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ORIGINAL ARTICLE

Subtle Autonomic and Respiratory Dysfunction in Sudden Infant Death Syndrome Associated With Serotonergic Brainstem Abnormalities: A Case Report

Hannah C. Kinney, MD, Michael M. Myers, PhD, Richard A. Belliveau, BA, Leslie L. Randall, RN, MPH, Felicia L. Trachtenberg, PhD, Sherri Ten Fingers, RN, Mitzi Youngman, AA, Donald Habbe, MD, and William P. Fifer, PhD

Abstract

Sudden infant death syndrome (SIDS) is characterized by a sleep-related death in a seemingly healthy infant. Previously, we reported abnormalities in the serotonergic (5-HT) system of the medulla in SIDS cases in 2 independent datasets, including in the Northern Plains American Indians. The medullary 5-HT system is composed of 5-HT neurons in the raphé, extra-raphé, and arcuate nucleus at the ventral surface. This system is thought to modulate respiratory and autonomic function, and thus abnormalities within it could potentially lead to imbalances in sympathetic and parasympathetic tone. We report the case of a full-term American Indian boy who died of SIDS at 2 postnatal weeks, and who had subtle respiratory and autonomic dysfunction measured prospectively on the second postnatal day. Cardiorespiratory assessment of heart rate variability suggested that the ratio of parasympathetic to sympathetic tone was higher than normal in active sleep and lower than normal in quiet sleep in this case. At autopsy, arcuate nucleus hypoplasia and 5-HT receptor-binding abnormalities in the arcuate nucleus and other components of the medullary 5-HT system were found. This case suggests that medullary 5-HT system abnormalities may be able to be identified by such physiological tests before death. Replication of these findings in a large population may lead to the development of predictive cardiorespiratory assessment tools for future screening to identify infants with medullary 5-HT abnormalities and SIDS risk.

Key Words: Arcuate nucleus of the medulla oblongata, Autonomic nervous system, Autoradiography, Head-tilt, Heart rate variability.

INTRODUCTION

Despite substantial reductions in sudden infant death syndrome (SIDS) resulting from the recommendation of supine sleep position, SIDS remains the leading cause of post-neonatal infant mortality, with an overall incidence of 0.6 per 1000 live births (1). SIDS is the death of an infant less than 1 year of age that remains unexplained after review of the clinical history, complete autopsy, and death scene investigation (2). A wide disparity in SIDS rates exists among different racial and ethnic groups, with a rate among the American Indians of the Northern Plains almost 6 times the national rate for white infants (3, 4). Several prospective studies of infants that subsequently die of SIDS suggest that subtle abnormalities in respiratory and/or autonomic control and arousal are involved in its pathogenesis (5–7). Moreover, studies in normal preterm and term infants indicate that the period of SIDS risk is associated with diminished arousal and altered respiratory and autonomic function in the prone position or face-covered, supine position that potentially increases the vulnerability to SIDS (8–11). We have reported abnormalities in the serotonergic (5-HT) system of the medulla oblongata of SIDS cases in 2 independent datasets, including one in the Northern Plains American Indians (3, 12). The medullary 5-HT system is comprised of 5-HT neurons in the midline (raphé) and lateral (extra- raphé) regions that are involved in control of respiratory and autonomic function, temperature, pain, chemosensitivity to carbon dioxide/pH, airway reflexes, and arousal (5, 13–20). This system is postulated to modulate autonomic and somatomotor responses to homeostatic stressors, for example, hypoxia, hypercarbia, and changes in blood pressure, according to the level of arousal (5, 17, 20). The arcuate nucleus at the ventral surface of the medulla is a component of this system (5) and contains 5-HT neurons homologous to 5-HT neurons at the ventral surface of the rat medulla shown to be sensitive to carbon dioxide/pH (5, 18, 19). Aplasia or

From the Department of Pathology (HCK, RAB), Children's Hospital and Harvard Medical School, Boston, Massachusetts; the Departments of Psychiatry and Pediatrics (MMM, WPF), Columbia University, New York, NY; Northwest Portland Area Indian Health Board (LLR), Northwest Tribal Epidemiology Program assigned from CDC, Division of Reproduction Health, Portland, Oregon; the Nursing Department (STF, MY), Oglala Lakota College, Pine Ridge, South Dakota; the Department of Pathology (DH), Rapid City Regional Medical Center, Rapid City, South Dakota; and New England Research Institute (FLT), Watertown, Massachusetts.

