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Review Article

Viral Infection and SIDS: A Multidisciplinary Approach for the Forensic Pathologist.

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Abstract

Sudden infant death syndrome (SIDS) is the sudden unexpected death of an apparent healthy infant under 1-year-old whose cause of death remains unknown despite a thorough death scene investigation, a review of the clinical history and autopsy. The risks factors for sudden infant death syndrome parallel those associated with susceptibility to or severity of infectious disease. This review assesses SIDS research in the context of clinicopathological features and focuses on the association of SIDS with a recent viral infection, most commonly a mild upper respiratory tract infection. The autoptic investigation of cases of sudden and unexpected death of the child must be carried out following standardized protocols and a multidisciplinary approach to establish the exact cause of death and in particular the role of respiratory tract infections as well as other exogenous triggers.

Keywords: Sudden infant death syndrome (SIDS), Sudden unexpected deaths in infancy (SUDI), Diagnosis, Classification, Viral infection, Human coronavirus HKU1

Introduction

Last century the scientist John Emery said that sudden infant death syndrome (SIDS) was in danger of becoming a "diagnostic dustbin [1]". The term SIDS was introduced in the mid-1960s [2], partly for humanitarian reasons, as it provided a recognised category of natural death for the sudden demise of an infant without an identified cause, shifting the focus from parental blame onto research aimed at prevention [3]. Since 2004 there has been widespread adoption of the 2004 SIDS definition of San Diego: "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 [4,5]", emphasizing the importance of thoroughly considering the circumstances of death in formulating the diagnosis. The San Diego definition introduced three subcategories of SIDS to enable researchers to more accurately specify the likelihood of a case being attributable to "SIDS". However, the more expansive sudden unexpected deaths in infancy (SUDI) grouping frequently appears to be erroneously used interchangeably with SIDS. Nearly 16 years on it appears that the San Diego definition is not working as well as it could as a definition/classification tool given that it does not appear to be applied rigorously or consistently [6]. There are now even proposals to use SUDI as the diagnostic term for unexplained sudden infant deaths, effectively becoming indistinct between unclassified sudden infant death (USID) and SIDS, which should only be recorded if all other possible causes of death have been excluded; this despite a quite robust framework being proposed for the use of SUDI by the Confidential Enquiries of Stillbirths and Deaths in Infancy (CESDI) group in 2000 [7]. Deaths due to SIDS account for about 1% of deaths under the year of life and is estimated that 250 SIDS cases occur in Italy every year [8].

SIDS affects families of all social, economic, and ethnic backgrounds. However, it is more likely to occur in babies born to mothers with limited or inadequate prenatal care, mothers who

smoke during pregnancy, male infants (male-to-female ratio 3:2), prone and side-lying position during sleep [9-12], preterm or low birth weight infants, and in Native American/Alaska Native and non-Hispanic black infants [13]. In recent years, the rate of SIDS remained stationary despite major public health efforts aimed at improving infant's sleep environment and focusing on high-risk groups [14].

Distinguishing between various causes of SUDI is complex, with classification issues long recognised as a "persistent and pervasive problem [15]". A number of international initiatives have been undertaken to try to establish appropriate definitions, with death scene and autopsy protocols being formulated and published [16-28]. There are some international protocols that have been validated by several studies [29-31], in accordance with European guidelines for medico-legal autopsies [32], very similar to the International Standardised Autopsy Protocol [33] of the Global Strategy Task Force of SIDS International. The autopsy consists of an external examination, a complete internal examination, an X-ray investigation, histology, full toxicology, microbiological and genetic exams. The major changes in the last years regard the importance of the investigation of infant deaths, in particular the examinations of the circumstances of death [34].

Many USA [35] and other international [36,37] states have laws related to SIDS/SUID. In Italy, according to the Law 31/2006 [38] and the Decree of the Ministry of Health 7th October 2014 [39], child who died suddenly within the first year must undergo an autopsy in reference centres specialized. Information regarding the familial and environmental situations, must be accurately recorded and verified, for the diagnostic completion and purpose, by the obstetric gynaecologist, the neonatologist, the personal pediatrician and by the pathologist.

