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ORIGINAL PAPER

Sudden infant death while awake

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Abstract Epidemiologic data suggest that SIDS is related to the sleep state, but exiguous literature has addressed infants who had been awake at the time of sudden catastrophic deterioration and subsequent death. The aims of this study are to: (1) Report five infants who were awake at the onset of the lethal event, and (2) Discuss potential lethal pathophysiological events that may lead to these circumstances. The demographic and pathologic profiles of these cases are similar to SIDS. Altered responses to severe hypotension, bradycardia, and apnea, perhaps elicited by aspiration and mediated by cerebellar and vestibular structures, might be involved in the pathogenesis of these deaths. Comprehensive medical history review, investigation of the circumstances of death, thorough postmortem examination with ancillary studies, and preservation of tissues for gene testing, are crucial to explaining these deaths. Careful attention should be given to the awake or sleep state immediately prior to the sudden clinical collapse, and death of infants; those who were awake should be reported to enhance understanding of this phenomenon.

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Introduction

Sudden infant death syndrome (SIDS) has been linked to sleep since its earliest description [1]. In 1973, Beckwith emphasized this relationship in his report of 425 SIDS cases [2]. As a result, the current definition for SIDS states that the lethal episode has its onset presumably during sleep [3]. On the other hand, there is a very little information describing infants who were reportedly awake prior to catastrophic deterioration and sudden death, despite efforts at cardiopulmonary resuscitation (CPR). Therefore, the aims of this study are to: (1) Report five infants who were awake at the onset of the terminal event, and (2) Discuss potential lethal pathophysiological events that may account for these circumstances.

Materials and methods

The Rady Children's Hospital and Health Center Institutional Review Board has reviewed and approved the San Diego SIDS/SUDC Research Project (SDSSRP). A retrospective search of the SDSSRP SIDS database revealed only two cases of sudden unexplained infant death while awake between 1991 and 2005. Three additional cases were identified from the consultation files of HFK.

Case 1

A 23-day-old female was being fed and had ingested approximately one ounce of formula when she suddenly

became limp. It had been 3 h since her last feeding. Information regarding her behavior during this interval is unavailable. Efforts to "burp her" by leaning her forward were unsuccessful. Her father attempted to resume feeding when she became very agitated and her body stiffened. She started crying very hard, and was not calmed by either parent rocking or holding her. Her face became red and she began sweating, followed by gagging and difficulty breathing while being held. Concerned that she might have been choking, her mother flipped her on to her stomach and administered back blows without response. In a few seconds, she calmed down, but her eyes rolled back, she became pale, and gasped very slowly. Emergency assistance was summoned and arrived in 4 min, when slow breathing was observed. Emergency personnel observed her pallor and placed her back into her mother's arms, when she became completely limp and sustained a cardiac arrest. She was immediately transported to the hospital by ambulance with CPR in progress and arrived in 18 min; death was pronounced shortly after the arrival.

Her medical history reveals that she was delivered at full term by scheduled c-section for cephalopelvic disproportion. Her Apgar scores were 9 and 8 at 1 and 5 min, respectively. She experienced transient tachypnea of the newborn (TTN) that resolved, and she was discharged after a chest radiograph revealed clear lungs. Her mother's medical history is significant for Crohn's disease and anemia. The father's medical history is unavailable.

At the postmortem examination, the body was well developed and well nourished. Radiographs did not reveal evidence of injuries or fractures. The body length was 53 cm (50th percentile for age) and weight was 3,629 g (25th percentile for age); the head circumference was 35.6 cm (25th percentile for age). The heavy lungs exuded frothy fluid from the cut surfaces. Microscopic examination revealed diffuse pulmonary congestion, focal mild hemorrhage, and evidence of distal aspiration of gastric contents. The small arterioles revealed peripheral extension of medial smooth muscle. The heart was structurally normal, but revealed focal, mild subendocardial necrosis without inflammation or fibrosis. The stomach contained <1 ml of white viscous fluid. Stress changes were not present in the thymus or adrenals.

