The Triple Risk Hypotheses in Sudden Infant Death Syndrome

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ABSTRACT. Sudden infant death syndrome (SIDS) victims were regarded as normal as a matter of definition (Beckwith 1970) until 1952 when Kinney and colleagues argued for elimination of the clause, “unexpected by history.” They argued that “not all SIDS victims were normal,” and referred to their hypothesis that SIDS results from brain abnormalities, which they postulated “to originate in utero and lead to sudden death during a vulnerable postnatal period.” Bergman (1970) argued that SIDS did not depend on any “single characteristic that ordains a infant for death,” but on an interaction of risk factors with variable probabilities. Wedgwood (1972) agreed and grouped risk factors into the first “triple risk hypothesis” consisting of general vulnerability, age-specific risks, and precipitating factors. Raring (1975), based on a bell-shaped curve of age of death (log-transformed), concluded that SIDS was a random process with multifactorial causation. Rognum and Saugstad (1993) developed a “fatal triangle” in 1993, with groupings similar to those of Wedgwood, but included mucosal immunity under a vulnerable developmental stage of the infant. Filiano and Kinney (1994) presented the best known triple risk hypothesis and emphasized prenatal injury of the brainstem. They added a qualifier, “in at least a subset of SIDS,” but, the National Institute of Child Health and Development SIDS Strategic Plan 2000, quoting Kinney’s work, states unequivocally that “SIDS is a developmental disorder. Its origins are during fetal development.” Except for the emphasis on prenatal origin, all 3 triple risk hypotheses are similar.

Interest in the brainstem of SIDS victims began with Naeye’s 1976 report of astrogliosis in 50% of all victims. He concluded that these changes were caused by hypoxia and were not the cause of SIDS. He noted an absence of astrogliosis in some older SIDS victims, compatible with a single, terminal episode of hypoxia without previous hypoxic episodes, prenatal or postnatal.

Kinney and colleagues (1983) reported gliosis in 22% of their SIDS victims. Subsequently, they instituted studies of neurotransmitter systems in the brainstem, particularly the muscarinic (1995) and serotonergic systems (2001). The major issue is when did the brainstem abnormalities, astrogliosis, or neurotransmitter changes occur and whether either is specific to SIDS. There is no published method known to us of determining the time of origin of these markers except that the injury causing astrogliosis must have occurred at least 4 days before death (Del Bigio and Becker, 1994). Because the changes in neurotransmitter systems found in the arcuate nucleus in SIDS victims were also found in the chronic controls with known hypoxia, specificity of these markers for SIDS has not been established. It seems likely that the “acute control” group of Kinney et al (1995) died too quickly to develop gliosis or severe depletion of the neurotransmitter systems. We can conclude that the acute controls had no previous episodes of severe hypoxia, unlike SIDS or their “chronic controls.” Although the average muscarinic cholinergic receptor level in the SIDS victim was significantly less than in the acute controls, the difference was only 27%, and only 21 of 41 SIDS victims had values below the mean of the acute controls. The study of the medullary serotonergic network by Kinney et al (2001) revealed greater reductions in the SIDS victims than in acute controls, but the questions of cause versus effect of the abnormalities, and whether they occurred prenatally or postnatally, remain unanswered.

Hypoplasia of the arcuate nucleus was stated to occur in 5% of their SIDS cases by Kinney et al (2001), but this is a “primary developmental defect” according to Marter et al (2002) with a larger series, many of whom were stillbirths. These cases should not be included under the rubric of SIDS, by definition.

There are difficulties with Filiano and Kinney’s (1994) explanation of the age at death distribution of SIDS. They postulate that the period between 1 and 6 months represents an unstable time for virtually all physiologic systems. However, this period demonstrates much less instability than does the neonatal period, when most deaths from congenital defects and severe maternal anemia occur. We present data for infants born to mothers who were likely to have suffered severe anemia as a consequence of placenta previa, abruptio placenta, and excessive bleeding during pregnancy; these infants presumably are at increased risk of hypoxia and brainstem injury. The total neonatal mortality rate in these 3 groups of infants is 4 times greater than the respective postneonatal mortality, and in the postneonatal period the non-SIDS mortality rate is between 14 and 22 times greater than the postneonatal SIDS rate in these 3 groups. A preponderance of deaths in the neonatal period is also found for congenital anomalies, a category that logically should include infants who experienced prenatal hypoxia or ischemia; this distribution of age of death is very different from that for SIDS, which mostly spares the first month and peaks between 2 and 3 months of age.