The Triple risk theory

According to the triple risk theory, SIDS occurs when (1) there is a vulnerable infant (2) in a critical but unstable period of development of homeostatic control (the highest risk period is at ages 2 to 4 months, with 90% of instances occurring before age 6 months) and (3) with previous exogenous stressor (e.g., prone or side resting position, soft bedding, or in utero or environmental tobacco exposure). Based on the model, all three factors must be present for a death to occur [40]. The combination of these factors leads toward a terminal respiratory pathway, and death occurs when protective mechanisms fail in the face of a life-threatening event [41]. This model has evolved suggesting that the mechanisms in SIDS is multifactorial [42]. Please see (Figure 1).

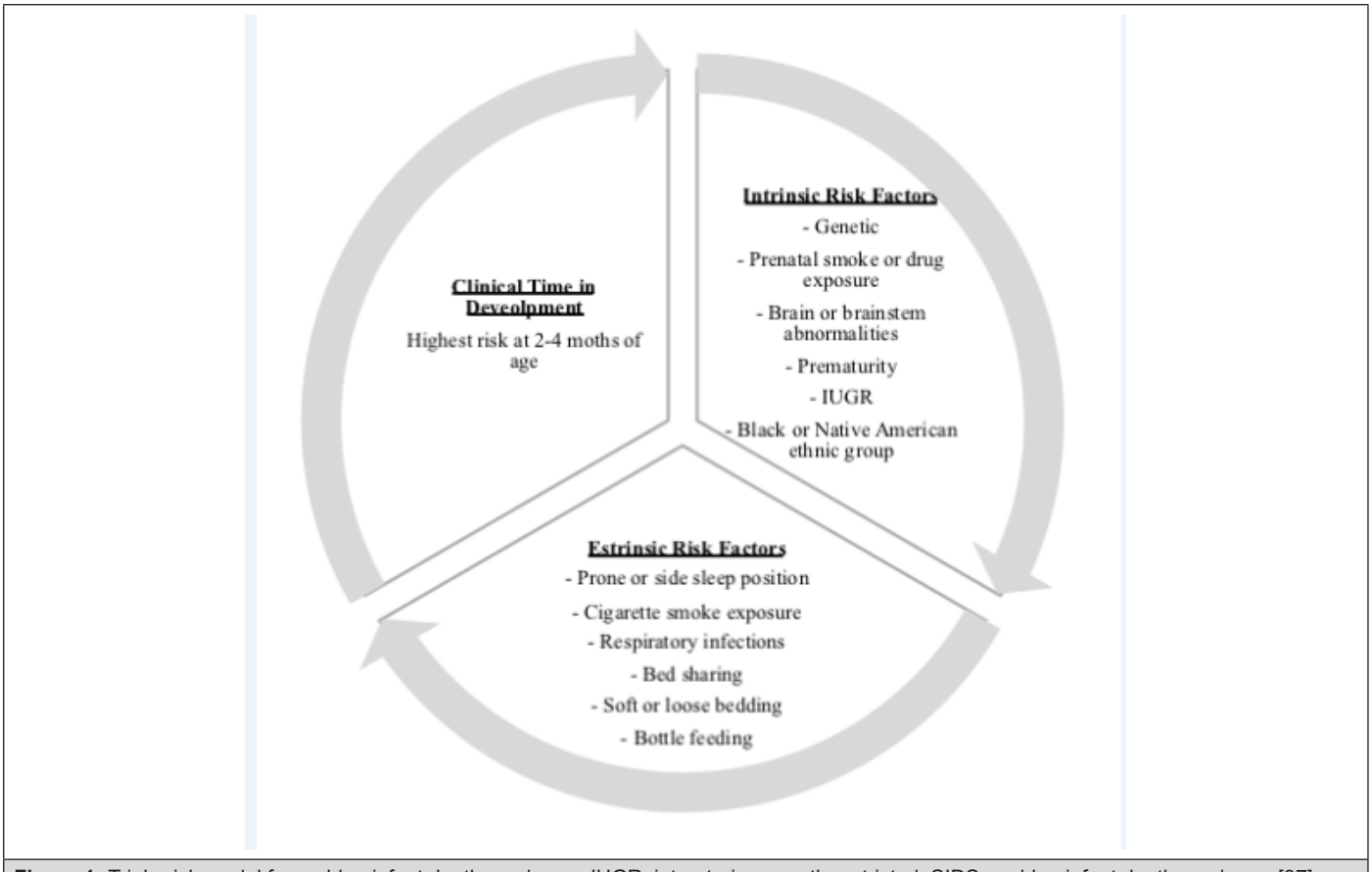

Figure 1: Triple-risk model for sudden infant death syndrome. IUGR, intrauterine growth restricted; SIDS, sudden infant death syndrome [37].

Infection and SIDS

The idea that inflammation might be involved in these infant deaths in not new. In an article published in 1956, 126 non-traumatic sudden ("unexplained") infant deaths were investigated, 106 (84%) revealed microscopic inflammatory changes in one or more sites of the respiratory tract, and there was histologic evidence of inflammatory disease in other organs in many cases [43]. Blood-Siegfried underlined the role of infection and inflammation in SIDS [44]. Also, Blackwell et al [45] found serum findings of inflammatory markers. These reviews confirm the existence of a link between infection/inflammation and SIDS. There is in fact evidence of an increase in interferon-γ [46] and interleukin [47] in infants who died of SIDS. Some recent studies show changes in the gut microbiome of SIDS babies and healthy babies [48,49]. Such a mechanism could operate in SIDS wherein an inflamed gut mucosa could promote microbial translocation into the bloodstream and cause overwhelming sepsis [50]. Respiratory infections are the leading causes of infant morbidity and mortality worldwide and new studies stressed the link of a recent viral infection and SIDS [51-53]. Please see (Table 1) [54-65].

