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IS SIDS AT "BORKMANN'S POINT?"

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ABSTRACT. AIM: To test whether Sudden Infant Death Syndrome (SIDS) is at "Borkmann's Point". "In every investigation, he [Borkmann] insisted, there is a point beyond which we actually don't need more information. When we reach it we know enough to solve the case with help of only mental effort." (Authors' translation from Borkmanns punkt, Håkan Nesser, 1994). METHODS: We examine five universal clues to solving the mystery of SIDS that determine its gestalt and must be explained simultaneously by any causation mechanism. They are: (i) Absence of evidence for cause of death at forensic autopsy; (ii) Male excess of 50%; (iii) Lognormal-type distribution of ages; (iv) Seasonal variation with a winter maximum and summer minimum; (v) Increase in rate with parity. We survey the literature to determine whether any published hypothesis for the cause of SIDS can meet these five criteria. RESULTS: The five universal characteristics of SIDS appear to be satisfied by an absence of an X-linked ability to withstand cerebral anoxia that is related to seasonal respiratory infections and age-dependent risk factors such as neurological prematurity and physiological anemia leading to cerebral anoxia. CONCLUSION: SIDS is now at 'Borkmann's point' because there is sufficient published information in the medical literature to show that SIDS must be an X-linked cerebral-anoxic condition.

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INTRODUCTION

Foreword: "In every investigation, he [Borkmann] insisted, there is a point beyond which we actually don't need more information. When we reach it we know enough to solve the case with help of only mental effort" (authors' translation). [1]

This report hypothesizes that we now are at "Borkmann's point" where there is already sufficient published information and data available on the mystery of Sudden Infant Death Syndrome (SIDS) to solve its cause. SIDS has been investigated by countless pediatricians, epidemiologists and pediatric pathologists. Although numerous books and literature surveys have attempted to provide an oversight of SIDS they do not explain its gestalt [a pattern of biological phenomena so integrated as to form a functional unit with properties not derivable from the summation of its parts]. This gestalt demonstrates that SIDS is an entity in itself, and not a collection of different subsets of explainable causes of death. Today, more than 5,800 articles on SIDS are abstracted by the PubMed service of the U.S. National Library of Medicine. There are hundreds of hypothesized causes of SIDS, and one author has offered 21 different explanations for SIDS [2]. The major failure of virtually all SIDS causation hypotheses so far has been that although they may be based on a finding of a 'risk factor' in SIDS cases, such as maternal cigarette smoking that is significantly greater than found in non-SIDS control cases, these risk factors cannot explain the five universal characteristics of SIDS described below that must be met simultaneously.

The fundamental nature of SIDS cannot be seen by looking at one individual case by itself. The clues emerge in the patterns that only can be recognized when all individual cases are viewed together, and then a cause must be found that explains them all. The following analysis of the available literature and data leads to a mechanism that explains all the characteristic findings of SIDS. These research results in the published literature also provide a mathematical basis for the SIDS age and gender phenomenon, and allow predictions to be made for testing the validity of the hypothesized mechanism and mode of terminal events.

METHODS

We examine the characteristics of SIDS required to be met by any causation hypothesis to determine whether the published literature reveals a hypothesized mechanism that completely explains its gestalt. SIDS was first defined by Beckwith [3,4] as "The sudden death of an infant or young child which is unexpected by history and in which a thorough post mortem examination fails to demonstrate an adequate cause of death." SIDS cases share five universal characteristics in all data sets from all countries throughout the world with high standards of forensic autopsy and where complete and accurate medical statistics are kept. These characteristics are shown in TABLE 1:

CLUE 1: ABSENCE OF EVIDENCE

SIDS, by definition, is characterized by the absence of any finding at autopsy capable of causing death. Therefore the cause of SIDS must exist at a level that is not attained during forensic autopsy, such as DNA analysis, or it already would have been found. The evidence of causation may not be the presence of a factor causing death, but the absence of a factor preventing death. Such a factor may be an X-linked enzyme necessary for catalyzing anaerobic oxidation during transient periods of cerebral anoxia in the respiratory control center of the brainstem.

