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Developmental alterations of the auditory brainstem centers — Pathogenetic implications in Sudden Infant Death Syndrome



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ABSTRACT

Sudden Infant Death Syndrome (SIDS), despite the success of campaigns to reduce its risks, is the leading cause of infant death in the Western world. Even though the pathogenesis remains unexplained, brainstem abnormalities of the neuronal network that mediates breathing and protective responses to asphyxia, particularly in the arousal phase from sleep, are believed to play a fundamental role. This is the first study to identify, in SIDS, developmental defects of specific brainstem centers involved in hearing pathways, particularly in the cochlear and vestibular nuclei, in the superior olivary complex and in the inferior colliculus, suggesting a possible influence of the acoustic system on respiratory activity. In 49 SIDS cases and 20 controls an in-depth anatomopathological examination of the autonomic nervous system was performed, with the main aim of detecting developmental alterations of brainstem structures controlling both the respiratory and respiratory network components were observed in SIDS victims compared with matched controls. Even if there is not sufficient evidence to presume that developmental defects of brainstem auditory structures can affect breathing, our findings, showing that developmental deficit in the control respiratory areas are frequently accompanied by alterations of auditory structures, highlight an additional important element for the understanding the pathogenetic mechanism of SIDS.

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1. Introduction

The current definition of SIDS (acronym of Sudden Infant Death Syndrome) is, as well known, "the sudden unexpected death of an infant <1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history" [1]. Despite the success of campaigns to reduce the risks introduced worldwide, the rate of SIDS has remained relatively stable since 2001, with around 2300 infants dying each year in the USA

[2]. Even if the pathogenesis of this syndrome remains unexplained, a disturbance in respiratory activity, due to developmental alterations of a specific central neural network, is believed to play a prominent role [3,4]. Indeed, breathing is the result of connections and interactions among several neuronal populations within the brainstem, including the preBötzinger nucleus (preBötN) in the medulla oblongata, and the Retrotrapezoid/Parafacial complex (RT/PFC) and the Kölliker–Fuse nucleus (KFN) in the pons [5–10]. This network is crucial in generating respiratory rhythm and in controlling the breathing, particularly in the responsiveness to arousal from sleep, that demands an increased ventilatory activity.

Acoustic stimulation has been shown to interfere with this central respiratory pattern [11]. Animal and human research has demonstrated that specific brainstem centers are involved in the hearing pathways, namely: the dorsal and ventral cochlear nuclei (DCN and VCN), the medial and inferior vestibular nuclei (MVN and IVN) in the rostral medulla oblongata, the superior and lateral vestibular nuclei (SVN and LVN), the superior olivary complex (SOC) in the caudal pons, and the inferior colliculus (IC) in the caudal midbrain [12–14]. The anatomical proximity of the auditory centers to the respiratory network components in the brainstem allowed us to presume, given obviously the impossibility to perform experiments in humans, that there are synaptic connections between them, thus explaining the influence of acoustic inputs on respiratory activity [15]. We therefore hypothesized that an intact

Abbreviations: ABS, auditory brainstem system; ANS, autonomic nervous system; CN, central nucleus; DC, dorsal cortex; DCN, dorsal cochlear nucleus; EC, external cortex; IC, inferior colliculus; IVN, inferior vestibular nucleus; KFN, Kölliker–Fuse nucleus; LSO, lateral superior olivary nucleus; LVN, lateral vestibular nucleus; MSO, medial superior olivary nucleus; MVN, medial vestibular nucleus; PO, periolivary nuclei; preBötzinger nucleus; RT/PFC, Retrotrapezoid/Parafacial complex; SIDS, Sudden Infant Death Syndrome; SOC, superior olivary complex; SVN, superior vestibular nucleus; TEOAE, transient evoked otoacoustic emission; VCN, ventral cochlear nucleus.

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development and function of the auditory brainstem system (ABS) might be necessary to maintain a regular ventilatory activity, above all during the vulnerable sleep phase in infancy, and that a disruption or defective development of auditory nuclei might play a critical role in inducing a predisposition to SIDS. Previously, we have already reported cytoarchitectural and functional alterations of the SOC and of the IC in victims of sudden perinatal death, suggesting a potential association between hearing centers and ventilatory activity [16,17].

