

## **Review Article**

# **Why Mainstream SIDS Research Is Not Achieving Its Goal**

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**Abstract:** The cardiorespiratory paradigm is used to explain the aetiology of SIDS and has been the focus of intense research for many decades without providing consistent and meaningful data to support such an hypothesis. Despite this, papers citing central nervous system, cardiac and sleep arousal findings continue to be unremittingly published but without addressing SIDS risk and other factors. This paper is a succinct analysis of current cardiorespiratory SIDS research and its relationship (or not) to the established clinicopathological data and epidemiological risk factors. Epidemiological research into the aetiology of SIDS produced a milestone with the discovery of the prone sleep position risk factor which provided support for the cardiorespiratory control hypothesis which in itself defines the approach used by mainstream researchers. Since then mainstream research has stalled. The question is why? This analysis shows that there is very poor correlation between brainstem and other central nervous system pathological findings and other clinicopathological data and SIDS risk factors. A few studies show a link to a small number of risk factors, however, for the majority of papers there remains a glaring absence of data to link central nervous system pathology findings with the key risk factor of prone sleep position which is the central column upon which the cardiorespiratory paradigm stands. Nor do the studies correlate central nervous system findings with recent infection, contaminated sleeping surfaces, maternal/obstetric/higher birth, ethnicity, non-breast-feeding, etc. or with the usual gross pathological findings of SIDS (intrathoracic petechiae, liquid blood, congested fluid-laden lungs). Because of these shortcomings, this paper should provoke questions over current research directions and invites research into other more plausible hypotheses, such as the infection paradigm.

**Keywords:** Sudden Infant Death Syndrome, Research, Cardiorespiratory Control, Infection

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## **1. Introduction**

Epidemiological research into the aetiology of Sudden Infant Death Syndrome (SIDS) produced a milestone in regard to the discovery of the risk factor of prone sleep position which in turn provided support for the cardiorespiratory control hypothesis which, in essence, defines the mainstream approach. Since then mainstream research, prodigious in its volume but low in meaningful correlations, has stalled. There is a need to ask why? In preparing this paper a number of search engines were used and included PubMed, Google Scholar, and Web of Science.

## **2. Discussion**

Previously it was shown that mainstream research engaged in the hypothesis of central homeostatic control has focussed on the central nervous system including the brainstem, limbic forebrain and hippocampus and other brain sites [1]. The isolated brain-related pathological findings (e.g. hypoplasia of the arcuate nucleus (respiratory chemosensitive zone of the ventral medulla), or gliosis of cerebral white matter, etc. reported by mainstream researchers were shown to occur in a minority of cases [2]. In addition, this research has tended to ignore overall morbid pathology (beyond the central nervous system) or epidemiological risk factors. This has left the central homeostatic control hypotheses bereft of substantial and necessary support. Clinicopathological and epidemiological supporting evidence is required to establish

aetiological connections. Other mainstream researchers have used intrathoracic petechiae to support the idea of an asphyxial event [3]. It was shown previously that there is no basis to support a link between intrathoracic petechiae and asphyxia [4, 5]. Variation in distribution and number of petechiae are affected by the age, ethnicity, parity, exposure to cigarette smoke and sleep position and paradoxically that SIDS infants placed prone show a reduced frequency of pleural petechiae [4].

Research directions which pivot on a single finding (seemingly interpreted as to compromise respiration) such as prone position found, bedding over head, sleeping and dying in the parental bed (overlying) all occur in a minority of cases and ignore potential risk factors and clinicopathology. Cardiac dysrhythmia such as QT interval genetic pathology and other causes of genetic channelopathies [6-10] are also limited to a minority of SIDS cases. The finding does not mean the inherited channelopathy was fatally causal. Nor does anatomical abnormality of brain stem neuronal nuclei necessarily relate to causation of death given that similar findings are observed in brain stems of non-SUDI deaths (albeit in a smaller proportion) [2]. These hypotheses remain speculative and animal models are lacking or have not provided clear answers [11].