Send correspondence and reprint requests to: Hannah C. Kinney, MD, Department of Pathology, Children's Hospital Boston, 300 Longwood Avenue, Boston, MA 02115; E-mail: hannah.kinney@childrens.harvard.edu

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hypoplasia of the arcuate nucleus has been reported in 5% to 56% of different SIDS populations (12), and lowered tritiated-lysergic acid diethylamide (^{3}H-LSD) binding to 5-HT_{1A-D} and 5-HT_2 receptors, in addition to altered binding in raphé and extra-raphé regions containing 5-HT cell bodies, has been reported in this site as well (3, 12).

The medullary 5-HT system is likely abnormal before the death of SIDS infants but this defect is not lethal until exposure to exogenous stressors during a critical period of development (Triple Risk Model [5]). To date, however, there are no published studies that demonstrate a medullary 5-HT system abnormality in a SIDS infant with subtle dysfunction in respiratory and/or autonomic control documented before death. As a result of a fortuitous overlap of prospective physiological and autopsy studies of American Indian infants in the Northern Plains, we were able to examine the medullary 5-HT system in a 2-week-old SIDS infant at autopsy in whom sensitive studies of respiratory and autonomic function were performed at birth and subsequently found to be abnormal. This case, reported subsequently, is important because it suggests that an abnormality in the medullary 5-HT system may be able to be identified by such physiological tests before death. These results underscore the need to confirm the findings in a larger population to develop potentially predictive autonomic assessment tools for future pediatric screening.

Clinical Report

The infant's mother was 22 years old, gravida 3, para 3. Her medical history was remarkable for alcohol abuse starting at age 14, suicidal ideation, and the diagnosis of codependency syndrome at the age of 16 years. She relapsed after participation in an alcohol treatment program. She reported drinking 6 drinks per day, 5 days per month in the 3 months before recognition of pregnancy, no drinks during the first and third trimesters, and 6 drinks per day, 4 days per month in the second trimester. She began cigarette smoking when she was 17 years old. She reported smoking 3 cigarettes per day in the periconceptional period, 2 cigarettes per day in the second trimester, and no cigarettes in the first or third trimesters. Of note, maternal drinking and smoking during pregnancy are major risk factors for SIDS (4, 21, 22). There were 2 prenatal visits, the first at 26 gestational weeks.

The case infant died at 2 postnatal weeks. He was born at 38 gestational weeks with a birth weight of 3402 g, length of 48 cm, and head circumference of 35.5 cm. The delivery was spontaneous and vaginal. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. There was thin meconium staining. The infant was admitted to the routine nursery and was discharged on the third day. No medical problems were noted at any time before death. Physiological studies were performed on the second day of life (see subsequently). On the day of death, the mother fed the infant formula at approximately 6 AM and then placed him to sleep. She found him dead 2.5 hours later in the supine position with his face covered by a sheet, blanket, and quilt.

The autopsy was performed under the auspice of the Aberdeen Area Infant Mortality Study (3, 4). There were intrathoracic petechiae (a characteristic finding in SIDS), as well as a minimally patent ductus arteriosus that was considered slightly delayed in closure but clinically insignificant. The heart and lungs were otherwise normal. Standard neuropathologic examination revealed heavy brain weight (430 g; expected, 358–382 g) consistent with agonal vascular congestion, moderate astrogliosis of the cerebral white matter and inferior olive of the brainstem, borderline delayed myelination, and a microscopic, focal scar of the cerebellar cortex, all findings previously reported in SIDS brains and postulated to reflect perinatal hypoxia (21). The death was classified as SIDS by the regional Perinatal Infant Mortality Review Committee without knowledge of the physiological and/or brainstem neurochemical studies.