Finally, evidence inconsistent with prenatal injury as a frequent cause of SIDS comes from prospective studies of ventilatory control in neonates who subsequently died of SIDS; no significant respiratory abnormalities in these infants have been found (Waggener et al 1990; Schechtman et al 1991).

We conclude that none of the triple risk hypotheses presented so far have significantly improved our understanding of the cause of SIDS. Bergman’s and Raring’s concepts of multifactorial causation with interaction of risk factors with variable probabilities is less restrictive...
and more in keeping with the large number of demonstrated risk factors and their varying prevalence. If prenatal hypoxic damage of the brainstem occurred, it seems likely that the infant so afflicted would be at risk for SIDS, but it is even more likely that their death would occur in the neonatal period, as we have demonstrated in infants who have known maternal risk factors that involve severe anemia. This is in contrast to the delay until the postneonatal period of most SIDS deaths. A categorical statement that the origin of SIDS is prenatal is unwarranted by the evidence. Brainstem abnormalities have not been shown to cause SIDS, but are more likely a nonspecific effect of hypoxia. Pediatrics 2002;110(5).

ABBREVIATIONS. SIDS, sudden infant death syndrome; CNS, central nervous system.

For many years, the victims of sudden infant death syndrome (SIDS) were regarded as having been previously normal, inherent in the 1969 definition by Beckwith: “the sudden death of an infant which was unexpected by history and in which a thorough postmortem examination failed to demonstrate an adequate cause of death.” Kinney and colleagues argued against part of Beckwith’s definition, namely “unexpected by history,” claiming its elimination as “the single most important lesson of SIDS research over the last 20 years.” They asserted that “not all SIDS victims were entirely normal.” (Actually, Beckwith’s definition made no such assertion; the context was one of exclusion of disorders that might reasonably be lethal on the basis of history.) This publication began with an introduction to their hypothesis that SIDS is state-related and results from a brain abnormality in the state-modulated regulation of cardiopulmonary mechanisms. This brain abnormality is further postulated to originate in utero and lead to sudden death during a vulnerable postnatal period.

In the 1969 conference, Bergman stated that SIDS did not depend on any “single characteristic that ordains an infant for death,” but on an interaction of risk factors with variable probabilities. In 1972, Wedgwood agreed with Bergman’s concept and presented an explicit “triple risk hypothesis” involving 3 classes of risk factors: 1) general factors that increase the probability of death from any cause, including poverty, prematurity, gender, and race; 2) age-specific risks relating to the infant’s developmental status; and 3) precipitating factors, including sleep state, position, and infection.

In 1975, Raring published a scholarly and mathematical analysis of the implications of the age at death of SIDS. His plots were based on averaging 7 different data sources and have stood up well, as we will see later in our plots from more recent data with larger numbers. He also plotted the age at death of SIDS on a log-scale producing a normal (bell-shaped) curve, and then confirmed the normal distribution by plotting the distribution on “probability” paper versus the log of age and obtained a straight line that included 97% of the data points. He concluded that SIDS behaved like a random process and was a “multifactor” disease with a normal or Gaussian distribution of age of death.

More recently, Rognum and Saugstad proposed a “fatal triangle in SIDS,” a hypothesis that also involved 3 types of risk factors: 1) a vulnerable developmental stage of central nervous system (CNS) and mucosal immunity, 2) predisposing factors (astrogliosis, genetic make-up), and 3) a trigger event, such as an infection.