The scalp, calvarium, cranial fossae, and dural sinuses were unremarkable. The 500 g brain (expected 422 g [4]) was grossly normal, and the meninges were thin and transparent. Microscopic sections of the cortex, subcortical white matter, cerebellum, and pons showed no abnormalities; specifically, hypoxic ischemic injury and disordered maturation were not seen.

Postmortem toxicology and microbiology were negative; vitreous chemistry and metabolic screening were apparently not performed. The medical examiner assigned the cause of death as "undetermined." The decedent's tissues were tested by Dr. Michael Ackerman, Mayo Clinic, for Long QT syndrome (LQTS) with negative results.

Case 2

An awake 5-week-old male had been crying intermittently while being held supine by his grandmother after being bathed, dried, and diapered. He then appeared to gasp, and subsequently became apneic. CPR was initiated by the parents and continued by police who found him without vital signs. CPR was sustained *en route* to the hospital emergency department, where initial blood pressure was measured at 126/102 mmHg, and 225/168 mmHg 10 min later. Abdominal palpation suggested hepatomegaly. He was pronounced dead shortly thereafter.

He had been born vaginally following an uncomplicated pregnancy. Birthweight was 2,920 g (approximately the 10th percentile for age). Crown–heel length and head circumference at birth measured 51 cm (50–75th percentile for age) and 34 cm (10–25th percentile for age), respectively. Perinatal diagnoses were term neonate with right jaw flattening with tilt and right torticollis. He had been seen by a pediatrician 2 weeks prior to his death for colic but was otherwise healthy. He was exclusively breastfed.

At the postmortem examination, the body weight and length were 3,880 g (10–25th percentile for age) and 55 cm (25–50th percentile for age), respectively. Head circumference measured 36 cm (approximately 5th percentile for age). There was evidence of resuscitation. The lungs were congested, but not edematous or consolidated. The heart weighed 37 g (expected heart weight for body weight 21 g; 95th percentile confidence limits 14–31 g [5]), but was structurally and microscopically normal. The liver weighed 133 g (expected 136 g [4]) and revealed mild microvesicular change in hepatocytes. Stress changes were not present in the thymus or adrenals.

The brain weighed 470 g (expected 489 g [4]), and had a normal appearance and configuration. Microscopic examination revealed scattered reactive astrocytes in the hippocampus and medulla. Cerebellar tissue was not examined microscopically.

Toxicology and microbiology were negative. Vitreous chemistry and metabolic screening were within normal limits. The originally assigned cause of death was "sudden infant cardiac arrest of undetermined etiology," with mild nonspecific cardiomegaly contributing.

Case 3

An awake 6-week-old white male became "irritable" while being breastfed. His mother sat him up, patted his back,

and then placed him on her shoulder to burp him when he let out a cry and became limp. Medical assistance was summoned and he was transported to a hospital, where he died despite resuscitative efforts.

He had been delivered vaginally at 40 weeks gestation. His birth weight was 3.6 kg (50th percentile for age) and his Apgar scores were 9 and 9 at 1 and 5 min, respectively. His immunizations were current. He was breastfed with formula supplementation. His anamnestic history was unremarkable.

At autopsy, the body was well developed and normally nourished, weighing 5,430 g (75th percentile for age) and measuring 62 cm (95th percentile for age) in length; his head circumference was 38.5 cm (25–50th percentile for age). Postmortem radiography of the head, torso, pelvis, and extremities showed no bony abnormalities. Foreign material and gastric contents were not present in the lumens of the oral cavity or airways; however, frothy fluid was present in the distal trachea and main bronchi. The heavy lungs revealed moderate diffuse edema but not consolidation. The stomach contained mucoid red fluid without gastric contents. The middle ears did not reveal purulent or serous fluid. Moderate microvesicular fatty change was present in the 192 g liver (expected weight 200 g [4]).