Our interest in the present study was focused on the developmental state of all the brainstem centers involved in hearing control, in a cohort of infants who died in the first year of life of known and unknown causes. The main aim was to validate the supposed intersection between auditory function and arousal and, in particular, to evaluate whether alterations of the ABS development may contribute in triggering a sudden infant death, thereby taking a further step toward a fuller understanding of the pathogenesis of SIDS.

2. Materials and methods

2.1. Study subjects

The study included 69 infants, sent to our Research Center and diagnosed according to the application of the guidelines stipulated by Italian law n.31/2006 "Regulations for diagnostic post mortem investigation in victims of Sudden Infant Death Syndrome (SIDS) and sudden fetal death" [18]. This law decrees in particular that all infants who died suddenly within the first year of age, of suspected "SIDS", must undergo an in-depth anatomo-pathological examination, with a specific in-depth study of the autonomic nervous system (ANS). Parents of all subjects provided written informed consent to the autopsy examination, under protocols approved by the institutional review board (IRB) of the "Lino Rossi" Research Center, University of Milan.

After the routine autopsy and clinical history analysis, the death remained unexplained and hence a diagnosis of "SIDS" was made for 49 infants, 21 females and 28 males, who died within the first 8 months of life (mean age \pm SEM, 3.64 + 0.47 months). In the remaining 20 cases (10 females and 10 males, mean age \pm SEM, 3.57 + 0.42 months), a precise cause of death was formulated at autopsy. Specific diagnoses were congenital heart disease (n = 10), severe bronchopneumonia (n = 4), myocarditis (n = 1), pulmonary dysplasia (n = 3), pneumonia with acute respiratory distress (n = 1), and mucopolysaccharidosis type I (n = 1). These cases were regarded as "controls", also being similar with regard to gender, ethnicity and age at the time of death to SIDS cases.

2.2. Neuropathological examination

In all cases an in-depth histological examination of the ANS was performed, with the principal aim of detecting even fine developmental alterations of the brainstem structures controlling the vital functions. The study methodology is available at the website: http://users.unimi.it/ centrolinorossi/en/guidelines.html of the "Lino Rossi" Research Center, University of Milan.

Briefly, after fixation in 10% phosphate-buffered formalin, the brainstem was processed and embedded in paraffin. Then three specimens were taken. The first specimen included the upper third of the pons and the adjacent caudal portion of midbrain, below the superior colliculus and including the inferior colliculus; the second specimen extended from the upper third of the medulla oblongata to the adjacent caudal portion of the pons; and the third specimen included the obex. Transverse serial sections from the midbrain, pons and medulla oblongata samples were made at intervals of 60 µm. For each level, six 4 µm sections were obtained, three of which were routinely stained for histological examination using hematoxylin–eosin, Klüver–Barrera and Bielschowsky's silver impregnation technique. The remaining sections were saved for further investigations and stained as deemed necessary.

2.2.1. Histological examination of the brainstem

The routine histological evaluation of the brainstem was focused on the hypoglossus, the dorsal motor vagal, the tractus solitarius, the ambiguus, the inferior olivary, the pre-Bötzinger, the arcuate, the dorsal and ventral cochlear nuclei, the medial and inferior vestibular nuclei, and the obscurus and pallidus raphé nuclei in the medulla oblongata; on the locus coeruleus, the retrotrapezoid/parafacial complex, the superior olivary complex, the superior and lateral vestibular nuclei, the Kölliker-Fuse, and the median and magnus raphé nuclei in the pons; and on the inferior colliculus, the substantia nigra, and the dorsal and caudal linear raphé nuclei in the caudal mesencephalon. Histological and histochemical observations were carried out blindly by two independent pathologists. Comparison of results was performed employing K statistics (K Index – KI) to evaluate the inter-observer reproducibility. The Landis and Koch system [19] of K interpretation was used, where 0 to 0.2 is slight agreement, 0.21 to 0.40 indicates fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 strong or substantial agreement, and 0.81 to 1.00 indicates very strong or almost perfect agreement (a value of 1.0 being perfect agreement). The application of this method revealed a very satisfactory KI (0.87).

