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ORIGINAL ARTICLE

Anatomopathological changes of the autonomic nervous system controlling the respiratory rhythm in sudden infant death: advances over the last 30 years

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ABSTRACT

Sudden infant death syndrome (SIDS) is an irreparable loss for the parents and has life-long consequences for the grieved family

Objective: This systematic review aims to compile all the researches conducted so far on the possible involvement of respiratory neuronal structures of brainstem in SIDS

Methods: Studies were extracted by using MeSH words “Sudden infant death syndrome, neuropathology” on Pubmed database and also search through hand screening.

Results: A total of 114 studies were identified which were later further screened for inclusion criteria such as SIDS cases, original articles and case reports and brain nuclei involved in SIDS, while review articles and editorials were excluded. After further screening 40 studies were shortlisted. All the data was analyzed through excel, yearwise, country wise comparison was also conducted. Maximum studies (24) were published from Italy, most publications were from 2010-2020 (27). Upon final screening according to the inclusion of neuronal brain nuclei studies in SIDS, 27 studies were finalized and used for analysis. Altogether there were 805 SIDS cases and 270 controls reported in these 27 studies. Alterations in the brain nuclei included arcuate nuclei, Dorsal raphe nuclei, preBötzinger complex, vagal nuclei, Kölliker-Fuse complex, Tractus solitarius, Parabrachial Kölliker-Fuse complex, Trigeminal nucleus, Parafacial/facial complex, Dentate gurus and others

Conclusions: This study highlights the importance of further research in the underlying mechanisms of SIDS. It should be investigated at neuropathological as well as molecular level to understand the mechanisms. It may guide and help to identify the vulnerable infants and save their lives in future.

Key words: Neuropathology, Sudden infant death syndrome, crib death, Cot death, brainstem, breathing

INTRODUCTION

Sudden infant death syndrome (SIDS) is an unforeseen death of a apparently active infant within twelve months or first year of life that could not be explained after detailed history, careful investigation of death scene and even after thorough autopsy [1]. It is also called as ‘cot death’ or ‘diagnosis without a disease’ [2]. In an analysis of US Period Linked Birth/ Infant Mortality Files from 1990 to 2017 SIDS has been declared as a most leading cause of death in infants in the United States of America (USA) [3]. The role of neuropathological mechanism in SIDS manifestation, is highly controversial and mostly found to be related with healthcare disparities during pre- and post-natal periods. These issues can be illustrated by a proposed triple-risk model hypothesis relay upon three coinciding factors; an underlying biological abnormality increasing the vulnerability of the infant; a critical developmental period during homeostatic-control; and the application of an external stressor like asphyxia [4, 5]. It has been observed that all these three risk factors when affect together, can contribute to the critical situation of SIDS in an fully active infant. Hence, considering this model is very significant in supporting the future research on SIDS [5]. Since brainstem is playing a crucial role in control of vital activities of human life, like control center of cardiac activity, respiratory and blood pressure control, thermoregulation of human body and many other important functions. Further investigations have revealed many abnormal patterns of respiration, impaired autoresuscitation (gasping) and arousal deficits with episodes of obstructive breathlessness during sleep [6].

Based on such observations, investigations were directed towards respiration related neurotransmitters and neural pathways of medulla oblongata which are responsible for all respiratory control mechanisms, arousal, chemosensitivity and autonomic functions. Breathing is highly integrated process which is constantly adapted to metabolic demands of our body. Breathing integration is maintained by several respiratory neurons which are concentrated in the ventral respiratory group (VRG) in medulla, these neurons include parafacial respiratory group, pre-botzinger complexes (PBC), botzinger complexes, kolliker fuse, retrotrapezoid nucleus and some cerebellar and cortical networks [7]. The dynamic interaction of structures and functions of these components determine the motor pattern of respiratory rhythm. Core control region of generation and coordination of respiratory rhythm is PBC especially, eupnea, sighs and gasping are three important rhythms associated with response to decreased oxygen supply [8]. These medullary nuclei act

as a pacemaker and have their special role in the establishment of breathing control on failure of normal respiratory homeostasis mechanisms [9].

Multiple neuromodulator defects were considered responsible for SIDS in previous experimental studies through postmortem of human infant's brain tissues [10, 11]. These developmental alterations in brainstem neural networking, predominantly affect the berating control. Particularly underdeveloped nuclei like Kolliker Fuse Nucleus (KFN) of brainstem may play an important role in compromised vital functions like breathing control on any fall of oxygen supply from atmosphere [12, 13].