Filiano and Kinney in 1994 proposed their own triple risk hypothesis, that “SIDS results from the intersection of 3 overlapping factors”: 1) a vulnerable infant; 2) a critical developmental period in homeostatic control; and 3) an exogenous stressor. An infant will die of SIDS only if he/she possesses all 3 factors; the infant’s vulnerability lies latent until he/she enters the crucial period and is subject to an exogenous stressor. The timing of the insult and the duration of the latency period (time from insult to death) was not specified by Filiano and Kinney. However, given the age at death for most SIDS, 2 to 6 months, latency would have to last for some months, and even death in the first month of life would require a few weeks if the injury had occurred in the prenatal period as Kinney et al suggest in their 1992 paper. Except for this emphasis on prenatal origin by Filiano and Kinney, all 3 hypotheses of triple risk are similar; Wedgwood and Rognum and Saugstad did not stipulate a prenatal factor for SIDS, and thus latency was not required. Without the prenatal emphasis, there is little about the triple risk hypothesis of Filiano and Kinney that is unique except their numerous studies of neurotransmitter systems. If the prenatal origin is accepted, it changes the etiologic paradigm substantially, as evidenced by the National Institute of Child Health and Development SIDS Strategic Plan 2001 that stated unequivocally “SIDS is a developmental disorder. Its origins are during fetal development.”

We here explore the evidence for the specifics of the triple risk hypotheses, with special attention to that of Filiano and Kinney.

VULNERABLE INFANT

Some of Wedgwood’s examples of vulnerability included risks that originated during pregnancy, but were not specific to SIDS. They are not controversial, because they consist of well-established epidemiologic risk factors for infant mortality in general. The vulnerability referred to by Rognum and Saugstad included a “vulnerable developmental stage of CNS and mucosal immunity.” The latter is proposed to cause astrogliosis by means of an immunologic mechanism, either by “blood-born mediators or by so-called retrograde axonal transport.” They have described this as an “over-stimulation of the immune system [that] may be due to viral infections or alimentary factors.” There seems to be no general consensus on the biological plausibility of this concept.

Filiano and Kinney provided 4 lines of evidence for prenatal origin: “1) subtle CNS and/or systemic
abnormalities in SIDS victims detected by quantitative or rigorous methods at autopsy; 2) neonatal abnormalities in neurologic or autonomic function in at least some infants who subsequently die of SIDS; 3) postneonatal abnormalities in cry, cardiac and ventilatory patterns, and state organization in some future SIDS victims, and 4) maternal and pregnancy-related factors associated with increased SIDS risk.” They continued, “together, these risk factors point to a suboptimal intrauterine environment, and suggest that the mechanisms for risk for SIDS develop in fetal life in at least some cases.”6 What follows is a detailed review of these 4 lines of evidence.

1) “Subtle CNS and/or systemic abnormalities in SIDS victims detected by quantitative or rigorous methods at autopsy.”6 Naeye reported in 1976 significant proliferation of astroglial fibers in the brainstem of half of his SIDS cases;12 the other half had no more nor less astrogliosis than did controls who had died of trauma or acute asphyxia. (Because 4 days or more are required to develop astrogliosis,13 its presence cannot be attributed to a single acute episode ending in death.) Although the gliosis occurred in the reticular formation that controls respiration, Naeye thought it likely that the lesions were secondary to chronic hypoxia or to repeated episodes of acute hypoxia, rather than the cause of SIDS. Naeye found widespread brainstem involvement as well as histologic markers of hypoxia in other organs in SIDS victims.14 He noted an absence of astrogliosis in some SIDS victims, a somewhat older group that had histologic evidence of mild infection. This lack of brainstem gliosis in older infants is compatible with a single, terminal episode of hypoxia without previous hypoxic episodes or prenatal injury, with mild infection as a trigger.

Kinney and colleagues15 also had reported reactive gliosis in the brainstem in 1983, although in only 10 (22%) of 45 SIDS cases did their counts exceed the highest count in a control case. Of these 10 cases, some would be expected by chance to have had a postnatal hypoxic-ischemic event causing the gliosis, which would make the percentage of SIDS cases that had a possible prenatal origin even smaller.