Organ system	Response
Respiratory tract	Peribronchial inflammatory infiltrates [54,55] Increase in IgM producing cells in trachea [56] Mast cell degranulation [57]
Digestive tract	Increased IgA producing cells in duodenum Increased salivary IgA [58]
Nervous system	Interferon alpha in neurons of the medulla of the brain [59] Increased levels of IL-6 in spinal fluid [60] Lymphocyte infiltration [61]
Blood	Decreased IgG response to bacterial toxins [62] Increased IgM response to core endotoxin [63] Increased levels of mast cell tryptase Increased levels of mannose binding lectin [64] Cross-linked fibrin degradation products [65]

Table 1: Inflammatory or immune responses identified in SIDS infants [54-65].

A Standardized infant autopsy in Italy

According to Decree of the Ministry of Health 7th October 2014 "Diagnostic protocols in infant victim of SIDS deceased suddenly within the first year of age…omitted" we propose the following steps. Clinical history examination and circumstances of death. The following information were collected: investigation data, witness interview, infant's medical history, infant's dietary history, pregnancy history, incident scene investigation. The first step is the knowledge of the case history and death scene investigation, following specific guidelines [66].

Complete autopsy. The term "complete" autopsy is used when a thorough external and internal examination has been performed. The concept was discussed by Matshes et al. [67], who said that a complete autopsy is when "every conceivable test has been performed".

Photography

It starts with the documentation of the initial lividity pattern, as early as possible after death. Then, during the autopsy, are collected photos of all external body surfaces, all major soft tissue dissection planes and a photograph of the thoraco-abdominal organs.