This systematic review will keep focusing on the collection of data of SIDS victims with proven neurological defects in respiratory control system, from all previous experimental studies. As per our observation, this systematic review is a one of its type to provide a comprehensive report on the past studies on neuropathologies related to SIDS.

METHODOLOGY

Search Strategy: We searched PubMed database for studies published on sudden infant death syndrome till to-date (September, 2021). MeSH terms used for searching were "sudden infant death, neuropathology". A further screening was performed hand searching the reference lists of retrieved included studies. All references were maintained by utilizing Endnote.

Eligibility Criteria: All Original studies follow-up duration, study plan, geographical region, age and gender restrictions were evaluated to confirm Neuropathological disturbances in breathing mechanism as a reason of SIDS or Crib death in infants. The Author's affiliations and their names, the enrolled duration, and setting were checked to find whether same population were used in studies. We included all these studies irrespective of the publishing year, geography and population. All the original studies and case reports were included while personal opinions, editorials, meeting abstracts, book reviews, computational analysis, reviews, frequency studies, survey reports, protocols and guidelines, sudden intrauterine death, still birth and animal research were excluded. Article selection were completed in two phases, first phase included the titles and abstracts screening of initially selected articles and second phase includes, reading the complete text of those articles. However, unmatched article was excluded from the study by following eligibility criteria

Data Extraction: The manually extracted data from the chosen articles after reading complete text, then completing a data collection form in a standardized manner using Excel v.2015 (Microsoft. Redmond, WA).

RESULTS

Literature Search: The study selection procedure and obtained results is illustrated by flow diagram (Figure 2). Total 85 publications were obtained from PubMed. 29 additional publications were identified through hand screening (Figure 2). Initially there were a total of 114 publications. Records were screened for duplicates, title and abstract and 40 publications were identified to be potentially eligible. Reviews, editorials, opinion articles and retrospective frequency studies, cohort studies, sudden intrauterine death, stillbirth and animal studies were excluded. Excluded publications were 72, based on the criteria. Original articles and studies on human brain, discussing the neuronal centers involved in breathing and vital functions were further screed to be included and final studies included were 27 (Figure 2). It ranged from 1993 till 2021.From the selected 40 publications, first publication was in 1993, 2 publications till 2000, 10 publications from 2001-2010, 27 from 2011-2020 and 1 in 2021(Table 1).

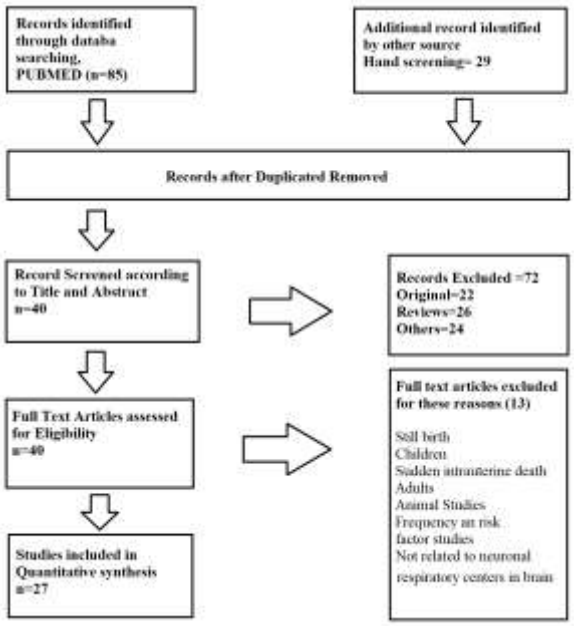

Figure 2: Flow chart of search strategy for publications on Sudden Infant Death Syndrome (SIDS) and neuropathology

Table 1: Studies related to SIDS or Sudden Infant Death Syndrome and neuropathological alterations of respiratory centers in brainstem, extracted through literature

No	Year	SIDS	Controls	Neuronal structure	Physiology of brain nucleus	Results of study
1	1993 [14] Canada	30	29	Vagus nerve	neural regulation of respiration	Delayed vagal nerve maturation, CNS myelination and dendritic development
2	1995 [15] Australia	11	11	-	-	no specific differences with age wise increase in total neuronal number, nuclear position and nuclear volume
3	2004 [16] Italy	41	7	Arcuate nucleus (AN)	feeding, metabolism, fertility, and cardiovascular regulation, release dopamine	Results shows that smoking may leads towards hypoplasia of AN that affect the expression of homeobox En-2 gene.
4	2005 [17] Japan	26	12	dorsal raphe nucleus (DRN) of the midbrain and pedunculopontine tegmental nucleus (PPTN)	Serotonergic, release enkaphalins which inhibit pain, regulate sleep/wake state, thermoregulation	Neuronal plasticity, sleep apnea and glial apoptosis plays important role in SIDS arousal.
5	2008 [18] Italy	38	-	preBötzinger complex (pre-BotC)	pre-BötC complex includes a variety of neurons involved in the generation of respiratory rhythm as well as crucial to control of all vital functions	Hypoplasia of pre-BotC complex

