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Cardiovascular Pathology 20 (2011) 302–306

CARDIOVASCULAR PATHOLOGY

Review Article

Sudden infant and perinatal unexplained death: are we moving forward yet?

Giulia Ottaviani*

Dipartimento di Scienze Materno-Infantili, Fondazione IRCCS Ospedale Maggiore Policlinico Mangiagalli Regina Elena, Università degli Studi di Milano, Milan, Italy

Abstract

Autonomic nervous system and cardiac conducting system dysfunctions have been proposed to be implied in the pathogenesis of sudden infant death syndrome (SIDS). However, most clinicians and even pathologists lack experience with detailed examination of the brainstem and cardiac conducting system and may not recognize lesions within those systems that potentially could be crucial factors in the sudden unexpected perinatal and infant death. Recent anatomical, pathological, and bacteriological studies in SIDS confirm that the multidisciplinary approach provides the best approach to the challenging problems of SIDS and sudden unexplained perinatal death.

Keywords: Sudden unexplained infant death; Sudden unexplained perinatal death; SIDS; Grey zone; Post-mortem investigation; ALTE; Genetics; Multidisciplinary approach

1. Introduction

Sudden infant death syndrome (SIDS) is defined as the sudden and unexpected death of an infant under one year of age, with onset of the lethal 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 decrease of its incidence following the back to sleep campaign, SIDS remains one of the three leading causes of infant mortality in the United States [2].

According to the World Health Organization, in developed countries, one in 100–200 pregnancies ends in stillbirth and unexplained stillbirth has a six- to eightfold greater incidence than that of SIDS, being one of the most common but least studied adverse pregnancy outcomes. A total of 50–80% of the fetal deaths after the 22nd week of gestation remain unexplained even after a traditional autopsy investigation [3–10].

The pathogenesis of SIDS and sudden perinatal unexpected death has been reported to be related to autonomic nervous and cardiac conduction dysfunctions. Neurogenic factors are interplaying in all the driving pathogenic hypotheses, i.e., the cardiac, the respiratory, and the visceral dyskinetic hypotheses [9–19].

Most physicians and even pathologists not only lack the experience of having done a close examination of the brainstem and cardiac conduction system but also fail to understand how crucially important a lesion in the autonomic nervous system and/or in the cardiac conduction system could be in the pathogenesis of both sudden unexplained perinatal death and SIDS. Just recently, Kinney and Thach [20] reported advances in the current knowledge on SIDS, but failed to stress that post-mortem investigations should focus not only on the brainstem but also on the cardiac conduction system and that there is a clear continuum between SIDS and unexplained perinatal death. From the careful evaluation of the recent anatomopathological [9–19]

Competing Interests Statement: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article. In particular, there are no competing interests related to this article. The author has no conflict to disclose.

Dr. Giulia Ottaviani is supported by 2008 PUR personal funding, University of Milano, project "Cardiovascular pathology of sudden infant and perinatal death with clinicopathological correlations".

* MED-08 Anatomic Pathology, Università degli Studi di Milano, Dipartimento di Scienze Materno-Infantili, Via della Commenda, 9, 20122 Milan, Italy. Tel.: +39 02 50320822.

E-mail address: giulia.ottaviani@unimi.it.

URL: http://users.unimi.it/giuliaottaviani/.

1054-8807/10/$ – see front matter
doi:10.1016/j.carpath.2010.08.001

and bacteriological [21–24] results, it is now possible to apply a new multidisciplinary approach to the study and prevention of the challenging problem of SIDS and sudden unexplained perinatal death.

2. Discussion

2.1. Continuity between SIDS and unexpected perinatal death: brainstem

There is a continuity between SIDS and unexpected perinatal death as common developmental abnormalities have been detected, such as development of the arcuate nucleus and the other centers of regulation of the vital functions, i.e., hypoglossus nucleus, vagal dorsal motor nucleus, nucleus of the solitary tract, ambiguous nucleus, reticular ventrolateral formation in the medulla oblongata; the locus coeruleus; and the parabrachial Kölliker-Fuse complex in the pons [9–14]. Such alterations are represented by hypoplasia, neuronal immaturity, and gliosis. In addition to these, the main immunohistochemical brainstem findings are: intense positivity for somatostatin in the hypoglossus nucleus; negativity for tyrosine hydroxylase in the locus coeruleus [13].