External examination

Major body measurements (unclothed body weight with medical treatment removed, crown-heel length, crown-rump length, occipito-frontal circumference, chest circumference at nipples, abdominal circumference at umbilicus) are recorded. A full external examination of all body surfaces including the anogenital region, nose, and ears should be undertaken as soon as possible after death. The major reasons for this are to check for any unexplained injuries or lesions that may raise suspicions of accidental or inflicted injury. Internal examination Complete internal examination with

evisceration and dissection of all organs and extensive histology; some organs are harvested as heart-lung bloc, tongue-hypopharynx bloc and the whole brain. With the proper use of radiographic examination, is possible to find traumatic injuries [68].

Ancillary techniques

Radiological screening

X-rays were performed to highlight major anatomic abnormalities or traumatic injuries. Is recommended to use three views (anteroposterior, lateral, and Towne's) for the skull. When available, it is recommended the use of PMCT [69].

Toxicology

According to the German SIDS Study Group (GeSID) body fluids, tissue samples and stomach contents were taken and toxicological analysis was performed for general drug screens as sedative-hypnotics.

Microbiology/Virology

Where histopathology confirmed infection, virology screening was done for the detection of defined viruses by PCR methods in tissues (e.g., lung tissue: influenza A, influenza A H1N1, influenza B, respiratory syncytial virus A, respiratory syncytial virus B, human parainfluenza 1, human parainfluenza 2, human parainfluenza 3, human

parainfluenza 4, human coronavirus 229E, human coronavirus NL63, human coronavirus HKU1, human coronavirus OC43, human rhinovirus, human metapneumoviruses A/B, human bocavirus, human parechoviruses, entoroviruses, adenoviruses).

Genetics

Molecular analysis of post-mortem blood samples has been shown to be beneficial in the identification of cardiac channelopathies in otherwise negative autopsy [70-78]. In case of suspect, is necessary to distinguish between lethal mutations leading to diseases such as medium-chainacyl-CoA dehydrogenase (MCAD) and long QT syndrome (LQTS), and polymorphisms (for instance, in the IL-10 gene and mtDNA) that are normal gene variants but might be suboptimal in critical situations and thus predispose infants to sudden infant death [79]. Please see (Table 2). We propose a standardized infant autopsy workflow to the autopsy of all unexpected infant deaths. Please see (Figure 2).

Procedure	Details
Histopathologic examination	Right and left kidney Adrenals Liver, right and left lobes Thymus Lymph node Trachea and Thyroid Lungs, peripheral and central/hilar sections from all lobes Psoas Heart Small bowel, colon Gonads Pancreas Spleen Rib Skin Additional dissection and sampling of cardiac conduction system or brain stem, depending on the clinical context (not routinely samples in all cases)
Tissue retention	Additional samples from all the above organs retained in formalin fixative to facilitate further histopathologic samples, if required
Toxicology	Blood, liver, stomach contents (as indicated by clinical context and circumstances) – includes screening for alcohol and commonly abused drugs
Microbiology/Virology	Cerebral cortex; Myocardial tissue; Lung; Blood; Liver; Spleen; Cerebrospinal fluid
Genetics	Blood

Table 2: Autopsy Protocol for Histopathology and Ancillary Testing.

An Exemplary Case

Relevant clinical and scene data

At birth, in doubt of a LQTS at the first ECG control the infant had undergone a cardiological examination with a negative opinion for the presence of the canalopathy. There was an upper respiratory tract infection in the clinical history and diarrhoea two weeks before death.

Post-mortem findings

Well-developed and well-nourished infant with no apparent physical anomalies. Dark purple post-mortem hypostasis involved ventral surfaces. Petechial haemorrhages were on the epicardial surfaces of the heart, the lungs and thymus. Lungs were markedly congested and oedematous, with larger haemorrhages. Brain was slightly swollen but normal in size.

Histology

Vacuolar degeneration of hepatocytes. Lungs had oedema, hyperaemia, intra-alveolar haemorrhages and a small number of hystiocites with diffuse panbronchitis and eosinophilic and lymphoplasmacellular elements as shown in the image below. Please see (Figure 3). The other organs showed intense hyperaemia.