Neuropathological evaluation revealed no evidence of scalp or skull trauma. The brain weighed 560 g (expected weight 660 g [4]), and was externally normal. Atrophy and hydrocephalus *ex vacuo* were not identified. Bilateral acute hypoxic-ischemic neuronal injury was identified microscopically in Sommer's sector of the hippocampus. Sections of the cerebral cortex and white matter, midbrain, pons, cerebellum, medulla, spinal cord, and the eyes and optic nerves, were normal.

Microbiology and metabolic screening were within normal limits. Vitreous chemistry revealed glucose 14 mg/dl, urea nitrogen 6 mg/dl, creatinine 0.7 mg/dl, sodium 164 mmol/l, and chloride 148 mmol/l. The prosecting pathologist attributed the death to SIDS with mild dehydration.

The EKGs of both parents and an older sibling were normal, and without any evidence of long QT syndrome. Molecular testing of the decedent's tissues did not identify mutations associated with long QT syndrome.

Case 4

This 2-month 3-day-old male was a subject in our previous report, in which we discussed difficulties in determining awake or sleep state in some cases of sudden infant death [6]. On the evening of his death, he had saline sprayed into each nostril to treat dried mucus. One minute later, his nasal passages were suctioned with a bulb syringe. Awake and happy, he was placed on his grandfather's chest when he suddenly wheezed twice and became immediately limp and gasping, followed by apnea. CPR was quickly initiated by a parent and continued by emergency personnel, who found him with fixed pupils, cool, and pale. The liver was palpated three finger breadths below the costal margin. He was transported to the emergency room by ambulance, where he failed to respond to CPR and was pronounced dead 15 min later.

His past medical history reveals that he was delivered vaginally of a 31-year-old woman, as the first born of twin boys at 34 weeks gestation after an otherwise uncomplicated pregnancy. His birth weight and length were 2,955 g (10–25th percentile for age) and 51 cm (50–75th percentile for age) respectively. Head circumference at birth was 34 cm (10–25th percentile for age). After 5 days hospitalization for evaluation and treatment of neonatal jaundice, he was discharged home. He was breastfed only, and had received his hepatitis immunizations. One week after hospital discharge, he had a single episode of sudden onset of limpness without cyanosis or apnea, from which he promptly recovered after his mother yelled his name.

The infant's mother has two great aunts, each of whom had prematurely born twin boys; one boy from each set died at an age of 6 weeks of an unexplained cause. The first born daughter of the infant's mother's great grandmother died of an unexplained cause at an age of 6 weeks.

The postmortem examination revealed a normally developed and nourished male infant. Weight, length, and occipitofrontal circumference measured 4,500 g (approximately the 10th percentile for age), 53.5 cm (<5th percentile for age) and 37.5 cm (5–10th percentile for age), respectively. The heart was structurally normal. The lungs were congested. Stress changes were not present in the thymus or adrenals. The liver weighed 166 g (expected 134 g [4]) and revealed congestion and mild centrilobular microvacuolar fatty change.

The brain weighed 562 g (expected 456 g [4]), and was grossly normal. Edema, ventricular compression, and hydrocephalus were not present. Microscopic sections of the cingulate gyrus, corpus callosum, caudate, central white matter, internal capsule, hippocampus, entorhinal cortex, and cerebellum without dentate nucleus revealed scattered astrocytes in the hippocampus, but no other abnormalities.

Postmortem toxicology was negative, microbiology was noncontributory, and vitreous chemistry was within normal limits. Metabolic screening was normal. The medical examiner signed the case out as SIDS.

Subsequently, the decedent's mother and maternal grandmother underwent electrocardiography; the QTc was 455 ms for the mother, and 452 ms for the grandmother.

Appropriate tissue from the decedent was unavailable for molecular testing for long QT syndrome.