2.3. Risk factor information

For each case, all available information about pregnancy, delivery and about the environmental and familial situation where the death occurred, besides information related to both "preventable" and "unpreventable" risk factors [20], was collected and categorized during post-mortem family interviews. All the information sheets were recorded in the registry of a dedicated data bank, as stipulated by Italian law n. 31. Attention has been given to the preventable factors well known in literature as associated with SIDS, and that could be avoided. In particular, mothers were asked to complete a questionnaire probing smoking habit and, if they were smokers, detailing the number of cigarettes smoked before, during and after pregnancy. Smoking habit was assigned to two categories (smokers vs. nonsmokers). Overall, 32 of the 69 mothers (46%) were smokers of more than 3 cigarettes/day already before the onset of pregnancy, and 37 were nonsmokers. Since the retrospective assessment of the smoking habit of a mother, mainly after the death of her son, is sometimes unavoidable, the negative self-reports were validated by the urinary measuring of cotinine, the main metabolite of nicotine.

Twenty-six women in the smoker group were mothers of a victim of SIDS and 6 of control cases.

2.4. Statistical analysis

Quantitative data were expressed as means \pm SEM. The significance of differences between parameters of the groups of victims was evaluated by the Student-t test, the χ^2 test or Fisher's test. In case of skewed distribution, a nonparametric Whitney rank sum test was used. One-way ANOVA was used for quantifying and partitioning variance between groups. Statistics were compiled and plotted using SigmaPlot® (version 13, Systat Software Inc., Chicago, IL). The threshold level set for statistical significance was p < 0.05.

3. Results

In accordance with the aim of this study, an in-depth histological examination of the ANS was mainly focused on the brainstem centers presiding over the sense of hearing.

3.1. Examination of the brainstem auditory network

3.1.1. Cochlear nuclei

The cochlear structure is the first synaptic relay station of the auditory pathway and the termination site of all auditory nerve fibers [21,22]. It is best analyzed at the rostral pole of the medulla oblongata at the



Fig. 1. (A) Entire cross-section of medulla oblongata from a 3 month-old control case. The framed area in (A) is represented at higher magnification in (B), showing localization of the main structures of interest. Klüver Barrera stain. Magnification: A) 0.5×; B) 4×. DCN – dorsal cochlear nucleus; icp – *inferior cerebellar peduncle*; IVN – *inferior vestibular nucleus*; MVN – *medial vestibular nucleus*; tsn – *tractus solitarii nucleus*; VCN – *ventral cochlear nucleus*; 4thv – *fourth ventricle*.

junction with the pons and, in transverse histological sections at this level, at the external lateral border of the medulla, adjacent to the inferior cerebellar peduncle. Two main regions are recognized: the dorsal and ventral cochlear nuclei (DCN and VCN, respectively) (Fig. 1). The cytoarchitecture of the DCN features scattered medium sized cells with a centrally lying nucleus and a bundle of parallel fibers of the cochlear nerve, running outwards immediately under the pial surface (Fig. 2 A,B). The VCN consists prevalently of small cells along the free border of the medulla and with an underlying layer of large neurons adjacent to the inferior cerebellar peduncle (Fig. 2 C,D). In 19 of the 49 SIDS cases (39%) and in none of the control group we observed hypoplasia of both the cochlear nuclei, with the predominant presence of nerve fibers, frequently with a laminar disposition, and only occasional shrunken neurons (Fig. 3).

3.1.2. Vestibular nuclei

The vestibular nuclei carry out a variety of sensorimotor functions, including the control of movement and the position of the head [23, 24]. There are four vestibular nuclei, not visible in the same histological cross section since they are distributed rostrocaudally in a broad brainstem portion. The medial and inferior vestibular nuclei (MVN and IVN) are located adjacent to each other in the rostral medulla,

near to the DCN, beneath the floor of the fourth ventricle and ventrally to the tractus solitarii nucleus (Fig. 1). Both these nuclei show numerous glial cells with scattered, large, prevalently round neurons characterized by the presence of darkly stained Nissl granules that form a dense hole at the periphery of the cell bodies (Fig. 4). The lateral and superior vestibular nuclei (LVN and SVN) are visible in transverse sections of the caudal pons, below the lateral floor of the fourth ventricle. They include large fusiform/multipolar cells with darkly stained Nissl granules, mingled with numerous fibers (Fig. 5).