6	2008 [19] Italy	158	-	pre-BötC nucleus hypoplasia, tractus solitaries nucleus (TCN), hypoplasia of the parabrachial (PB)/Kölliker-Fuse complex (KFC, arcuate nucleus (AN)	Pre-BotC (as above) KFN plays potent role during intrauterine life, inhibiting the response of central and peripheral chemoreceptors and hence works as an respiratory reflex	Neoplastic lesions of the cardiac conduction system, Brainstem encephalitis + moderate myocarditis, TCN necrosis, Area postrema (AP) hemangioendotelioma, Pneumonia + hypoglossal nucleus hypoplasia. hypoplasia of the AN, PB/ KFC. Pre-BotC. complex and parafacial nucleus (PFN)
7	2009 [20] Italy	28	17	Raphe nuclei (RN)	neuronal development in fetal brain. Serotonergic, release enkaphalins which inhibit pain, regulate sleep/wake state, thermoregulation	Smoking during pregnancy leads towards SIDS with hypoplasia of RN.
8	2009 [21] Italy	29	16	Guillain and Mollaret (G-Mt), olivary nucleus (ON), dentate nucleus (DN), red nucleus (RN)	G-Mt refers to the neuronal brainstem or cerebellum network known for its strong connection with pathogenesis of the palatal myoclonus, in unusual and unidentified perinatal and infant death.	increase of lesions of the three nuclei was found in unexplained death victims Increased number of lesions of three nuclei was found in SIDS victims
9	2010 [22] Belgium	28	10	solitary nucleus/tractus (TCN; vagal center), and the spinal trigeminal nucleus/ tractus (TTCN; receives vagal afferents). arcuate (AN) and the dorsal vagal (DVN) nuclei	IL-2 is a cytokine involved in the critical functions of those neuronal networks	Acute neuronal IL-2 immune-reactivity in the SIDS brainstem in TCN and/or TTCN was detected
10	2010 [23] Italy	36		intermediolateral nucleus (ILN)	ILN refers to the neural center that is responsible to produce initial spontaneous bursts of respiratory rhythmic activity in beginning of fetal stages.	ILN abnormalities were found almost exclusively in SIDS
11	2011 [24] Italy	32	11	Tractus solitarius nucleus (TTCN)	receives and responds to stimuli from the respiratory, cardiovascular, and gastrointestinal systems	TCN alterations smoking during pregnancy leads towards penetration of cigarette smoke in uterus with lower functional activity of TTCN.
12	2012 [25] Italy	29	-	Area Postrema (AP)	AP is an vital part of the autonomic CNS. A normal AP structure and functionality is important to guard a complete development of brain	High incidence of AP alterations in SIDS with poor vascularization, formation of cysts, hypoplasia and reactive gliosis, were appear due to smoking during pregnancy
13	2012 [26] Italy	30	12	Medial superior olivary nucleus (MSO),	breathing and, more extensively, all the vital activities. MSO plays vital part in the processing of signals of sounds	Abnormal organ development (dysgenesis) of contiguous structures found in respiratory rhythm generating circuits with relation to Hypoplasia of facial nuclei and retrotrapezoid nuclei
14	2013 [27] Germany	9	9	Cerebellar purkinje	respiratory and cardiovascular control	Structural changes of cerebellar development were not found to be involved in development of SIDS
15	2013 [28] Italy	30	15	fourth ventricle choroid plexus	fetal brain formation, main source of CSF secretion, have a strong link between the CNS and blood	Choroidal neuropathological parameters shows direct relation with smoking during pregnancy
16	2014 [29] Italy	3	-	vagal-glossopharingeal neuronal circuitry	neural regulation of respiration	Suffocation by hypotonic tongue caused by damaged parahypoglossal glossopharingeal brainstem while sleeping in supine position
17	2015 [30] Italy	14	8	Nicotinic receptors (nAChRs) in brainstem, Cholinergic system	α7 subunit of the nAChRs have a vital function in the regulation of growth, differentiation and plasticity of developing neurons	Alterations in nAChRs in SIDS
18	2015 [31] Italy	1	-	Area postrema (AP)	As above	alteration in the AP in SIDS
19	2015 [32] USA	114	39	hippocampus	Balances autonomic/respiratory control along brainstem connections	Defective development of dentate gyrus that shows damaged neuronal proliferation, migration, and/or survival
20	2015 [33] Canada	1	-	tractus solitarius nucleus (TTCN)	As above	Premature birth and some SIDS cases shows slowed formation of synapses/ myelination in TCN. It may leads towards neonatal hypoventilation
21	2016 [34] Italy	25	18	pontine Kölliker–Fuse nucleus (KFN)	Necessary for unlabored breathing at the time of birth	Defect in orexin expression in KFN plays important role to initiate SIDS
22	2017 [35] Italy	35	35	Nicotinic acetylcholine receptors (nAChRs)	enhance cholinergic transmission	nAChRs, smoking,alterations in cerebellar cholinergic transmission in areas of the brain involved in vital functions
23	2017 [36] Italy	1	-	Kölliker-Fuse nucleus (KFN)	As above	KFN is crucial for unlabored/ eupneic breathing at birth
24	2017 [37] Italy	10	8	Purkinje cell layer, cerebellar corten,BDNF	development of the cerebellar cortical structure	Modified BDNF, of synaptic transmission in the respiratory circuits, shows less rate of survival
25	2018 [13] Italy	22	10	pontine Kölliker-Fuse nucleus (PKFN)	As above	PKFN hypoplasia, an important respiratory center
26	2020 [38]Italy-Pakistan	26	20	Substantia nigra (SN)	SN pars compacta, majorly controls dopamine brain center, controls Several more activities like sleep-arousal phase	Maternal smoking can lead to low neuronal density, low TH expression in the pars compacta and hypoplasia
27	2021 [39] Italy-Pakistan	26	20	periaqueductal gray (PAG), an area of gray matter surrounding the cerebral aqueduct of Sylvius,	Breath and awakening regulation	65% of SIDS had been observed with hypoplasia of the PAG subnucleus medialis but never in controls; although TH expression was essentially more controllable than in SIDS