The possibility that deficiencies and other abnormalities of neurotransmitter binding and concentrations are a result of general, nonspecific hypoxic damage has been conceded by Kinney et al.16 Nevertheless, they assert that they have shown specificity by demonstrating a difference for neurotransmitter receptor binding defects between acute and sudden infant deaths of known cause compared with infant victims of SIDS and chronic controls that had “chronic or repetitive hypoxemia from cardiac, pulmonary, or central breathing disorders.”17 The chronic controls had deficiencies similar to those found in SIDS. The acute controls died suddenly and certainly had no chance to develop astrogliosis,15 and there is reason to doubt they had time to deplete the neurotransmitter system. In short, the evidence that the changes in the neurotransmitter system in SIDS are specific is inadequate.

It is hard to find a more ubiquitous neurotransmitter than serotonin; Kinney points out that 5-HT innervates “virtually all CNS regions.”16 Because it is broadly involved in vital functions, its exhaustion in defense of life seems predictable. In rats, moderate hypoxia failed to modify 5-HT binding, whereas severe hypoxia did.18 In support of terminal exhaustion of serotonin are the findings of increased levels of serotonin metabolites in the cerebrospinal fluid.19 Cann-Moisan20 found that several neurotransmitters and metabolites were increased in the cerebrospinal fluid of SIDS victims compared with living controls; they also found high levels of these in cerebrospinal fluid in infants after they had survived severe asphyxia.

Filiano has reported the detection of 2 instances of isolated hypoplasia of the arcuate nucleus in a series of 41 SIDS cases;21 inclusion of these cases does not meet the requirements of the definition of SIDS, because these anatomic anomalies are known to cause death. The diagnosis should be simply a congenital defect. Nine autopsies on infants who presented as stillbirths with isolated hypoplasia and even agenesis of the arcuate nucleus were reported by Matturri et al22; of particular interest, they demonstrated an absence of gliosis in these patients. They described the anomaly as a “primary developmental defect.”

2) “Neonatal abnormalities in neurologic or autonomic function in at least some infants who subsequently die of SIDS.”6 Filiano and Kinney referenced a study by Hoffman et al23 in support of this statement. However, that study had 2 control groups and group B, the one that was matched for birth weight and race, reduced the odds ratio of SIDS for all newborn risk factors, such as Apgars, to nonsignificance.23

3) “Postneonatal abnormalities in cry, cardiac and ventilatory patterns, and state organization in some future SIDS victims.”6 In contradiction to the hypothesis that SIDS victims were born with abnormalities of the brainstem function, crucial evidence comes from ventilatory recordings in infants who subsequently died of SIDS; there was no difference between them and matched controls.24 Similarly, in a study based on recordings of 6914 normal infants, Schechtman et al25 found no differences in frequency of either short or long apneic pauses during the first month of life among controls and 16 infants who subsequently died of SIDS. Abnormalities in the infant’s cry and other abnormalities were reported in retrospect,26 and were significant at the .05 level, but the authors cautioned that “many siblings of SIDS victims had the same behavioral pattern as the victims. None of these siblings have died.”

4) “Maternal and pregnancy-related factors associated with increased SIDS risk.”6 This was supported by reference to “prematurity, low birth weight, maternal anemia, maternal illicit substance abuse, and maternal cigarette smoking (nicotine) during pregnancy. Together, these risk factors point to a suboptimal intrauterine environment—one potentially complicated by hypoxia-ischemia—and suggest that the mechanisms for SIDS risk develop in fetal life.”16 This group had previously stated that “the transmitter systems most at risk may be those implicated by prenatal risk factors for SIDS,”2 and
embarked on a series of studies on these neurotransmitters in brainstem nuclei.

Certainly, the above prenatal risk factors for SIDS are supported by epidemiologic data. For example, the risk of cigarette smoking has been acknowledged since 1966 and has generally been regarded as the best case for prenatal risk factors in SIDS. However, the time when these risk factors operate is arguable; Kinney’s group studied 14 brainstem centers and found no difference in nicotine receptor binding in SIDS victims compared with acute and chronic controls. In contrast, the presence of nicotine and cotinine in SIDS victims established a strong postnatal effect of passive exposure to cigarette smoke, considering that the half-life of these substances is only 12 to 16 hours.