It is rare for mainstream researchers to include general autopsy findings (intra-thoracic findings or nature of the heart blood (clotted/unclogged) or organ weights) in their publications. Such information could provide useful information. Publication of pertinent information could clarify possible associations between a specific pathological picture and a purported cardiac channelopathy. In this regard, absence of intrathoracic petechiae might explain the <10 percent of all SIDS cases that do not exhibit typical pathological findings (intrathoracic petechiae, liquid cardiac blood, large brain, heavy congested lungs, etc.). Very few studies have examined intrathoracic petechiae in relation to brainstem nuclei staining. Those that have, could not establish correlation [12, 13].

Brainstem studies that have failed to address clinicopathological and modifiable risk factors are too numerous to list here. A series of papers repeating this failure was published recently in the book on SIDS by Duncan and Byard [14]. These studies stand as examples of poorly considered and wasteful research. On the other hand, there is a small minority of brainstem studies that have appropriately tried to examine a possible link to some risk factors and clinicopathological findings. For example, Machaalani and Waters [12] sought associations between brainstem nuclei staining (TUNEL for apoptosis) and the presence of petechiae, history of cigarette smoke exposure, recent URTI and immunization, sleep position and bed sharing, alas, no significant interactions were observed. On the other hand, when the same group examined serotonergic receptor 1A staining [13] associations with some clinical risk factors (cigarette smoke exposure, bed sharing and sleep position) were inconsistently observed in relation to the dorsal motor nucleus of the Vagus (DMNV) [13]. Male gender regrettably

did not feature in the brainstem associations. Necessary caution in interpretation of positive TUNEL staining is required as it should not be considered as a specific marker of apoptosis but can also indicate necrotic cell death as may occur in sepsis [15].

Machaalani and Waters [12] also examined growth characteristics (including body length, head circumference, brain weight, body weight) in relation to TUNEL staining in the dorsal column nuclei (DCN): there was a positive association between prone sleeping and bed sharing in SIDS cases but no correlation with smoke exposure or male gender. Other studies using similar approaches found no correlations, for example, Sawaguchi et al. [16] found no SIDS-specific correlation with the pathological findings of apoptosis and concluded this did not support an apnoea-related hypothesis.

In other attempts to find pathological brainstem associations with risk factors, Kinney et al. [17] examined the medullary 5-HT system. Medullary 5-HT abnormalities were seen in prone and supine, facedown and not face down, in bedsharing and non-bedsharing cases and both premature and term SIDS cases. The brainstem findings "were common among SIDS infants irrespective of particular risk factors [17]." In the absence of correlation with risk factors, the findings are rendered as wanting in many respects and must lead to the question of the soundness of the cardiorespiratory model of SIDS. The same group had previously shown no effect of male gender or other risk factors in relation to tissue 5-HT/serotonin levels [18].

There are numerous other examples in the SIDS-CNS literature that repeat the problem, for example, the study by Machaalani et al. [13] which examined gender, showed that within the SIDS group, no caudal or rostral nucleus of the inferior olive had greater staining in males over females making the findings largely irrelevant. Moreover, what is to be made of isolated findings such as a significant relationship with risk factors (cigarette smoke exposure, bed sharing and sleep position) for decreased immunoreactivity for serotonergic receptor 5HT(1A)R, especially in the dorsal motor nucleus of the Vagus (DMNV)? Does it suggest that 5HT(1A)Rs are highly vulnerable to various insults within the SIDS DMNV as the authors speculate? As mentioned above, the same group examined TUNEL staining (apoptosis) and did find one isolated correlation in the AN rostral medulla with male gender in SIDS cases while in non-SIDS cases females had significantly more staining in the same area. All other areas examined produced no significant male excess for TUNEL staining which must cast doubt on the meaning of the isolated finding [12].

Kinney et al. [2] examined the hippocampus and failed to show in males significance between presence or absence of focal granule cell bilumination, therefore suggesting the findings were irrelevant. Previously, Kinney et al. [19] sought evidence of prenatal brainstem injury in SIDS and examined the inferior olive. Reactive astrocytes were present in the inferior olive in SIDS cases, but their number, density, and developmental profile were not significantly different from that of control infants dying of diverse known causes. SIDS

cases found dead in cribs, beds, and sofas, prone or supine had subtle olivary abnormalities making interpretation difficult. The paper failed to mention the effect of gender on the findings.