An altered morphology of all the vestibular nuclei, consisting of the absence of the typical neuronal bodies of the MVN and IVN and/or the presence of rare neurons and very few processes in the LVN and SVN, was detected in 31% of SIDS (15 cases). In 2 control cases the pontine vestibular nuclei were not identifiable.

3.1.3. Superior olivary complex

In the same pontine histological sections showing the LVN and SVN, the SOC is recognizable as a dense roundish area, lying anteriorly and medially to the Retrotrapezoid/Parafacial complex (RT/PFC) (Fig. 6). It includes a group of nuclei that are prevalently involved in sound source localization [25,26]: the lateral superior olivary nucleus (LSO), the medial superior olivary nucleus (MSO) and a large number of smaller cell



Fig. 2. (A) and (B): dorsal cochlear nucleus (DCN). In (B) the cytoarchitecture of this nucleus is well visible with an external bundle of fibers of the cochlear nerve overlying numerous medium sized cells. (C) and (D): ventral cochlear nucleus (VCN). (D): the cytoarchitecture of this nucleus consists of many widespread small cells and an inner layer of large neurons adjacent to the inferior cerebellar peduncle. Control newborn (2 months old). Klüver Barrera stain. Magnification (A) and (C) 4×; (B) and (D) 20×.



Fig. 3. Hypoplasia of the cochlear nuclei in a SIDS infant (4 months old). (B) and (C): histological features of the dorsal cochlear nucleus (DCN) and of the ventral cochlear nucleus (VCN), respectively, with numerous nerve fibers and small-shrunken neurons. Klüver Barrera stain. Magnification (A) $4 \times -$ (B) and (C) $20 \times$.

groups defined as periolivary nuclei (PO). The MSO is the major and most easily recognizable component. It appears as a compact layer of neurons included in a narrow column with a ventral/dorsal orientation (Fig. 7A). A marked disarrangement of the MSO was frequently observed in SIDS victims. In particular, the MSO column was largely devoid of fibers, featuring very few scattered neurons provided with rare dendrites in 12 cases (24%) (Fig. 7B). Decreased number of neurons with a rarefaction of the fibers in the MSO was found in only 1 control case.

3.1.4. Inferior colliculus

The inferior colliculi (IC), that are the caudal eminences of the corpora quadrigemina in the tectal region of the midbrain, play an important role in the synthesis of acoustic information [27,28]. The IC shows a predominant large dark core, the central nucleus (CN), with marked cellularity, surrounded by a light peripheral layer subdivided in a dorsal cortex (DC) and an external cortex (EC) that, by contrast, shows very few, small neurons (Fig. 8). This structure was highlighted in all control cases. Developmental cytoarchitectural alterations of the IC were instead detected in 41% (20 cases) of SIDS. In particular, the central nucleus was unidentifiable in all the serial histological sections of caudal midbrain or showed a marked disarrangement, with subdivisions into two or three portions.

Two or more alterations of the auditory nuclei among those listed above were present together in the same SIDS infant. Overall, SIDS cases showed a significantly higher incidence of histological alterations of the auditory nuclei, as compared with age-matched controls. In fact, 23 of the 49 (47%) SIDS victims and only 2 of the 20 (10%) control subjects showed developmental modifications of the auditory nuclei (χ^2 test, p = 0.003). Table 1 represents all the above results.

3.2. Examination of the brainstem respiratory network

Morphological alterations of one or more brainstem structures assigned to respiratory control were detected in 18 of the sudden infant death victims, namely hypoplasia/agenesis of the preBötN, the RT/PFC and the KFN in the medulla oblongata/pons. These alterations are frequently associated with developmental alterations of the auditory centers (in 11 cases). The most frequent association was between MSO hypoplasia and hypodevelopment of the adjacent RT/PFC.