Pregnancy disorders that could result in maternal anemia and fetal hypoxia include placenta previa, abruptio placentae, and excessive bleeding. As shown in Table 1, these disorders have a greater effect on the risk of infants born of these pregnancies succumbing to a non-SIDS death than to SIDS in the postneonatal period. Furthermore, the neonatal mortality after these pregnancy disorders is >4 times greater than the postneonatal mortality rate for all causes combined. The data in Table 1 suggest that any hypoxic injury reduces the ability of the infant to survive in both the neonatal and postnatal era in a nonspecific manner.

**TABLE 1.** Mortality Rates per 1000 Infants at Risk in the Neonatal and Postneonatal Periods Related to Prenatal Experiences—United States, 1989–1991

<table>
<thead>
<tr>
<th>Prenatal Experience</th>
<th>Neonatal</th>
<th>Postneonatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placenta previa</td>
<td>0.10</td>
<td>30.3</td>
</tr>
<tr>
<td>Abruptio placentae</td>
<td>0.09</td>
<td>61.5</td>
</tr>
<tr>
<td>Excessive bleeding</td>
<td>0.06</td>
<td>21.3</td>
</tr>
<tr>
<td>All pregnancies</td>
<td>0.08</td>
<td>5.7</td>
</tr>
</tbody>
</table>

CRITICAL DEVELOPMENTAL PERIOD IN HOMEOSTATIC CONTROL

Filiano and Kinney, in their triple risk model, proposed that “infants who eventually die of SIDS may appear normal clinically, but their vulnerability lies latent until they enter the critical developmental period between 1 and 6 postnatal months.” This “critical development period is based on the consistent age distribution for SIDS,” but their evidence for instability is vague, “major changes occur in virtually all physiologic systems.” The physiologic changes that occur from 1 to 6 months are incremental, and not nearly so severe and abrupt as the dramatic changes that occur at birth—and the first month is an uncommon time for SIDS. A later statement by Kinney et al in 2001 seems to contradict the earlier suggestion of instability, “in no instance did we find dramatic changes in binding levels in any nucleus related to autonomic, respiratory, or state control at 2–4 months.” In fact, in this same report, they stated that “serotonergic binding sharply decreases from high levels in the fetal period to low levels in infancy that are comparable to the low levels in adulthood.” These 2 statements do not suggest instability at birth.

The distribution of the age at death in SIDS is also against the concept that SIDS is of prenatal origin and depends on a critical developmental period. If the occurrence of SIDS is related to a prenatal abnormality in a subset of SIDS, then by definition there exists a pool of susceptible infants at birth. The distribution of age at death for these SIDS victims then should resemble that of any other congenital anomaly (Fig 1), but they are dramatically different. There are few SIDS deaths in the first month of life, rising to a peak at 75 days of life, and falling markedly after 165 days. The age distribution at death for all congenital defects, which would include infants with prenatal brainstem abnormalities, has a monotonic distribution, with an extremely high percentage of all deaths in the first month, similar to the distribution between neonatal and postnatal deaths demonstrated in Table 1.

An alternative explanation of the age at death distribution for SIDS, particularly partial sparing of the first month of life, could be an early protective mechanism that is limited in duration. For example, gasping is capable of restoring regular respiration in neonates, but the efficacy of the gasp depends on the glycogen stores in the cardiac muscle, since the improved oxygenation of the pulmonary capillaries does not resuscitate unless that oxygen is delivered to the brain. The notable ability of the fetus for anaerobic metabolism is obviously still present in the neonate, but gradually diminishes in the first few weeks.

A second alternate explanation for the relative sparing of the very young infant from SIDS also postulates the possession of an innate but temporary protective mechanism that disappears with increasing age (including the gestational age at delivery). This mechanism is hypothesized to be negatively associated with the infant’s level of maturity, thus accounting for the age of maximum risk for SIDS increasing as gestational age increases, as well as the tendency for black infants to die earlier than infants of other races, reflecting their greater level of maturity at birth.