Case 5

An awake 8-month-old white male was being fed by a babysitter when he "arched back, threw up and went limp." Cardiopulmonary resuscitation (CPR) was initiated in <5 min and continued by first responders, but he could not be revived. Newborn screening results were within normal limits, and his past medical history was unremarkable.

At autopsy, the body weighed 9545 g (50–75th percentile for age), and the body length and head circumference measured 78.7 cm (>95th percentile for age) and 45.7 cm (75th percentile for age), respectively. Injuries were not identified by external examination or radiographs. The lungs were congested, and the heart was normal. Superficial mucosal hemorrhages were focally present in the gastrointestinal tract; the liver revealed focal mild microvacuolar fatty change.

The dura displayed acute intradural hemorrhage without fibrosis, hemosiderin deposition, or neomembrane formation. The brain weighed 980 g (expected weight 1,050 g [4]), and with the exception of mild fourth ventricular dilatation, was normal without gross and microscopic evidence of edema, hypoxic-ischemic injury, heterotopias, gliosis, storage disease, inflammatory infiltrates, cystic change, or calcification in the right frontal cortex, hypothalami, right hippocampus, distal medulla, and upper cervical spinal cord. The arcuate nucleus, olive, cranial nerve nuclei, and subiculum were normal bilaterally. The right hippocampal dentate was folded back upon itself; however, other abnormalities were not seen. The meninges were normal.

Postmortem toxicology was negative. Microbiology, vitreous chemistry, and metabolic screening were apparently not performed. The prosecting pathologist's diagnosis was "sudden unexpected death in infancy."

Discussion

Selected demographic and pathologic data of the five cases discussed in this report are summarized in Tables 1 and 2. All were white, and four were male. Only one was born prematurely. Exposure to pre- or post-natal smoking was not known in any case. Intrathoracic petechiae were identified in four of the five cases. Gross and microscopic examination and ancillary postmortem studies did not reveal evidence of clinically unrecognized metabolic

Table 1 Selected demographics and clinical findings

Case	Age (week)	Sex	Gestation	Delivery	APGAR		Perimortem circumstances	CPR attempted
					1 min	5 min		
1	3	F	Full-term	Cesarean	9	8	Bottlefed	Y
2	5	M	Full-term	Vaginal	Unknown	Unknown	In caregiver's arms after bath	Y
3	6	M	Full-term	Vaginal	9	9	Breastfed	Y
4	8	M	Premature[a]	Vaginal	Unknown	Unknown	In caregiver's arms following nasal suctioning	Y
5	35	M	Full-term	Unknown	Unknown	Unknown	Bottlefed	Y

[a] Prematurity is defined as <37 weeks gestation

Table 2 Selected postmortem findings

Case	Brain weight/ expected g	Scleral or conjunctival petechiae	Intrathoracic petechiae	Pulmonary hemorrhage[a]	Aspiration of gastric contents	Bladder contents	Metabolic screening	Vitreous chemistry	Postmortem cultures	Toxicology
1	500/422	No	No	3	Yes	Empty	NP[b]	NP	Negative	Negative
2	470/489	No	Yes	0	No	Empty	Normal	Nondiagnostic	Negative	Negative
3	560/660	No	Yes	1	No	Empty	Normal	Nondiagnostic	Contaminants	Negative
4	562/456	No	Yes	3	No	Empty	Normal	Nondiagnostic	Negative	Negative
5	980/1,050	No	Yes	Unknown	No	Unknown	NP	NP	NP	Negative

[a] Pulmonary hemorrhage semiquantitative score: 0 = absent; 1 = mild; 2 = moderate, focal; 3 = moderate, multifocal; 4 = diffuse, severe [7]

[b] NP = Not performed

disorders, congenital anomalies, neoplasms, dysplastic growth, inflicted injuries, immunodeficiency disorders, poisoning, or electrolyte imbalance. There was no evidence of trauma in any of the cases.