3.3. Correlation of findings with preventable risk factors

A significant correlation was highlighted between the presence of developmental alterations of the auditory system components and maternal smoking. Twenty-two of the 23 SIDS cases with auditory nuclei defects (78%) and only 1 case of the control group with rarefaction of fibers in the MSO and unidentified LVN/SVN, had a mother smoking already before the pregnancy (χ^2 test, p = 0.02).

4. Discussion

Auditory information is communicated from the outside environment to the hearing apparatus through precisely organized neural circuits in the brainstem, that make up the "auditory brainstem system" (ABS) [11].

Hearing in humans begins around the 22nd week of gestation [29]. At this stage, behavioral responses to sounds are produced only by intense airborne stimulation, since the fetus is in a highly sound-attenuated environment, the outer and middle ears are fluid-filled, and the auditory



Fig. 4. Typical morphology of the neurons of the medial and inferior vestibular nuclei (MVN and IVN) in the medulla oblongata, with darkly stained Nissl granules at the periphery of the cell bodies. Same case of the Fig. 1. Klüver Barrera stain. Magnification $40 \times$.



Fig. 5. (A) Entire cross-section of caudal pons from a 6 month-old case control. The framed area in (A) is represented at higher magnification in (B), showing the localization of the lateral vestibular nucleus (LVN) and of the superior vestibular nucleus (SVN). (C): fusiform neurons of the LVN assembled in dense neuropil. Klüver Barrera stain. Magnification: (A) 0.5×; (B) 4×: (C) 20×.

apparatus is structurally and functionally immature. After birth, sensitivity to sound is rapidly acquired, and many simple aspects of hearing achieve maturity during the first year of life.

While the development, the anatomy and the physiology of the main components of the auditory apparatus are well delineated, much less is known about the neuronal circuits presiding over the sense of hearing. Current knowledge indicates that the auditory centers in the brainstem develop very early. From the 7th–8th gestational weeks, it is already possible to identify, at the edge of the medulla oblongata, the immature neurons of the cochlear nuclei with several axons that reach the caudal pons and innervate the superior olivary complex, and others that project through the lateral lemniscus to the inferior colliculus in the midbrain [29–31]. All the components of the ABS are well recognizable as from the second trimester of gestation, although the neurons are still immature [32]. The perinatal period is the time when major developments of the auditory nuclei occur, with growth, arborization and myelination of neuronal dendrites [29,32].

The ABS has been demonstrated to play an important role in respiratory control, especially during sleep, in the first months of life [33,34]. Stimulation of the vestibular nuclei, in particular, has been established to cause arousal, by promoting the body and in particular the head dynamics, and increasing the firing of the respiratory central pattern generator [35–37].

Arousal from sleep occurs spontaneously in response to physiological requirements, but can also be an important survival reaction to noxious factors [38–40]. Awakening basically consists of two simultaneous events: 1) a respiratory component that causes an increase in ventilation and 2) the initiation of specific body movements, including a head shift that is a very important defense mechanism to escape a life-threatening situation, such as the presence of a suffocating gas mixture. This movement allows for inhalation of fresh oxygenated air to counteract a possible depressed ventilator response to hypoxia, the leading cause in sleep-related sudden infant deaths [41,42].

In this study we hypothesized that an altered development of the auditory brainstem nervous structures occurring in the early postnatal period may have dramatic effects on arousal, affecting the function and/or development of the connected respiratory brainstem centers, thereby with a final fatal outcome.

Therefore, suppression of the arousal response to a hypoxic environment, the most frequent cause of SIDS [42,43], may be due at least in part to a neuropathological hearing mechanism [33,34,44,45]. The results of the present study allowed us to validate our assumption. In fact, we found a significantly higher incidence of abnormalities in the auditory structures of the brainstem, namely hypoplasia and/or cytoarchitectural alterations, including a reduction of both dendritic arbors and neuronal numbers, of the cochlear and vestibular nuclei, the superior olivary complex and the inferior colliculus, in SIDS infants compared to age-matched controls (47% vs. 10%). These defects were frequently associated with delayed maturation of the respiratory network nuclei.



