPORT

Witnessed sleep-related seizure and sudden unexpected death in infancy: a case report

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Abstract Witnessed reports of sudden death are rare, but critical to deciphering its mechanism(s). We report such a death in a seemingly healthy 8-month-old boy in whom seizures and respiratory distress in the prone position were witnessed upon discovery during a sleep period. Following cardiopulmonary resuscitation, anoxic encephalopathy resulted in "brain death" and withdrawal of life support after 2 days. The autopsy did not reveal a primary anatomic cause of death. Metabolic evaluation failed to uncover an inborn error of ammonia, amino, organic, or fatty acid metabolism. Seizures in this case may have been secondary to cerebral hypoxia–ischemia complicating cardiorespiratory arrest of unknown etiology. Yet, they may represent the first manifestation of idiopathic epilepsy, triggering cardiopulmonary arrest, analogous to the terminal events postulated in sudden and unexplained death in epilepsy. This report alerts the forensic community to the possibility that sudden and unexplained death in infants may be due to seizures.

Keywords Apnea · Apparent life threatening event · Epilepsy · Hypoglycemia · Sudden infant death syndrome (SIDS) · Sudden unexpected death in epilepsy (SUDEP)

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Introduction

The purpose of the forensic investigation in sudden and unexpected death in infancy (SUDI) is to explain the manner and cause of death; otherwise, the death remains unexplained, and is classified as in the sudden infant death syndrome (SIDS). SIDS is the sudden and unexpected death of an infant <12 months of age in which the terminal event is related to a sleep period, and the death remains unexplained after a complete autopsy and death scene investigation [1]. Typically a seemingly healthy infant is found dead after a sleep period, having died during sleep itself, or in one of the many transitions between sleep and waking during a sleep period [2, 3]. Virtually all instances of sudden and unexplained death in infants that occur during a sleep period are un-witnessed, with only one published witnessed account [4]. Parenthetically, sudden death in seemingly healthy infants during an awake period has been reported [5, 6]. Without witnessed reports, however, it is difficult to begin to discern the mechanism(s) of death during a sleep period, as silent death without a struggle suggests central apnea, cardiac arrhythmia, and/or failure to arouse to such adverse cardiorespiratory events; death with respiratory distress (e.g. grunting, stridor) suggests obstructive apnea or ineffectual gasping; and episodic movement of the extremities suggests seizures. In the one reported witnessed account, the infant was asleep on the sofa beside the day care provider and died within 15 min of the last check; the death was during sleep, silent, and without observations of tonic–clonic movements [4].

Seizures have long been suspected as a lethal factor in some SIDS deaths [7]. Presently, however, the limited available information for seizures in sudden death in infants has never included a report of a witnessed seizure immediately preceding death. In the following account, we

report the case of a seemingly healthy, 8-month-old infant discovered prone by his father, experiencing a convulsive seizure and in respiratory distress. Death post-cardiopulmonary arrest occurred after 2 days of ventilator support, and an autopsy did not reveal the primary cause of death.

Case report

Clinical history

The male infant was the product of a repeat cesarean delivery to a 30-year-old G4P4 mother with a pregnancy history notable for maternal depression treated with the selective serotonin reuptake inhibitor (SSRI) sertraline (dose and timing uncertain). The mother was not treated for depression in the preceding pregnancies, but continued her treatment with sertraline following the birth of the case infant. The mother smoked ½-1 pack of cigarettes/day throughout this pregnancy, as in previous pregnancies; there was no history of alcohol intake. Apgar scores are unknown, as are the results of placental examination. Birth weight was 7 pounds 2 oz (35 ‰) and length was 20 inches (50 ‰). The infant was discharged from the routine nursery without complications.

Initially the infant slept in a playpen; from approximately 6 months onward, however, he was routinely placed in the supine position in the adult bed between the two parents due to changes in their working schedules and infant feeding patterns. In the first month, the infant "spat up" at least 1 time/day, with occasional projectile vomiting, although he continued to gain weight. Gastro-esophageal reflux was not diagnosed, and the spitting decreased to 2–3 times/week by 6 months. At 5–6 months, the infant developed episodes when eating that consisted of arching of the back, approximately twice weekly. He stared upward and toward his left for up to 5 s around these episodes, followed by a wide smile and vigorous head shaking. The mother described these episodes as "like a tic," but did not consider them worrisome, and did not discuss them with the pediatrician. Only after the infant's death did she consider them to possibly be significant. These episodes were captured on videos when the infant was 6 months of age. The video documents the episodes as described, but there was no consensus by us that the brief staring spells were definitively seizures. Developmental milestones were appropriate, and the infant was described as a "happy, healthy" boy. The infants immunizations were up to date, and he did not have any adverse reactions to them. There was a positive family history of depression, but none of seizures, syncope, cardiac disorders, or sudden death.