MATERIALS AND METHODS

Cardiorespiratory Analyses

The infant was one of 275 enrolled in a prospective study to identify autonomic and respiratory parameters potentially predictive of SIDS in the high-risk population of American Indians in the Northern Plains. Cardiorespiratory assessments were made within 72 hours of birth. Infants were tested shortly after feeding in the prone position. When possible, cardiorespiratory measures were taken during both active and quiet sleep, as defined by us previously (23) and were continued during sleep through a standardized tilting protocol (24). Values for heart rate, respiratory rate, and several indicators of variability in r-wave to r-wave intervals (RRi) were computed in 1-minute blocks throughout the test period (Table 1).

Brainstem Analysis

One half of the brainstem was fixed in formalin at autopsy and examined in serial sections according to standard methods. The other half was frozen and analyzed in serial sections with quantitative tissue receptor autoradiography. Tritiated-LSD binding to 5-HT_{1A-D} and 5-HT_2 receptors (4, 5, 12), and ^{3}H-nicotine binding principally to $\alpha4\beta2$ nicotinic receptors (22) were analyzed in alternate sections. In Table 2, the binding values of the infant are compared with the mean values of binding in selected nuclei in the medulla and pons of SIDS ($n = 75$) and control ($n = 21$) cases from our American Indian (3) and non-American Indian datasets (5, 12). The comparison values from the 2 studies were combined because there were no overall differences in binding levels in either the 2 SIDS groups or the 2 control groups from these datasets (3, 12). The controls died of acute known causes that were established at autopsy, as previously described (3, 5, 12, 22).

RESULTS

Analyses of State-Related Cardiorespiratory Function

For 2 global measures of RRi variability, standard deviation of RRi (SD-RRi), and intraquartile range of RRi (IQR-RRi), the infant exhibited higher than average variability in active sleep and below average variability in quiet sleep (Table 1). A similar state-dependent pattern was observed for the root mean square of successive differences in RRi (RMSSD), an index of high frequency variability (23). Extreme values were noted for several measures in respiratory or

TABLE 1. The Physiological Characteristics of the Reported Case (Case) Compared with All Other Infants in the Study (Cohort, total n = 275) in Active Sleep (top panel), Quiet Sleep (middle panel), and the Difference Between Active and Quiet Sleep (lower panel)*

Measures	Cohort Mean ± SD	Case Value	Percentile
Active Sleep			
RspR (cpm)	53 ± 9	70	100
HR (beats/min)	125 ± 12	120	38
SD-RRi (msec)	28 ± 13	39	83
IQR-RRi (msec)	10 ± 6	13	80
RMSSD-RRi (msec)	10 ± 3	12	61
Sustained-RRi (%)	38 ± 9	61	99
Change in HR to tilt (bpm)	+1.3 ± 6.5	+5.7	76
Quiet Sleep			
RspR (cpm)	46 ± 10	69	97
HR (beats/min)	121 ± 13	128	71
SD-RRi (msec)	24 ± 12	19	36
IQR-RRi (msec)	8 ± 4	7	41
RMSSD-RRi (msec)	11 ± 4	10	39
Sustained-RRi (%)	35 ± 8	30	23
Change in HR to tilt (bpm)	—	Not available for case infant†	—
Active Sleep Minus Quiet Sleep			
RspR (cpm)	+8.0 ± 7.5	+1.2	18
HR (beats/min)	+3.1 ± 6.8	−8.5	98
SD-RRi (msec)	+4.5 ± 10.7	+20.1	93
IQR-RRi (msec)	+2.2 ± 3.6	+6	92
RMSSD-RRi (msec)	−0.9 ± 2.0	+2	92
Sustained-RRi (%)	+2.2 ± 7.7	+31	87

*, Each variable was ranked from lowest to highest, and the percentile score of the case for each variable was computed. Changes in heart rate to tilt were those from the 30 seconds before a gradual 30° head-up tilt to the second 30-second period while in the tilted position.

†, Before the head-up tilt, the infant was in quiet sleep (QS) for 3 minutes before transitioning to active sleep (AS). Five minutes of active sleep were recorded before initiation of the tilt. After returning to the flat position from the head-up tilt, the infant became "fussy" and the test ended.