It is noteworthy that the ages of three of these cases were ≤6 weeks, an age range younger than that associated with most SIDS cases, whose deaths occur most commonly between 8 and 20 weeks [8]. Given the small number of cases, conclusions can not be reliably drawn about ethnicity, gestational age, and family history, although, in Case 4, there was a history of multiple sudden infant deaths suggesting an underlying inherited disorder. It is unfortunate that data regarding exposure to cigarette smoke were unavailable, given its important contribution to the risk of SIDS [9].

The original assigned cause of death was SIDS in two cases, undetermined in two cases, and sudden unexpected death in infancy (SUDI) in one. From 1989 to 2004, sudden infant death syndrome (SIDS) was defined by the NICHD as: "the sudden death of an infant less than 1 year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history"[10]. Each of the cases with the available information would fulfill the NICHD criteria for SIDS [10], and the original SIDS definition proposed by Beckwith in1969 [11]. But in order to incorporate information gained during the 15 years after the NICHD definition was put forth, SIDS was redefined by an expert panel meeting in San Diego, California, in January 2004 as "the sudden and unexpected death of an infant under 1 year of age, *with onset of the lethal episode apparently occurring during sleep*, that remains unexplained after a thorough investigation, including performance of a complete autopsy, and review of the circumstances of death and the clinical history" [3]. Therefore, the awake state of these five cases precludes categorizing them as SIDS [3]. However, they do fulfill criteria for another category of sudden infant death created by the San Diego panel, Unclassified Sudden Infant Death (USID), which includes "deaths that do not meet the criteria for category I or II SIDS, but for which alternative diagnoses of natural or unnatural conditions are equivocal" [3].

Irrespective of the diagnostic label, the precise underlying mechanisms of death in each of these cases remain unknown. It is noteworthy that three cases (1, 3, and 4) underwent a change in body position immediately preceding the onset of the terminal event; case 1 also sweated and became pale before collapsing, thus raising the possibility of dysautonomia, especially since some of these disorders are occasionally associated with sudden death [12, 13]. These disorders may also be familial; hence it is of interest that a history of multiple sudden deaths was noted in the family of Case 4. Disordered cerebellar/vestibular compensatory responses (including severe hypotension and bradycardia) to respiratory or cardiovascular challenges, such as changes in position, may precede sudden death [14, 15]. Signals resulting from position change are transmitted from the vestibular nuclei and inferior olive to the cerebellum, from which projections are made to reticular and rostral ventrolateral medullary sympathetic areas [16]. Compensatory cardiovascular responses are mediated via vestibular signals transmitted to sympathetic preganglionic neurons in the spinal cord; vestibular effects on respiratory motor neurons are mediated partially by neural circuits, apart from those typically involved in the generation of respiration. In a study of term born infants with a mean age of 7.9 weeks, the head-up tilt to 60° maneuver from the prone sleep position resulted in diminished blood pressure responses, as a consequence of reduced vasomotor tone and peripheral vasodilatation [17]. The relationship of these responses to published subsets of SIDS cases with known defects in neurotransmitter receptors involving chemoreception and cardiovascular control may be relevant to our cases, since there might have been a failure in adequate autonomic compensation to an event which elicited a cardiovascular collapse [14, 15, 18–23].

Gasping was observed in three infants (1, 2, and 4), and has been documented elsewhere in infants being monitored immediately prior to death. In his analysis of nine such infants, Poets documented that three were already gasping at the time of the first monitor alarm, and in four others, it occurred within 2.7 min [24]. Bradycardia without evidence of heart block or ventricular tachycardia occurred in seven infants as the primary cause of the alarm. Since gasping only occurs if PaO_2 is <5–15 mm Hg, he concluded that the seven infants who gasped at or shortly after the first monitor alarm were already severely hypoxemic. In his subsequent review of data pertaining to mechanisms of apparent life-threatening events (ALTE) and sudden infant death, Poets concluded that severe hypoxemia and gasping, but not prolonged apnea, were common; the mechanism causing hypoxemia and reasons for ineffective gasping to resuscitate the infant from hypoxemia remained unexplained [25].