On the morning of the death at 8 months of age, the infant awoke around 7 a.m., and "played, laughed, smiled." There was no fever or respiratory tract symptoms. At approximately 8 am, the infant was placed to sleep in the parents' bed with a bottle in the supine position. The father went into the bedroom to wake the infant at noon, his usual feeding time, and found the infant lying prone with his head turned to the side and repeatedly arching his back; he was making "grunting" sounds without cyanosis. The father called the mother who rushed home from work. She reported that the infant was unresponsive and grunting with his "eyes…rolled back in his head." Approximately every 30 s the infant reportedly arched his back and "curled [his hands] inward." The mother called 911 and told the responder that the infant was "having a seizure."

The paramedics took the infant to the local hospital where seizures were diagnosed, the infant was intubated and given intravenous anti-seizure medication (diazepam, lorazepam, phenytoin) with eventual cessation of the convulsions. A chest radiograph revealed normal heart and lungs. Metabolic evaluation included plasma ammonia, amino acid and acylcarnitine analyses, plus urine organic acid quantitation, which were all unrevealing. A severe metabolic acidosis with an increased anion gap and lactate elevation was clinically observed, thought consistent with the low perfusion state. The QT interval was not prolonged on electrocardiogram. Fundoscopic examination by ophthalmology revealed preretinal and interretinal hemorrhages bilaterally, considered secondary to valsalva retinopathy, a possible complication of seizures [8]. Magnetic resonance imaging of the brain revealed swollen gyri in the cerebral cortex, bilateral putamenal hyperdensities, and cerebellar tonsillar herniation, all consistent with acute (post-arrest) anoxic encephalopathy. The gyral pattern appeared normal without subtle malformations; the hippocampi, temporal lobes, and brainstem were well formed. The electroencephalograms after the onset of seizures and during clinical coma were diffusely abnormal. Subsequently a brain scan revealed bilateral lack of cerebral perfusion. The parents were questioned by social services; no evidence of foul play was found. There were no prior reports to Child Protective Services. A toxicology panel and skeletal survey were negative. The infant was declared "brain dead" 50 h after discovery, and ventilatory support was withdrawn.

Autopsy

Procurement of the grossly normal heart, liver, kidneys, intestine, and portions of the thymus, pancreas, and adrenal gland was performed for donation according to parental consent. Autopsy revealed a well-developed infant with no evidence of trauma except a small forehead contusion. The thoracic cavity did not have petechiae; the thymus was mildly involuted. Mild, focal bronchopneumonia was

present without aspiration. Mild mesenteric lymphadenopathy was noted by the forensic pathologist at autopsy. The brain was approximately 100 g above normal for body length; it was severely edematous with flattened sulci, broad gyri, and tonsillar herniation. There was no epidural, subdural, or subarachnoid hemorrhage. There were acutely shrunken neurons in the cerebral cortex, vacuolated and fragmented cerebral white matter, and hyper-eosinophilic Purkinje cells and pyknotic internal granule cells in the cerebellum; the thalamus was unremarkable. The brainstem and hippocampus were not examined. The brain changes were consistent with an acute (post-cardiac arrest) anoxic encephalopathy. The case was signed out as "Sudden Unexplained Infant Death" with "unsafe sleeping conditions" as contributing, and the manner of death as undetermined.

Discussion

We report a case of sudden death in an 8-month-old boy discovered seizing in the prone position during a sleep period. Within 2 days of the concurrent respiratory failure, he was declared "brain dead" and support was withdrawn. This case suggests that seizures may be a cause of sudden and unexpected death in infants that would otherwise remain unexplained had the seizures not been witnessed. The most appropriate classification of this infant's death, however, is problematic, as we envision three possibilities—death due to: (1) a primary cardiopulmonary "SIDS" event resulting, possibly, from primary brainstem pathology [2, 3] or cardiac channelopathy with secondary hypoxia-induced seizure; (2) a fasting-induced seizure in an undiagnosed inborn error of metabolism; or (3) an idiopathic seizure (as the sentinel "SIDS" event) which for the first time is witnessed in our case, and, analogous to sudden unexplained death in epilepsy (SUDEP), leading to cardiopulmonary arrest and sudden death. We believe it is impossible to determine the primary disorder in this case. Given that seizures do not invariably cause cardiopulmonary arrest [9], the present case nevertheless raises the possibility that primary seizures can play a causative role in sudden infant death.