Others have conducted studies without any mention of risk factors [20]. Whereas, Kinney's group examined the sleeping environment but could not produce a correlation [21]; and "found no direct relationship between the presence of potentially asphyxial conditions in the sleep environment and the brainstem abnormalities analysed in infants dying suddenly [21]."

Ozawa and Takashima [22] showed there are no differences of brainstem gliosis and catecholaminergic neuron changes between the prone and supine positions. Such findings therefore weaken and undermine a respiratory control hypothesis.

A report examining pulmonary arterial smooth muscle thickness showed correlation with a small number of risk factors: for example, increased pulmonary alveolar wall thickening was significantly associated with males [23]. However, prematurity had a negative association and being placed prone was positively associated with arterial thickening but was oddly not associated with "found prone." Other risk factors were insignificant (e.g. race, smoke exposure, upper respiratory infection in previous 48h). No pathological finding including pulmonary haemorrhage was significantly associated with the arterial findings. Overall, in comparison to age-matched controls there were no significant differences found, thus, negating the hypothesis of pre-existing chronic anoxia proposed by the authors.

Groups previously reporting correlations with risk factors for a single immunohistopathological brainstem finding are unable to reproduce correlations with other features such as decreased orexin immunoreactivity and previously identified risk factors for SIDS, including prone sleeping position and cigarette smoke exposure [24].

The list of targeted CNS sites has lengthened to include Pituitary adenylate cyclase activating polypeptide (PACAP) and its receptor 1 (PAC1) [25] and brain-derived neurotrophic factor and TrkB receptor [26]. Correlations were found between PACAP and PAC1 with the risk factors of smoke exposure, bed sharing, upper respiratory tract infection (URTI) and seasonal temperatures. The authors claim the findings show that some abnormalities of the PACAP system are evident in the SIDS brain and could contribute to the mechanisms of infants succumbing to SIDS. Tang et al. [26] compared the expression of BDNF (proBDNF and rhBDNF forms) and its receptor TrkB, in the medulla of SIDS and non-SIDS infants and evaluated these markers in association with SIDS clinical risk factors including sleep position, cigarette smoke exposure and gender. Compared to non-SIDS, SIDS infants had lower rhBDNF in the caudal nucleus of the solitary tract and higher TrkB in the caudal dorsal motor nucleus of the vagus (DMNV). Within the SIDS cohort, prone sleep position was associated with lower rhBDNF in the caudal arcuate nucleus, and cigarette smoke exposure was associated with lower rhBDNF and TrkB in the inferior

olivary nucleus. Gender exhibited a significant interactive effect on findings in the DMNV.

Ramirez' group [27] have studied the role of the preBöttzinger complex (preBötC) in relation to responses to hypoxia and have proposed a potential association with male gender and age and prematurity. However, other associations and/or SIDS risk factors have not been documented. Their findings have been derived from animal studies and centre upon the theme of control of gasping responses and respiratory control.

Mainstream researchers argue that physiological findings support the hypothesis of abnormal homeostasis of cardiorespiratory control in SIDS babies [28-30], however, the cardiorespiratory hypothesis presupposes that because prone sleep position is a risk factor it must have some role in causation. This is clearly erroneous because babies die in other non-prone sleeping positions. Physiological studies have not examined whether or not infection alters physiological findings. Something important is happening when infection combines with prone sleep position (*vide infra*), but we are unable to say whether or not prone position affects physiological responses directly or prone position is important in acquisition (through inhalation or ingestion) of infectious agents from a contaminated sleeping surface. Subjecting normal babies to potentially asphyxiating conditions and observing that they have difficulty in raising their heads does not prove an association between babies' breathing conditions and SIDS or SUDI.