DISCUSSION

The prime explanation of a lethal triangle consideration on interplay of 3 elements was suggested in 1993: (i) a susceptible section in the improvement of the imperative fearful gadget and the immune device during the early days after birth, (ii) prompt elements, including heredity or brainstem astrogliosis and (iii) an activated episode together with hypersensitive immune gadget [40]. Studies suggest that SIDS instances would possibly take place resulting from the aggregate of 3 elements coming collectively: susceptible little one (premature birth or smoking exposure), prone section of growth, and a last offense going on this window of susceptibility (placed susceptible to sleep or mattress sharing) [4, 40]. SIDS arises while a little one at the moment is in a susceptible developmental level, with a rapid growth of each the significant nervous machine (CNS) and the immune machine. Approximately 1/2 of the SIDS sufferers have had signs and symptoms of mild infection within the days earlier than demise [41]. The most crucial danger elements for SIDS are the snoozing role, the status of susceptibility and side sound asleep situations appreciably extra riskier compared to that of supine one [42]. The advice for the supine sleeping position was already suggested for many years in the past [43] for all babies up to at least one year of age.

In present study we have tried to analyze the fact that most of the victims of SIDS have a dysfunctional homeostatic control of breathing by medullary respiratory control center, leading to impairment of response to

decreased oxygen supply [44]. SIDS is extensively suggested to involve immature cardiorespiratory manage in response to the arousal from sleep. Developmental autonomic nervous system, malfunctioning of arousal responsiveness of sleep serotonin transport and premature cardio respiratory autonomic control are suggested to be the main causes of SIDS. Deficits in the area of brainstem involved in cardiorespiratory manage and activation, in particular inside the serotonergic device, had been recognized in infants who died from SIDS [24, 45]. Persisted studies to pick out the pathophysiology [23] and genetics of SIDS [46] must therefore, be supported and accelerated to consist of large pattern sizes of each affected and manipulate babies from the best groups at risk.