Fig. 6. (A) Entire cross-section of caudal pons (the same as shown in Fig. 5). The framed area in (A) is represented at higher magnification in (B), showing the localization of the superior olivary complex, ventrally to the Retrotrapezoid/Parafacial complex. Klüver Barrera stain. Magnification: (A) 0.5×; (B) 10×. LSO – lateral superior olivary nucleus; MSO – medial superior olivary nucleus; PO – periolivary nucleus; RT/PFC – Retrotrapezoid/Parafacial complex; SOC – superior olivary complex.



Fig. 7. Medial superior olivary nucleus. (A): normal structure in a control infant (3 months old) showing a compact group of neurons included in a narrow column. (B): hypoplasia with lack of fibers and sparse peripheral neurons in an age-matched SIDS case. Klüver Barrera stain. Magnification (A) and (B) 20×.

A potential relationship between inner ear abnormalities and predisposition to SIDS has been previously proposed by Rubens et al. [46], though only assessed through a newborn transient evoked otoacoustic emission (TEOAE) hearing screening test, without any neuromorphological validation. The study has received serious criticism in the literature for various reasons (the small number of SIDS cases included, the means by which the SIDS diagnosis was made, the inappropriate control group included, the applied statistical test, etc.) [47–50]. Our findings, however, seem to sustain the Rubens hypothesis, with the more convincing histopathological evidence.

What we want to emphasize is the importance of considering impaired hearing in the first months of life as a new factor characterizing vulnerable infants with possible breathing problems, then susceptible to SIDS. We are hoping for the introduction of standard newborn screening tests after birth with the aim to identify hearing deficit that could be predictive of future SIDS death, thereby allowing for necessary preventive measures. Moreover, newborn hearing screening is already standard care in the United States, with 90% of newborns being screened annually [51].

A limitation of the study is its focus only on the brainstem auditory pathway and not on the more rostral auditory components of the forebrain (the "auditory thalamocortical system"), where additional integrative aspects of hearing are processed [52,53]. The main reason for this choice is that the brainstem auditory structures are anatomically located in close proximity to the main neuronal centers checking the respiratory activity, and that these two networks are fully developed as one at the end of the perinatal period. On the contrary, whereas at this age the thalamus and the auditory cortex are still quite different from those of an adult, and will reach the final steps of maturation only in later childhood. However, we are now fully aware of the clear need to extend our research to the superior auditory nervous system, in order to gain a more comprehensive neurophysiological understanding of the relations between the overall central auditory and central respiratory networks.

4.1. Conclusions

This study provides additional issues to the definition of the pathogenetic mechanism leading to SIDS. In fact, our findings demonstrate that developmental brainstem deficits are not limited to respiratory nuclei, as unanimously recognized in literature, but are extended to auditory structures. Thereby, in the absence of any functional evidence of an effective link between hearing and breathing systems, we cannot sustain that alterations of hearing centers can affect breathing. The only solid conclusion that we can draw at this moment is that brainstem auditory structures represent another site of developmental deficit in SIDS victims, with implication for novel indicators/markers of increased risk of SIDS, including the application of newborn hearing screening tests to identify auditory deficits potentially predictive of future sudden death.

Conflict of interest

The authors declare that they have no conflicts of interest, financial or otherwise to declare.



Fig. 8. (A) Entire cross-section of caudal midbrain in an infant of the control group (seven-months old). The framed area in (A) is represented at higher magnification in (B), showing ^{the} localization of the components of the inferior colliculus: the central nucleus (CN), the dorsal cortex (DC) and the ventral cortex (VC). Klüver Barrera stain. Magnification (A) 0.5×; (B) 4×.

Table 1

Neuropathological findings in auditory brainstem centers.

Auditory brainstem centers		$\begin{array}{l}\text{SIDS}\\(n=49)\end{array}$	Controls $(n = 20)$
Cochlear nuclei	Normal	30 (61%)	20 (100%)
	Altered structure	19 (39%)	
Vestibular nuclei	Normal	30 (69%)	18 (90%)
	Altered structure	15 (31%)	2 (10%)
Superior olivary complex	Normal	37 (76%)	18 (90%)
	Altered structure	12 (24%)	2 (10%)
Inferior colliculus	Normal	20 (41%)	20 (100%)
	Altered structure	29 (59%)	-

Two or more alterations of the auditory nuclei among those listed above were present together in the same SIDS infant.

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