As an example of the hunt for a presence, a recent candidate for a previously undetected substance capable of causing sudden death is a gut-derived E. coli soluble curlin antigen [5]. Maternal antibodies against E. coli are transmitted to nursing babies through secretory IgA in their mothers' breast milk which could explain why bottle feeding is a SIDS risk factor [6]. However, as for almost all risk factors, there is no known explanation why such a substance as curlin antigen would meet the requirements of causing ~50% male excess, the seasonal variation, the age distribution, and the parity relation of SIDS.

CLUE 2: THE ~50% MALE EXCESS

There is a consistent ~50% male excess of SIDS per 1000 live births of each gender in all countries

TABLE 1: THE GESTALT OF THE FIVE DEFINING CHARACTERISTICS OF ALL SIDS

CLUES OF CONSISTENT CHARACTERISTICS IN ALL DEVELOPED COUNTRIES	IMPLICATION OF FINDINGS
1. No visible cause of death at forensic autopsy of SIDS cases.	The cause must be found at a level that is not reached at forensic autopsy (e.g., on the DNA). SIDS may be caused by something that is absent, not by something that is present.
2. A 50% excess of male SIDS per 1000 live births of each gender.	The cause of SIDS must be gender related and this consistent male excess suggests a genetic basis with an X-linked gene involved.
3. A unique lognormal-type age distribution of SIDS.	The age distribution suggests that multiple age-dependent SIDS risk factors must come into play simultaneously.
4. A seasonal peak in rate of SIDS in the winter and minimum during the summer.	At least one of the SIDS risk factors must be seasonally dependent.
5. SIDS rates increase with parity (live birth order).	At least one of the risk factors is positively correlated with the live birth order of the SIDS cases.

with high autopsy standards and where complete and accurate vital statistics are kept [7]. In infancy, and at each age throughout life, males are more at risk of dying than females, but the importance of the ~50% male excess mortality from SIDS appears disregarded because it was incorrectly thought to be 'similar' to the male excess in all infant mortality [8, 9]. The male excess from all causes of infant mortality is ~25%, not ~50% [10]. In fact many contributory risk factors for SIDS such as the prone sleep position and hypothesized causes of SIDS such as a long-QT syndrome have no gender difference [11,12]. For example, there is a SIDS report on a genetic polymorphism of the IL-10 gene which is on an autosome (chromosome 1) which would be found with similar frequency for males and females [13]. Richardson [14] hypothesized that a fungus could create toxic gaseous compounds from plasticizer and fire-retardant compounds of phosphorous and antimony used to treat infant mattresses and cause SIDS. However, male and female infants would be equally likely to sleep on such mattresses, so that mechanism could have been rejected simply because it could not lead to the 50% male excess of SIDS. Any such model citing a gender-independent risk factor must be incomplete and thus cannot be an explanation of SIDS. Finally, this 50% male SIDS excess remained constant even after the campaign to change infant sleeping position from prone to supine which reduced the overall rate of SIDS [9].

An X-linked gene locus with a dominant allele that occurs with frequency 1/3 that is protective of SIDS, and a recessive allele with frequency 2/3 that is not protective of SIDS, leads to a 50% male excess of SIDS. The XY male is unprotected with frequency 2/3 and the XX female is unprotected with frequency 4/9, which predicts the ~50% male excess of SIDS susceptibility [7]. This is the only published explanation for the consistency of the ~50% male SIDS excess.

CLUE 3: THE SIDS AGE DISTRIBUTION

There is a unique age distribution of SIDS, with incidence rising from zero at birth to a maximum at ~2 months of age, with a rapidly falling rate which goes exponentially towards zero at one full year of life [15]. This consistent age distribution of SIDS is common to all nations and is a physiologic phenomenon, not an artifact, and it has only changed slightly since the campaign to change infant sleeping position from prone to supine [16]. Many researchers say that SIDS, or a subset of SIDS, are caused by the phenomenon they have studied, such as the long-QT syndrome [17], a prematurity of development of the respiratory neurons [18], or a lethal bacterial toxin [5]. It is very

unlikely that throughout the world the sum effect of such different causes happen to combine in just the same proportions and timing to create the same SIDS age distribution.

A study [15] presented 15 independent SIDS age data sets from around the world and showed that they all have the same general form. These data were fit with a Johnson S_B distribution, also known as a 4-parameter log-normal distribution. This model can be described by four independent risk factors:

1. A risk factor independent of age (genetic susceptibility, frequency of apnea);
2. A risk factor decreasing with age (residual neurological prematurity);
3. A risk factor increasing with age (exposure to respiratory infection [9]);
4. A risk factor increasing and decreasing with age (physiological anemia as fetal hemoglobin is replaced by adult hemoglobin [19,20]).