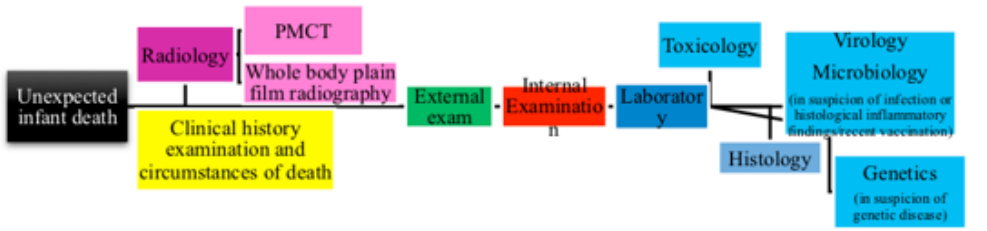

Figure 2: Unexplained infant death workflow chart.

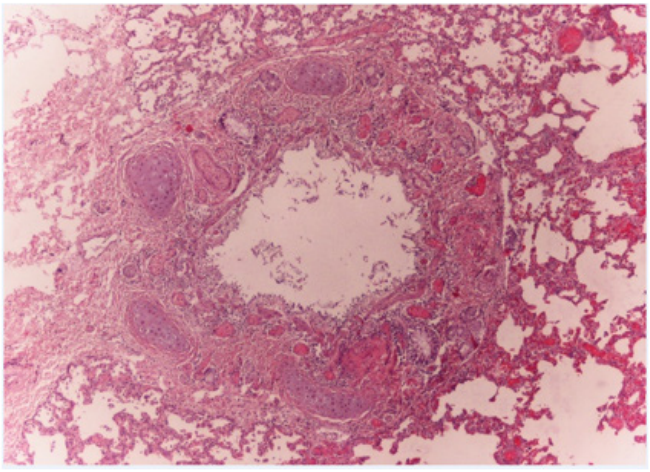

Figure 3: Diffuse panbronchitis.

Ancillary techniques

Radiological screening was performed with negative results. Microbiological analysis was performed with real time PCR and Human Coronavirus HKU1 and Human Rhinovirus were demonstrated in lung tissue.

Conclusion

Acute Respiratory Failure in Pan bronchitis In Viral Hku1 Coronavirus and Rhinovirus Infection.

Discussion

f cases of sudden and unexpected deaths in all age groups is one of the major areas of interest of forensic medicine. The investigation of infant deaths requires the application of special diagnostic methods and includes forensic pathology as well as other fields of forensic medicine, such as forensic toxicology, and medicine in general, e.g. radiology, microbiology, virology, neuropathology, pediatrics, epidemiology and genetics. Autopsy, although often considered the gold standard in the determination of the causes

of death, in often inadequate and allowed a definitive diagnosis in only 30% of the case in paediatric death [80]. Characteristic internal findings are exemplified by the triad of intrathoracic petechial haemorrhages involving the thymus, visceral pleura and epicardium. In most studies, ≥ 90% have the petechial triad, with significative differences from asphyxia [81,82]. Mainstream researchers attribute intrathoracic petechiae to changes in pulmonary pressure; however, this hypothesis does not stand up to scrutiny as argued in previous publications [83-85].

Krous et al. [86,87] disproved an association between intrathoracic petechiae and prone position, indicating that hypothetical upper airway obstruction attributable to face-down position is not causally related to development of intrathoracic petechiae. The lungs are congested and heavy [88] indicating pulmonary oedema/early shock lung as may occur in septic shock. Histopathology findings in these cases could provide important additional information which can be of help to establish the correct pathological diagnosis [89]. Histopathology shows very often mild inflammatory changes in the lungs [90,91]. Inflammatory alterations in the upper and lower respiratory tract are a common finding in sudden and unexpected death in infancy and up to 50-80% cases that can be explained after autopsy has detected to respiratory tract infections [92,93]. This is why most interest has focused on lung alterations, and especially on evidence of pulmonary inflammation. The typical hystological features in the lungs which can be seen in cases of suspected SIDS include pulmonary oedema, emphysema, atelectasias, increased number of alveolar macrophages, acute inflammation of the trachea and bronchi, pneumonia and prominent, hyperplastic bronchus-associated lymphoid tissue.