SD, standard deviation; RspR, respiratory rate; HR, heart rate; SD-RRi, standard deviation of the R-R interval; IQR-RRi, intraquartile range of the R-R interval; RMSSD-RRi, root mean square of successive differences in R-R interval.

autonomic function (Table 1). The infant had 1) high respiratory rates in both active and quiet sleep; 2) in active sleep, a high incidence of sustained RRi changes (that is, 2 consecutive increases or 2 consecutive decreases); 3) an unusually large state difference in heart rate and in the opposite direction from the majority of infants (66%) who have higher heart rate in active sleep; and 4) larger than norm differences between active sleep and quiet sleep in all 4 measures of RRi variability. In addition, the infant had a larger than average increase in heart rate in response to a 30° head-up tilt (Table 1).

Brainstem Analysis

The brainstem was histologically remarkable for almost complete absence of the arcuate nucleus (Fig. 1). As reported previously, in 5 of the 12 medullary nuclei analyzed, SIDS infants had significantly altered ^{3}H-LSD binding (3, 12), notably in the components of the medullary 5-HT system (that is, raphé obscurus, gigantocellularis, paragigantocellularis lateralis, intermediate reticular zone, and arcuate nucleus). In the arcuate nucleus, paragigantocellularis lateralis, and gigantocellularis, the case infant had levels of binding below the mean of the SIDS group (Table 2). This deficit was particularly striking in the arcuate nucleus with an 87% reduction in binding compared with controls (Table 2). In the case infant, lower ^{3}H-LSD binding was also found in nuclei in the pons, as well as the medulla, and involved the locus ceruleus and subdivisions of the reticular formation in the pons (nucleus pontis oralis and nucleus parabrachialis lateralis) and the basis pontis (cerebellar relay); for these regions, the mean binding values were not lower in the SIDS group in either published dataset (3, 4). Differences in binding between SIDS and controls were not detected for ^{3}H-nicotine binding measured in alternate tissue sections, and the case infant's values were within the SIDS and control range in all medullary and pontine nuclei analyzed, including the same nuclei in which abnormal ^{3}H-LSD measurements were found (Table 2). Of note, ^{3}H-nicotine binding

TABLE 2. The Binding Values for Serotonergic and Nicotinic Receptors in Nuclei in the Medulla and Pons for the Infant Compared With the Means (±Standard Deviation) of the Other Sudden Infant Death Syndrome (SIDS) Cases and Controls*

Nuclei	Case Serotonin	SIDS Serotonin	Controls Serotonin	Case Nicotine	SIDS Nicotine	Controls Nicotine
ARC†	2.2	6.3 ± 3.4	17.3 ± 5.0	NM	NM	NM
NTS	35.2	38.2 ± 17.4	45.1 ± 22.7	8.2	7.2 ± 3.5	6.4 ± 2.8
CENT	30.0	39.6 ± 14.8	35.3 ± 4.4	10.5	9.7 ± 4.2	9.2 ± 5.1
ION†	9.8	13.8 ± 6.9	19.9 ± 8.9	16.4	21.9 ± 6.7	21.0 ± 6.5
DMX	35.9	44.0 ± 20.1	47.2 ± 20.0	NM	NM	NM
PGCL	15.2	26.6 ± 13.8	42.6 ± 21.8	NM	NM	NM
GC†	24.8	31.3 ± 15.9	47.0 ± 23.3	NM	NM	NM
IRZ†	25.8	31.8 ± 17.2	44.9 ± 27.5	NM	NM	NM
PBL	17.3	34.4 ± 16.2	35.0 ± 13.2	13.4	12.1 ± 4.4	10.1 ± 4.3
POO	9.0	45.8 ± 24.6	46.5 ± 19.0	16.5	16.2 ± 5.3	13.3 ± 5.1
LC	8.2	42.1 ± 19.9	44.6 ± 17.5	15.4	16.0 ± 5.3	13.3 ± 4.7
BP	0.0	10.6 ± 6.5	9.7 ± 4.4	9.0	10.5 ± 3.4	9.2 ± 4.1

For the serotonergic binding, there are 72 other SIDS and 21 controls; for the nicotinic binding, there are 68 SIDS and 21 controls. There are differences in receptor binding for the 5-HT, but not for the nicotinic, radioligand in the case compared with controls. These data suggest that the receptor defect is not necessarily generalized, but may be relatively specific to 5-HT receptors.

*, The values are reported in femtomoles per milligram tissue.