The probability of having all four risk factors simultaneously is modeled as the product of these probabilities which rises and falls with age in infancy to match the age distribution of SIDS [15].

CLUE 4: SEASONALITY OF SIDS

There is a historical seasonal pattern of SIDS in all countries, with a maximum rate during the winter and a minimum rate during the summer. This seasonal pattern of SIDS occurred even in semitropical locations, such as Hawaii, where there are no major climatic changes with the seasons, with average daily maximum and minimum temperatures varying between ~30°C and ~20°C [21,22]. Therefore, innate physiologic variability cannot be the cause of the seasonal fluctuation of SIDS because risk factors such as prone sleep position and parental smoking, and congenital conditions such as cardiac, neurologic and respiratory anomalies are seasonally independent [11].

There must be a risk factor that varies with season, but not necessarily with outdoor air temperature, because the indoor environment where infants are kept is relatively isothermal in the developed countries. It is therefore hypothesized that the seasonal variation of respiratory infection is responsible for the historical seasonal variation of SIDS [22]. This is consistent with the modern attenuation of the winter peak of SIDS incidence after the recent campaign to switch infant sleep positioning from prone to supine [16]. Infants with a low-grade respiratory infection have an increased oxygen demand and prone sleeping would reduce the oxygen supply from the mechanism of rebreathing their own exhaled breath [23].

CLUE 5: INCREASING RATE OF SIDS WITH PARITY

SIDS rates increase with parity (live birth order) in virtually all studies. TABLE 2 shows the relationship of SIDS with parity in the U.S. 1995-1998 [24]. The presence of older siblings in the home may represent a potential infection vector. The contact of the SIDS infant with older siblings, who interact with other children at school and at play, could provide a linkage to upper respiratory infections that peak in the winter and are at a minimum in the summer when school is on vacation. The importance of this relationship may have been disregarded because of an artifact that makes it appear that the rate of SIDS decreases as sibship (number of siblings independent of birth order) is held constant [25,26].

Maternal tobacco smoking is a known risk factor for SIDS and the parity effect could be confounded by an increase in smoking rates with parity. Although such data on smoking rates and parity are not available to us, we examined the SIDS rates with parity as a function of maternal education because smoking rates are known to decrease with increasing education level. TABLE 2 shows that SIDS rates decrease with parity for women with 0 - 8 years of education who are most likely to smoke, and increase with parity for women with 16 or more years of education who are least likely to smoke. Thus we conclude that the overall increase of SIDS rates with parity is not confounded by maternal smoking.

DISCUSSION

There is a published model for SIDS that explains these five common and fundamental properties of SIDS cited above. It encompasses all

TABLE 2. INCREASE OF SIDS RATE WITH PARITY IN THE U.S. 1995-1998 [24]

MOTHER'S LIVE BIRTH ORDER OF THE INFANT	SIDS DEATHS TOTAL	LIVE BIRTHS TOTAL	RATE/1000 TOTAL	RATE/1000 MATERNAL EDUCATION 0-8 YEARS	RATE/1000 MATERNAL EDUCATION ≥ 16 YEARS
One child	3,643	6,350,211	0.57	1.01	0.23
Two children	4,069	5,030,252	0.81	0.99	0.28
Three children	2,321	2,517,504	0.92	0.59	0.27
Four children	1,172	967,094	1.21	0.75	0.41
Five children	533	359,697	1.48	0.65	0.48
Six or more children	450	290,851	1.55	0.55	0.82

the published risk factors that may act to 'enable' an infant to fall into a terminal spiral that leads to an increased probability of completion by SIDS. These risk factors which are present in some but not all cases are therefore neither necessary (present in all SIDS) nor sufficient factors (inevitably lead to SIDS). However, they can be a contributing cause rather than a primary cause of SIDS.