The significance of detecting viruses largely remains undetermined in the context of SIDS [94,95] and controversy exists same viruses are circulating at similar or higher frequencies in babies that died from other causes suchs as traumatic injuries and are also similar to those viruses circulating in the general population causing mild infections [96,97]. The presence of viral pathogens in lung tissue from SIDS cases in not always indicative of cause of deaths, for example dormant CMV has been found in numerous infants and babies without any pathological manifestation.

Fodha et al. [98] found that high nasopharyngeal RSV vital loads were shown to be a strong predictor of disease severity in infants, but a specific viral load that is required for respiratory infections to be deemed a significant contributing factor in causing death is still undefined [99]. Weber & Sebire [100] said to investigate the systemic responses to pathogens to find the role in disease progression [101]. Rambaud et al. [102] found that 62% of the sudden unexpected death in infancy cases had clinical symptoms of rhinitis and coughing prior to death. The pathogenicity of respiratory viruses can be low in immunocompetent individuals and is often associated with a good prognosis, but infants succumbing to SIDS have been suggested to be neither completely healthy, nor have normal defence mechanisms. Some may have underlying genetic and biological vulnerabilities which can predispose them to SIDS [103]. Virus infections and bacterial toxins induce cytokine activity, and it has been suggested that uncontrolled inflammatory mediators could be involved in some cases of SIDS [104-106]. In our case microbiological examination showed a viral infection. The aetiology of the inflammation was confirmed by microbiological investigations and Coronavirus HKU1 and Human Rhinovirus were demonstrated in lung tissue. Coronavirus HKU1 is an important pathogen in children under 3 years old with acute lower respiratory tract infection and the peak of its prevalence is spring and winter [107,108]. Coinfections show a more severe clinical outcome in comparison to single infections [109] and this could explain the fatal event in our case.

There is a big variation in cause of death determination and investigations practices for SUID among medical examiners. A recent study [110] highlights the lack of a uniformly applied and systematic approach to cause-of-death determination despite repeated calls for such [111]. Death certifiers need to develop mutually acceptable criteria and definitions to make cause-of-death determinations reliably and accurately, especially to differentiate suffocation and asphyxia from other SUID cases [112-114]. The National Academy of Sciences (NAS) [115] report highlights several factors that negatively impact progress toward developing and disseminating standardized best practices related to medico-legal investigation, including variation in medico-legal death investigation systems, unequal levels of expertise, and lack of resources for medico-legal professionals (e.g., facilities, equipment, staff, and training). Until we address these limitations, accurate and reliable causes-of-death determination for SUID will remain a challenge.

Conclusion

The SIDS autopsy should be undertaken according to well established protocols. The most likely environmental or exogenous trigger is a viral infection, and the proposed underlying vulnerabilities include immune deficiencies and poor control or over-expression of inflammatory mediators. Viral infections may act in combination with the immune response of the host to infection and the initiation of bacterial toxin production.

This review highlights important virological aspects regarding investigations into the infectious nature of SIDS, including the importance to follow standardized guidelines for appropriate specimen collection at autopsy and subsequent laboratory analysis.

Key Points

1. For the forensic pathologist tasked with paediatric SIDS autopsies, significant training and experience in paediatric pathology is ideal.

2. Respiratory tract infection in the clinical history seems to be a common feature prior to death.

3. Our case underlines the necessity of a multidisciplinary approach to researching SIDS, involving both clinicians and biologists, to determine the causes of these deaths.

4. Implementing autopsy protocol would appear to be an essential prerequisite to gaining a better understanding of SIDS.

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