2.2. Continuity between SIDS and unexpected perinatal death: cardiac conduction system

In support to the cardiac hypothesis of SIDS, Harper and Bandler [25] admitted that the brainstem abnormalities of children dying of SIDS are consistent with primary cardiovascular failure, encouraging the focus on the heart as the final common pathway in crib death.

Studies of the cardiac conduction system in both SIDS and unexpected perinatal death have identified similar abnormalities, including accessory atrioventricular pathways, mostly Mahaim fibers, cartilaginous hypermetaplasia, abnormal resorptive degeneration, junctional islands, persistent fetal dispersion, hypoplasia of the cardiac conduction system or of the central fibrous body, splitting of the atrioventricular node or of the His bundle, and Zahn node [11,15–17]. These cardiac conduction findings are associated with brainstem alterations in 30% of cases [14].

A long discussion could be started on each of these findings of the cardiac conduction system. The resorptive degeneration finding, that is itself a physiological event, consists of degeneration, cell death, and replacement in an orderly programmed way [26]. This process, if exaggerated, can provoke blocking disruption of the conduction pathway itself, and if defective can leave in place accessory pathways [15–17]. It is difficult to determine when the resorptive degeneration ceases to be a physiologic process and becomes a pathological one.

Nevertheless, disruption of the normal cardiac conducting system pathways by any of the above findings could block or disorganize the propagation of the cardiac impulse and lead to arrhythmia. Likewise, metabolic alterations, acidosis or alkalosis, unbalanced electrolytic state, hypoglycemia, or enzymatic defects could eventually provoke lethal cardiac electrical reflexes.

2.3. Genetic analyses

The search for an etiology for SIDS and unexplained perinatal death should always focus on genetic analyses.

Mutations in cardiac ion channel genes underlie many cases of inherited arrhythmia syndromes, including long QT interval syndrome (LQTS) [27]. It is known that the LQTS predisposes to ventricular arrhythmias and SIDS and genetic analyses of QT interval have identified at least eleven mutated genes [28].

Analysis of the medium-chain acyl CoA dehydrogenase genes is necessary to diagnose the deficiency of fatty acids β-oxidation [29].

The detection of frequent primary autonomic nervous system anomalies suggests in SIDS and unexpected perinatal death the need to study the inherent genetic bases in these developing structures. *En-2* gene has been shown by mutational analyses to be a candidate genetic marker for rhombic lip-derived structures, such as the arcuate nucleus. Therefore, it can be assumed that mutational or functional alterations of this gene are implicated in hypoplasia of the arcuate nucleus [30]. It has been observed that the expression of the *En-2* gene is very high in the arcuate nucleus neurons from the 17th to the 22nd gestational week, then decreases up to the first days after birth and later disappears [31]. The research has been extended to the detection of DNA mutations and polymorphisms potentially involved in SIDS etiopathogenesis.

The promoter long (L) allele of the serotonin transporter (*5-HTT*) gene was detected more frequently in SIDS infants (75%) than in controls (30%) [32]. The presence of the L allele represents a predisposing factor for sudden fetal and infant death in association with morphologic developmental defects of the raphé nuclei and prenatal smoke exposure [33].

Increasing attention to the genetic studies should be addressed to identify the involvement of abnormal genes in developmental cardiac and nervous defects underlying SIDS.

2.4. Clinical considerations

Many risk factors have been reported to be related to SIDS; they have been classified, according to Guntheroth's criteria [34], as "nonpreventable," such as sex, age, and time of death, and "preventable," such as parental cigarette smoking, prone position in the crib, and formula feeding. In a postmortem study of a large sample of cases, the histopathologic and immunohistochemical examination of the central autonomic nervous system revealed hypodevelopment of the arcuate nucleus, somatostatin positive hypoglossus nucleus, tyrosine hydroxylase negativity in the locus coeruleus, gliosis, and hypoplasia of the