In a study conducted on 30 SIDS and 29 controls of age 1-9 months, abnormalities in the cervical vagus nerve were observed where small and unmyelinated vagal fibers were frequent in SIDS. Vagus nerve is a main component of the neural regulation of breathing activity and its delayed maturation may be a cause of SIDS [14]. The neuropathological origin of SIDS that involves the cardiorespiratory dysfunction is a largely accepted hypothesis for the etiology of SIDS. A study was conducted in 1995 to understand the differences in neuronal sizes, volumes and numbers between the brainstems of SIDS and age-matched controls. However, no major differences were observed [15]. 41 SIDS cases were evaluated for the neuropathological investigation. Hypoplasia of Medullary arcuate nucleus (AN) in brainstems of SIDS with decreased neuronal density was frequently observed. Maternal cigarette smoking was found to have strong association for respective condition. The AN is located around the third ventricle and regulates the secretion of hormones such as prolactin and growth hormones. AN modulates many important physiological processes such as appetite, metabolism, cardiovascular regulation but its main function is homeostasis [16]. Positive correlation was observed between tryptophan hydroxylase neurons in dorsal raphe nucleus (DRN) and pedunculopontine tegmental nucleus (PPTN) of the midbrain with the duration of sleep apnea in victims of SIDS. DRN and PPTN might be involved in the sleep-arousal phase and cause SIDS [17]. In another study, 28 SIDS and 17 controls were examined for delineating raphe nuclei (RN) in the brainstems of these victims and to evaluate its association with serotonin transporter gene (5-HTT). RN hypoplasia was observed in SIDS brainstems, associated with maternal smoking and 5-HTT gene polymorphism [20].

Lavezzi and Matturri first identified the pre-Bötzinger complex (pre-BotC) in human brainstem. They evaluated 38 SIDS brainstems. Frequent alterations in pre-BotC were present in SIDS as compared to controls [18]. In another study conducted by Matturri *et al.,* 2008, 158 SIDS (28 neonatal and 130 infant death) cases were evaluated for the brainstem anatomopathological examination. One or more anomalies in the nuclei of brainstem and cerebellum were found [19]. Guillain and Mollaret (G-Mt), a neuronal brainstem/cerebellum network comprises of three nuclei: Dentate nucleus (DN), Nucleus ruber or Red nucleus (RN) and inferior olivary nucleus (ION). It was evaluated in 29 SIDS and 16 controls. Alterations in these three nuclei were observed in the SIDS cases [21]. Cardiorespiratory brain centers controlling the sleep/arousal pathophysiology are important underlying mechanisms in SIDS. The role of cytokines and immune cells in the etiology of SIDS remains debatable. A study reported intense Interleukin-2 (IL-2) immunoreactivity in the vital brain centers and may be contributing to SIDS [22]. Neuronal immaturity of intermediolateral nucleus (ILN) was observed in the brainstems of SIDS cases and a significant association with maternal smoking was observed. Mature ILN is essential for the first breathing bursts [23]. Spinal trigeminal nucleus (STN) was delineated in 32 SIDS and 11 controls by using Substance P (SP) immunohistochemistry. SP is released from STN and its expression may indicate STN in the brainstems. SP immunoreactivity was reduced in the brainstem of SIDS, showing an alteration in the function of STN, its hypoplasia and may be a possible cause of SIDS. Normal activity of STN is required for respiratory rhythmogenesis during the early phase of postnatal life. If altered, it may lead to SIDS [24].

Area postrema (AP) is a highly vascular circumventricular organ, outside of the blood-brain barrier. Apart from its routine functions such as emetic reflex, it has been also responsible in autonomic regulation of the cardiorespiratory rhythms. In a study, high alterations in AP were observed in SIDS victim brains as compared to the controls [25]. Anamalies in the cytoarchitechture of medial superior olivary nucleus (MSO) were observed in a study with 30 SIDS and 12 controls. MSO is important in the processing of hearing sensation. It was suggested that MSO has more important role than processing of acoustic information, i.e. respiratory rhythm generation and may cause SIDS, if altered [26]. Etiology and Pathogenesis SIDS does not include the involvement of cerebellar development. Cerebellar volume, morphology, neuronal numbers were similar in 9 SIDS and 9 controls, showing less significance of cerebellum in the etiology of SIDS [27].

Cardio-respiratory control in the brainstem required proper functioning and maintaining normal morphology of the nuclei. When these important brain centers are altered in morphology, functioning, secretion of neurotransmitters and neuronal numbers, it may be a causative factor for SIDS. These neuropathological findings must be further explored in detail and such diagnosis should be done in routine for all the SIDS cases.

CONCLUSIONS

Anatomopathological examination of SIDS brainstems is necessary to understand the neuropathological mechanisms as underlying cause of these deaths and molecular autopsies should also be conducted for a proper investigation of these death. It may serve as a preventive measure for future deaths in vulnerable infants.

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