This witnessed seizure with subsequent death in our case may represent the first clinical manifestation of idiopathic epilepsy (seizure disorder without recognized neurological conditions [10]). A primary brain lesion, potentially responsible for seizures, was not found at autopsy, but the severe changes of anoxic encephalopathy may have masked subtle epileptogenic anomalies. A consideration for an epileptogenic focus is a perinatal (hypoxic-ischemic) lesion that was too small to cause overt neurodevelopmental deficits. The metabolic evaluation and clinical chemistry data did not support the presence of an inborn metabolic error. In our case, the brief staring episodes around feeding noted first at 6 months raise the possibility of seizure activity prior to the lethal seizure at 8 months. Still, this diagnosis was not made when the infant was alive, there was not agreement within our group that the episodes on home videos were seizures, and there were no preterminal electroencephalograms performed. As a general observation, sudden, unexplained deaths occurring during bed sharing are typically silent, and do not wake the co-sleeper, which may be suspected with a seizure.

Of relevance to the potential role of seizures in SIDS is the link between acute life threatening events (ALTEs) and SIDS. ALTEs precede death in approximately 12 % of SIDS cases [11]. Seizures in turn occur in 6–16 % of ALTE cases, with episodic apnea and cyanosis as the predominate manifestation, and staring and stiffening additionally noted [12]. In-hospital recordings reveal that ALTEs can commence with an abnormality in the electroencephalogram, followed by hypoxemia within 30 s on average of the onset of epileptic discharges, and oftentimes apnea [12]. Severe hypoxemia has been implicated as a mechanism underlying SIDS, thought due, for example, to airway obstruction and rebreathing expired air [13]. Since epileptic discharges may induce hypoxemia, a seizure should likewise be considered a candidate [13]. Apnea has been reported in some infants who subsequently die of SIDS [13]. We speculate that apnea may be the sole manifestation of seizures, as ictal apnea without movement disturbances have been documented in infants [14]. Of note, while risk should not be confused with etiology, our case had several SIDS risk factors, including male gender, maternal smoking during pregnancy, and death in an adult bed [2, 3].

Although this case does not meet the SUDEP definition (lack of an epilepsy history), the purported mechanism of his death is nevertheless analogous to it. SUDEP is considered due to a seizure that triggers a fatal cardiac arrhythmia and/or respiratory arrest [11, 15]. Parallels have been made between SIDS and SUDEP, including the shared features of sudden unexplained death, male predominance, death typically during a sleep period, discovery prone, and rarely temporal lobe pathology [14, 15]. Moreover, defects in the brain's serotonergic network have been reported in both [2, 3, 15], with the suggestion that SIDS and SUDEP share common serotonergic mechanisms. (The relationship of prenatal SSRI exposure to brainstem serotonergic abnormalities or sudden death in infants is unknown). SUDEP as currently defined is rare in infants, representing approximately 4 % of pediatric cases of epilepsy [10]. Yet, we speculate it may be more common in infants if the first seizure is fatal and un-witnessed, and/or seizures are subclinical autonomic manifestations during sleep. Indeed, these cases may represent an infantile

SUDEP variant currently under the rubric of SIDS. In conclusion, our case alerts the forensic community to the possibility that sudden "unexplained" death in infants can be due to seizures.

Key points

1. A case of sudden unexpected death in a previously healthy 8-month-old infant boy who was discovered seizing and in respiratory distress during a sleep period is reported.
2. The case suggests that seizures may be a cause of sudden and unexpected death in infants whose death would have been unexplained had the seizures not been witnessed.
3. The cause of the seizures is unknown, but may have been the first manifestation of idiopathic epilepsy
4. The seizures may have represented a secondary complication of a primary cardiorespiratory event of unknown etiology that is postulated to underlie at least a subset of unexplained deaths, i.e. sudden infant death syndrome (SIDS), or alternatively, may have represented the "sentinel event" in SIDS that typically is unwitnessed.

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