Finding abnormalities in brainstem nuclei involved in responses to hypoxia or other brain loci that control head and neck movement does not necessarily "explain why SIDS infants are unable to lift their heads out of challenging environments [31]." This audacious statement (in quotes) illustrates seemingly blind adherence to an hypothesis and abandonment of basic scientific principles. While these mainstream researchers found two SIDS risk factors (prematurity and male gender) associated with abnormal brainstem NK1R binding, their list of risk factors is too small to claim causal association. The relationship to smoke exposure, prone sleep position, socioeconomic risk factors, etc. is not mentioned and this apparent void undermines any proposed hypothesis. To claim their findings provide support for the hypothesis that abnormalities in SIDS deaths involve a multi-neurotransmitter network is premature. The statement "SIDS has a complex and heterogeneous pathogenesis with multiple abnormalities in a number of physiological functions that may involve neurological, cardiovascular, respiratory, gastrointestinal, nutritional, endocrine, metabolic and immunological systems, with infectious, environmental and genetic components [31]" begs the question of why do over 90 percent of SIDS cases have very similar pathological findings which include intrathoracic petechiae, liquid (unclotted) heart chamber blood, congested lungs and characteristic organ weight findings (large brain and thymus)? Heterogeneous pathogenesis would, on balance of probability, provide a panoply of pathological findings. Occam's razor would suggest otherwise and surely impose a

single mortal process because of the similarity of pathological findings in SIDS cases. Mainstream research has not yet seriously examined the effect of sepsis on the brainstem and other brain sites. This is surprising given that sepsis induces apoptosis [15], a common finding in the brainstems of SIDS cases [12]. It would be appropriate, therefore, to examine the CNS of babies dying of sepsis using the same methodologies.

Mage et al. [32] has clearly demonstrated the effect of gender on SIDS with the male fraction always being 0.61. This finding strongly points to an X-linked susceptibility to explain the male predominance. Mage et al. argue that an X-linked two-allele (aA) single gene may be responsible, with the absence of the A allele predetermining risk of SIDS [33]. Furthermore, this male excess is observed in most infectious diseases where similar genetics could apply. In particular, respiratory infection as an accompaniment to SIDS, is strongly supported by its relationship to prone sleeping position [34] (the effect of prone sleep position does not operate in uninfected infants) and high birth order (where older siblings provide the source of such infections by bringing home the infectious agents from their peers at schools, daycare centres and elsewhere [32]).

Infection and sepsis is known to increase serum levels of serotonin [35]. This neurotransmitter has lately been keenly explored by mainstream researchers. "Diagnosis of sepsis as the cause of death can be difficult at autopsy, especially when a clear macroscopic or histological focus of infection cannot be identified [36]." Thus, absence of findings does not mean absence of sepsis.

Studies based on the asphyxial/hypoxia model produce too variable brainstem changes in animals to consolidate the cardiorespiratory hypothesis. The findings of Poets et al. [37] should have long ago dissuaded researchers from following the asphyxia research path. Findings in relation to the DMNV [18, 26] could encourage exploration from the point of view of neuroimmunological effects and potential vulnerability to infection [38]. A recent systematic review of the relationship between infection and sudden unexpected death [39] highlights the need to rethink research directions that could provide better explanations.

### 3. Conclusion

The cardiorespiratory hypothesis of SIDS fails because of its lack of consistent correlation with clinicopathological and epidemiological data. The few appropriate studies have produced piecemeal or often conflicting data. Staining techniques designed to analyse a single feature (e.g. apoptosis) give conflicting results within the same dataset. It is noted that several of the abovementioned studies have shown brainstem changes in control infants dying of infectious causes which should stimulate animal studies to seek a more rational cause (such as sepsis) of brainstem changes. Indeed, while it is known that lethal sepsis stimulates release of serotonin resulting in increased serum levels, and causes thrombocytopenia (cf. liquid heart blood and raised fibrin

degradation products in SIDS), demands a question as to why mainstream research has not explored the sepsis link in relation to all purported changes in blood and in the brain and brainstem?

The above discussion invites researchers to debate the issue and to reconsider reasons why they should adhere to their hypotheses. The inherent failings of mainstream SIDS research described in this review should encourage researchers to explore the infection/sepsis hypothesis in view of its complete congruence with the clinicopathology and epidemiological risk factors of SIDS.

### Dedication

I dedicate this article to the memory of the late David Mage who tirelessly explored and contributed to our knowledge of the epidemiology of SIDS.

### Conflict of Interest Statement

The author confirms he has no possible conflicts of interest.

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