Case 4 had saline sprayed into each nostril before gasping, becoming limp, and finally apneic. Cases 1, 3, and 5 were all being fed at the onset of the terminal event. Case 1 revealed aspiration of gastric contents into the lungs. In a previous study, we identified aspiration of gastric contents into 10 (14%) of 69 cases of SIDS infants who had not undergone CPR [26]. Sudden death preceded by apnea, bradycardia, and hypotension after pharyngeal contact with gastric aspirate or foreign fluid has been documented in developing lambs [27], and recovery is dependent upon the

integrity of cerebellar and other medullary mechanisms that respond to extremes of blood pressure change [28, 29]. Antecedent events common in early development, including repeated minimally-hypoxic events, can compromise that integrity [30]. In mice that have had saline infused into the pharynx during hypoxic gasping, reflexive swallowing facilitates successful autoresuscitation [31]. In cases where swallowing does not occur, autoresuscitation fails, presumably because of intrapulmonary aspiration. This finding supports Stevens' observations of human infants who died rapidly from unknown causes when he witnessed repeated successful autoresuscitations in the absence of regurgitation; however, autoresuscitation eventually failed when vomitus appeared in the upper airway [32]. These data suggest that agonal aspiration may be the *coup de grace* in some cases of sudden infant death [33].

Fatal cardiac arrhythmias also deserve consideration as the cause of death in our cases. LQTS, for example, has been documented in a small percentage of infants dying suddenly and unexpectedly [34]. This may be especially important in case 4 with the strong family history of sudden death in early infancy across several generations. The QTc of the infant's mother and grandmother were both less than 460 ms, outside the range considered likely for the diagnosis of LQTS; however, these values do not exclude the diagnosis. Further, LQTS is usually an autosomal dominant disorder, whereas the distribution of familial infant deaths in case 4 is consistent with inheritance being either X-linked (with the one female case being unrelated), or dominant with incomplete penetrance. Recent studies have shown that the frequency of mtDNA T3394C polymorphism in SIDS did not differ statistically from control subjects [35]. Other studies from the same group of investigators have expanded the spectrum of functionally characterized SCN5A variants associated with SIDS that may correlate with enhanced susceptibility to arrhythmias and sudden death [36]. In the final analysis, we did not consider our cases as examples of SIDS, given their awake state prior to collapse and death. Therefore, literature associating SIDS with long QT syndrome may not be entirely relevant.

Minor pathologic findings (including but not limited to hippocampal and medullary reactive astrocytes, mild cardiomegaly, pulmonary congestion, pulmonary edema, moderate microvesicular hepatic fatty change, and hepatic congestion) were identified in individual cases, but none of these findings were considered sufficiently severe to account for or contribute to any of the deaths.

In conclusion, with the exception of being awake at the onset of their terminal events, the demographic and pathologic profiles of these cases are similar to those of SIDS. Altered responses to severe hypotension, bradycardia, and apnea perhaps elicited by aspiration and mediated by cerebellar and vestibular structures may be involved in the pathogenesis of these deaths. A genetic disorder with inheritance being either X-linked or dominant with incomplete penetrance cannot be excluded in the family of case 4. Comprehensive medical history review, investigation of the circumstances of death, thorough postmortem examination with ancillary studies, and preservation of tissues that may be used for gene testing are crucial to explaining these deaths. Reporting of cases of infants who were awake prior to sudden collapse and death is recommended.

Educational message

1. Historically and by its current definition, SIDS is believed to occur during sleep.
2. The demographic and pathologic profiles of our cases, who were reportedly awake immediately prior to their clinical collapse and subsequent death, are similar to SIDS.
3. The pathogenesis of these deaths may involve inappropriate responses to hypotension, bradycardia, and apnea, perhaps, elicited by aspiration and mediated by cerebellar and vestibular structures.

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