A third alternate explanation of age of death in SIDS suggested by Fleming et al involves heat stress. They found that younger infants with upper respiratory infections rarely developed a fever, compared with infants older than 3 months, who also had higher metabolic rates even without a fever, thus subjecting the infants beyond one month of age to greater vulnerability to heat stress and SIDS.
leagues argued for elimination of the clause, who do not succumb to SIDS. Common occurrences in thousands of healthy infants, and are not usually lethal because they are infections, have been identified by epidemiologic studies, and are not usually lethal because they are common occurrences in thousands of healthy infants who do not succumb to SIDS.

SUMMARY

SIDS victims were regarded as normal as a matter of definition until 1952 when Kinney and colleagues argued for elimination of the clause, “unexpected by history.” They argued that at least a subset of SIDS victims had a prenatal origin. Early on, Bergman argued that no single characteristic was necessary for SIDS; Wedgwood grouped risk factors into a “triple risk hypothesis” in 1972, consisting of general vulnerability, age-specific risks, and precipitating factors. Raring based on a bell-shaped curve of age of death (log-transformed), concluded that SIDS had multifactorial causation and was a random process. Rognum and Saugstad developed a “fatal triangle” in 1993, and included an emphasis on mucosal immunity. Filiano and Kinney in 1994 presented the best known triple risk hypothesis and emphasized prenatal injury of the brainstem. Although they frequently added a qualifier, such as “in at least a subset of SIDS,” the National Institute of Child Health and Development SIDS Strategic Plan 2000 stated unequivocally that “SIDS is a development disorder. Its origins are during fetal development.”

Interest in the brainstem of SIDS victims began with Naeye’s report of astrogliosis in 1976. He concluded that these changes were caused by hypoxia and were not the cause of SIDS. Kinney and colleagues also found gliosis in 22% of their SIDS victims and instituted studies of neurotransmitter systems in the brainstem, particularly muscarinic and serotenergic systems. The major issue is the extent to which prenatal brainstem abnormalities occur in SIDS. We have reviewed the lines of evidence of Filiano and Kinney and find them troublesome. In particular, it seems that their “acute control” group died too quickly to develop gliosis and abnormalities of the neurotransmitter systems, whereas their “chronic controls” were non-SIDS deaths who had known exposure to hypoxia and who had brainstem abnormalities similar to the SIDS victims. The other major problem is their inference that some of the neurotransmitter abnormalities had a prenatal origin; we suggest that there is no known method of determining when they occurred except at least 4 days before death, and that they have no meaning more specific than astrogliosis. The evidence is against a prenatal injury being a frequent factor for SIDS because neonatal studies of ventilatory control have been normal.

We also find difficulties with Filiano and Kinney’s explanation of the age at death distribution of SIDS. They postulate that the period between 1 and 6 months, the era of most SIDS deaths, represents an unstable time for virtually all physiologic systems. We suggest that this period demonstrates much less instability than the neonatal time, when most deaths from congenital defects and severe maternal anemia occur. We present data for infants born to mothers who have suffered severe anemia from placenta previa, abruptio placenta, and excessive bleeding during pregnancy. Their total neonatal mortality rate is 4 times greater than the postneonatal mortality rate from all causes, and 14 to 22 times greater than the postnatal SIDS rate of this population. A preponderance of deaths in the neonatal period is also found for congenital anomalies, a category that should include infants with prenatal hypoxia or ischemia; this is very different from the age at death for SIDS, which mostly spares the first month and peaks between 2 and 3 months of age.

CONCLUSION

The advantage of any of the triple risk hypotheses in understanding SIDS has not been demonstrated. Bergman’s and Raring’s concepts of multifactorial causation with interaction of risk factors with variable probabilities is less restrictive and more in keeping with the large number and varying prevalence of demonstrated risk factors.

Whether brainstem injury in SIDS victims originates in the prenatal or postnatal period cannot be proven. However, the evidence is against a prenatal injury being a frequent factor for SIDS, because neonatal studies of ventilatory control have been normal. Also unproven is whether abnormalities of neurotransmitter abnormalities are any more specific for SIDS than is astrogliosis.

We conclude that 1) prenatal occurrence is not a frequent factor based on normal ventilatory control in infants who subsequently die of SIDS, and 2) the preponderance of early deaths in infants who have known maternal risk factors that involve bleeding, is
in contrast to the delay in the occurrence of SIDS deaths.

REFERENCES


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