†, Nuclei for which ^{3}H-LSD binding to 5-HT$_{1A-D}$ and 5-HT$_2$ receptor subtypes was significantly altered in SIDS compared with control cases in the American Indian and non-American Indian datasets previously reported by us (4, 12). There were no significant differences in mean binding values for 3H-nicotine between the SIDS and control cases in either the American Indian or non-American Indian datasets (22). Data are not available for the raphé obscurus and hypoglossal nucleus in the case infant because the brainstem was hemisected just lateral to the midline at the time of autopsy, precluding measurements in midline and medial structures.

ARC, arcuate nucleus; NTS, nucleus of the solitary tract; CENT, central nucleus; ION, inferior olivary nucleus; DMX, dorsal motor nucleus of cranial nerve 10; PGCL, paragigantocellularis lateralis; GC, gigantocellularis; IRZ, intermediate reticular zone; POO, nucleus pontis oralis; LC, locus ceruleus; BP, basis pontis; NA, not available; NM, not measured (nicotinic binding was not measured because there was negligible binding by visual inspection in both the SIDS and control cases in this nucleus).

does not localize to the arcuate nucleus (22) and therefore could not be measured in the SIDS or control cases. It was not significantly different in all other regions between SIDS and controls in the 2 separate datasets.

DISCUSSION

We report the case of a SIDS infant with subtle respiratory and autonomic dysfunction measured on the second day of life that was associated with abnormalities in the brainstem 5-HT system, including arcuate nucleus hypoplasia, at autopsy at 2 postnatal weeks. The case infant was found supine with his face under a sheet, blanket, and quilt. This compromised sleep environment may have produced the exogenous stressors of hypoxia and hypercarbia associated with rebreathing of expired gases, and/or overheating resulting in peripheral vasodilation and hypotension. Indeed, the face-covered supine position is associated with unstable alterations in respiration, autonomic balance, and arousal threshold in healthy infants, which may be secondary to elevation in temperature, among other factors (8, 9). In addition, this infant had 2 recognized risk factors for SIDS that involve adverse prenatal exposures (that is, maternal cigarette smoking and alcohol). We suggest that death resulted in this case from inadequate protective reflexes resulting from abnormalities in the medullary 5-HT system which comprised, at least in part, intrinsic deficits in chemosensitivity to carbon dioxide, airway reflexes, maintenance of autonomic balance under stress, and/or altered temperature (5, 13–20, 25).

The physiological measurements indicate the infant had an altered profile of autonomic function during the early neonatal period. In particular, the infant had the highest incidence of sustained changes in RRi when in active sleep. Sustained changes in RRi were previously reported to be decreased in older infants that subsequently died of SIDS (6). High respiratory rates in the case infant may have constrained production of high-frequency, respiratory-linked changes in RRi, and thereby allowed more frequent sustained accelerations and decelerations in heart rate. A relative absence of respiratory sinus arrhythmia, paired with somewhat elevated levels of overall variability, may underlie the elevated levels in RRi in active sleep. In quiet sleep, this infant maintained high breathing rates but had relatively low levels of overall variability, and sustained changes in RRi were unremarkable. The pattern of heart rate and RRi variability state differences in this infant may be informative about possible underlying autonomic dysregulation. Most infants of this age have a higher heart rate in active sleep than quiet sleep, but this was reversed in the case infant. Finally, this infant, like most infants, had greater RRi variability in active sleep, but state differences in his RRi variability were extreme. Together these observations suggest that the ratio of parasympathetic to sympathetic tone was higher than normal in active sleep in this case and lower than normal in quiet sleep. Although a measure of respiratory sinus arrhythmia would inform us about this hypothesis, the very high respiratory rates of this infant precluded generation of valid respiratory-linked RRi variability. It may be that increased levels of baseline parasympathetic control in active sleep were related to the robust heart rate increase to head-up tilt, a stimulus for parasympathetic withdrawal. However, it is also possible that the greater than normal heart rate increase to the tilt resulted from poor vascular responses to the challenge.