THE MODEL FOR SIDS: FAILURE OF OXYGEN SUPPLY TO MEET DEMAND AT THE CELLULAR LEVEL

SIDS may occur when infants' oxygen supplies cannot meet their cerebral oxygen demands [15]. At that point, cerebral anoxia in the respiratory control neurons in the brainstem occurs first because that is the region of the body with the lowest oxygen tension. The brainstem is designed to generate signals of impending anoxic crisis that should result in a response such as a gasp for auto-resuscitation. Lavezzi et al. [27] report that positive c-fos immunoreactivity observed in SIDS suggests that the neurons of the dorsal motor vagal nucleus involved in the regulation of breathing are able to yield an intense, immediate ventilatory response to hypoxia, which they propose supports the respiratory theory of SIDS, which conforms to the ~50% male excess of respiratory causes of infant death [10]. Kinney et al. [28] report a risk factor of medullary serotonergic (5-HT) development abnormality in SIDS cases compared to non-SIDS controls.

At such a time, when cerebral oxygen supply cannot meet the oxygen demand, the brain cells must shift over from aerobic oxygenation to anaerobic oxygenation to provide the energy to sustain life. We propose that there is a protein that behaves similarly to the heat shock proteins, that responds to gradual reductions in oxygen tension by unfolding and creating an isomeric enzymatic form that can catalyze anaerobic metabolic processes that allows oxygen starved cerebral neurons to survive their anoxic crisis. There is evidence that some SIDS infants have been subjected to repeated episodes of hypoxia, and, if so, there could have been loss of cerebral neurons that bring down the total number of functioning neurons perilously close to the minimum number necessary for survival. It is proposed that there is an X-linked genetic basis for making at least one protein that allows survival of respiratory control brain cells under anoxic conditions, and those who do not have the survival capability of the dominant allele are the ones who do not recover from that rare but potentially-terminal crisis.

There are many anecdotal reports of female resistance and male susceptibility to hypoxia that fit this pattern. For example, on November 7, 2003, in Fullerton, California, a 20-month old girl who fell into a swimming pool and drowned, revived two hours later, 40 minutes after being pronounced dead [29]. In the cited Los Angeles Times article describing the infant's survival, it reports "On Jan. 7, 2002, a woman in her 50s was reported breathing

about 20 minutes after being pronounced dead at a hospital in central Japan. The next month, in Brooklyn, N.Y., a woman pronounced dead in her apartment by paramedics was later found to have a faint pulse and was revived at a hospital." That all three mentioned are female may not be a coincidence as described previously in the discussion of gender as a risk factor. In contrast, in Roskilde, Denmark, at the city's annual rock festival on June 30, 2000, 38 people were crushed against a fence in front of the stage by the crowd at a Pearl Jam concert. All nine people who died of suffocation from the crush of the crowd were male. Finally, Grémy et al. [30] report that there was a 45% male excess completion rate (58% male; 40% female) of suicide by gas asphyxiation in Paris between 1949 and 1962 similar to the ~50% male excess in SIDS. This also shows that adult mortality by asphyxiation approaches the hypothesized limits of 66.7% (2/3) for males and 44.4% (4/9) for females.

Hypoxia can arise from many mechanisms, and there are four basic ways that a fatal cerebral anoxia can arise: (i) hypoxic hypoxia where there is an insufficient oxygen supply available; (ii) anemic hypoxia where oxygen is sufficient but hemoglobin is insufficient to transport it in quantity; (iii) ischemic hypoxia, where oxygen supply and hemoglobin are sufficient, but blood supply to a tissue is restricted; (iv) histotoxic hypoxia, where oxygen, hemoglobin and blood supply are sufficient, but where a toxin interferes with the utilization of the oxygen from the blood by the tissue.

Most of the risk factors for SIDS interact by either decreasing the oxygen supply (e.g., prone sleep position resulting in rebreathing of exhaled air [23]) or its transport (e.g., physiological anemia [19,20]), increasing the oxygen demand (e.g., low grade infection slightly raising body temperature), or limiting the infants' abilities to respond to cerebral anoxia (neurological prematurity). When they all occur together, life may not be sustained without either an abrupt autoresuscitation of oxygenation by a gasp, or a shift to a form of anaerobic oxidation to allow brain cells to continue metabolism to allow eventual recovery.

In conclusion, any theory for the causation of the SIDS phenomenon must explain the five consistent factors that create the gestalt of SIDS. The published X-linked hypothesis meets this criterion, so we conclude that SIDS is now at Borkmann's point and its explanation is available from the published literature. At this time we know of no other published theory that also meets all these five constraints and suggest that research be focused on seeking and identifying the X-linked gene locus and its enzyme that may provide the missing link in the chain of SIDS causation.

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