The medullary 5-HT system, including the arcuate nucleus, modulates the function of the autonomic nervous

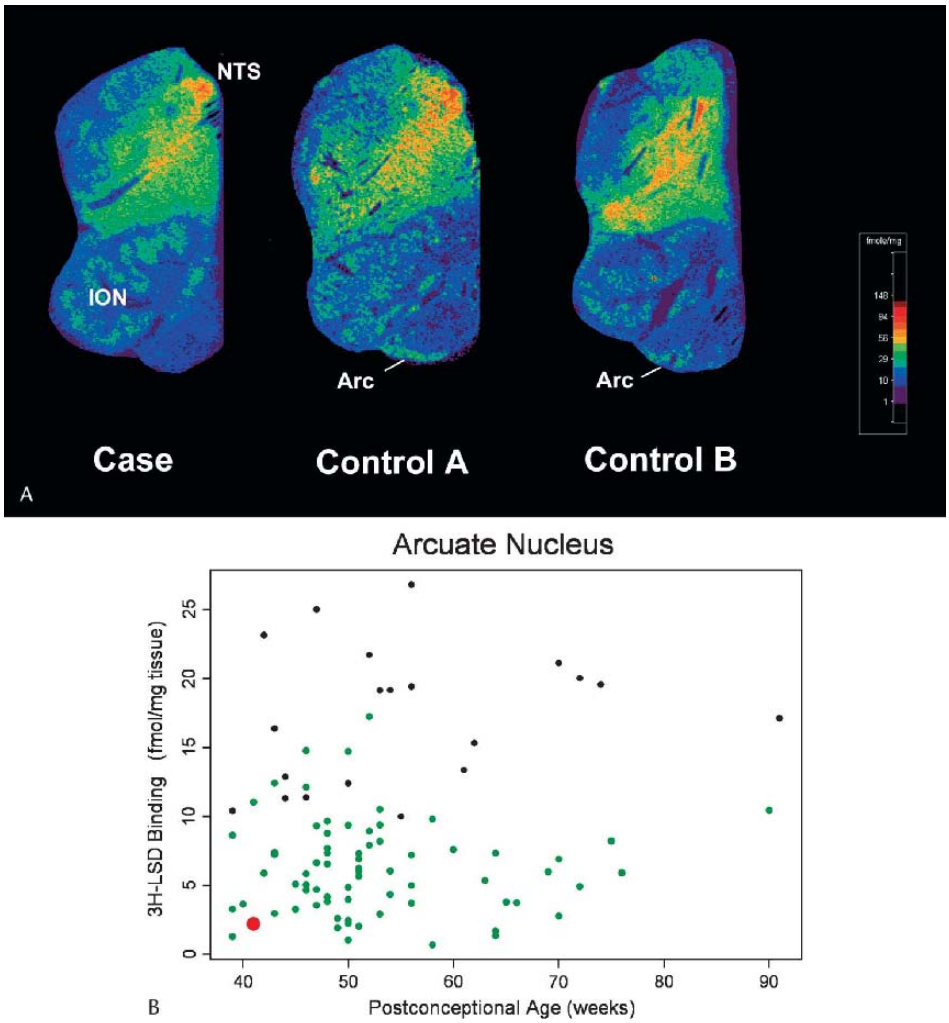

FIGURE 1. (A) Hemisected autoradiographs of the midmedulla illustrating the absence of the arcuate nucleus in the case infant (40 postconceptional weeks) compared with 2 control infants (control A, 44 postconceptional months; control B, 46 postconceptional weeks). Hypoplasia of the arcuate nucleus was confirmed by histologic examination of the tissue sections (through the entire rostrocaudal axis) that generated the autoradiograms as compared with control sections. The color-coded scale is presented in fmol/mg tissue. **(B)** Graph of ^{3}H-LSD binding to 5-HT receptor subtypes (fmol/mg tissue) in the arcuate nucleus of the case (red dot) compared with controls (black dots) and other SIDS cases (green dots). Each dot represents a single case. SIDS, sudden infant death syndrome; ARC, arcuate nucleus; ION, principal inferior olivary nucleus; NTS, nucleus of the solitary tract.

system, and thus abnormalities within it could potentially lead to imbalances in sympathetic and parasympathetic tone. This case demonstrated atypical patterns of state-dependent cardiorespiratory function that were detectable within a few hours of birth, and that were associated with an abnormal medullary 5-HT system at autopsy. Future confirmatory studies may indicate that the atypical autonomic and respiratory patterns in this case represent an important marker for an abnormal medullary 5-HT system and subsequent vulnerability to SIDS.

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