



Developmental neuropathology of brainstem respiratory centers in unexplained stillbirth: What's the meaning?

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ABSTRACT

Stillbirth is one of the most stressful life events affecting over 3 million pregnancies per year throughout the world. An accurate autopsy of the stillborn fetus, including the placenta and umbilical cord examination, should be performed promptly after delivery. A thorough maternal history also should be taken, including exposures to risk factors. In many cases a death cause, attributable to fetal, maternal, or placental pathology, is clearly identified. However, in 50% or more of cases the cause remains unknown.

The purpose of this study is to highlight possible developmental alterations of the autonomic nervous system in unexplained stillbirths to provide an explanation of the pathogenetic mechanism of their death.

We conducted a careful neuropathological study of the brainstem, where the main vital centers are located, in 85 unexplained stillbirths and 52 age-matched controls died of known cause. Information on the maternal lifestyle, including the smoking habit, was collected in all cases. Hypodevelopment of neuronal centers involved in breathing control, all connected together in a "respiratory network", precisely hypoplasia of the facial/parafacial complex, Kölliker-Fuse nucleus, pre-Böttinger nucleus and intermedialateral nucleus, were frequently observed in unexplained deaths, significantly related to maternal cigarette smoking.

We support the hypothesis of a strong action of maternal smoking during pregnancy on the development of brainstem respiratory nuclei and suggest an explanation of the high incidence of the respiratory network alterations in unexplained fetal death, when breathing not represents a vital function.

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1. Introduction

Stillbirth is generally considered as the death of a baby before or during delivery, or in any case before their first birthday (Fretts, 2009; Goldenberg et al., 2004). Each year about 24,000 babies are stillborn in the United States and over 3 million throughout the world (Macdorman and Gregory, 2015). Because of its apparent randomness, and the lack of any warning, stillbirth cuts across socio-economic classes, ethnicities, religions, and maternal age

groups. However, even if no woman is immune from stillbirth, there are some maternal factors associated to the condition that can increase the risk for stillbirth, including black race, age under 20 or over 35 years, obesity, nulliparity or a previous miscarriage (McClure et al., 2009; Flenady et al., 2011; Yudkin et al., 1987; Liu et al., 2014). A well-documented risk factor for unexplained stillbirth is maternal cigarette smoking during pregnancy. A huge number of works in the literature have, in fact, reported the harmful effects exerted by the crossing of nicotine into the bloodstream of the fetus (Lambers and Clark, 1996; Marufu et al., 2015; Raymond et al., 1994; Wickström, 2007).

It is universally recognized that the most important test in the search for a possible death cause in stillbirth is gross and microscopic fetal autopsy, complete with placental, umbilical cord and membrane examination, genetic analyses, and a detailed medical

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history evaluation (Faye-Petersen et al., 1999; Saller et al., 1995; McPherson and Valdes-Dapena, 1998; Bove, 1997).

Known causes of stillbirth can generally be subdivided into three broad categories, namely: 1) congenital fetal defects (including genetic abnormalities), 2) placenta and/or umbilical cord pathologies and 3) maternal disorders (such as obesity, hypertension, diabetes, etc.) (Bendon, 2001; Bukowski et al., 2011; Fatima et al., 2014).

However, despite the progress in medical diagnostics and antenatal care over the last 30 years, after a careful investigation one-half to two-thirds of stillbirths are still listed as deaths for undeterminable reasons. Because these deaths cannot be attributed to a specific identifiable cause, they are called “unexplained stillbirths” (Gardosi et al., 2005; Yudkin et al., 1987; Warland and Mitchell, 2014). We have proposed that a sudden death during pregnancy, that remains unexplained after a thorough study, should also be considered as a syndrome and referred to with the acronym “SIUDS”, i.e., “Sudden Intrauterine Unexplained Death Syndrome”, like “SIDS” for “Sudden Infant Death Syndrome” (Matturri et al., 2014). This suggested definition is based on the realization that several conditions simultaneously occurring may contribute to a given stillbirth and on the presence in these unexpected deaths of common developmental abnormalities of the autonomic nervous system, associated to the same risk factors related to SIDS.

It is necessary to point out that the lack of uniform post-mortem protocols applied worldwide for evaluating and classifying stillbirths has hindered significant studies in this field.

The “Lino Rossi” research Center of Milan University has developed an investigative postmortem protocol that includes, in particular, an in-depth examination of the autonomic nervous system (available at the webpage <http://users.unimi.it/centrolinorossi/en/guidelines.html>), according to the Italian Law 31/2006 “Regulations for Diagnostic Post Mortem Investigation in Victims of Sudden Infant Death Syndrome (SIDS) and Unexpected Fetal Death.” This law states in particular that all stillbirths that died suddenly without any apparent cause after 25 weeks of gestation must be submitted to a depth diagnostic postmortem investigation.

Herein, we report the autonomic nervous system findings obtained according to the above-mentioned protocol in a wide group of stillbirths previously diagnosed as “unexplained” after a routine fetal autopsy. Surprisingly, we frequently have observed in the brainstem of these victims hypoplasia of neuronal centers known to be involved in the autonomic control of breathing. So, our main purpose was to provide an explanation of the high incidence of these developmental alterations, also suggesting how they can lead to death in the womb, before breathing is yet required for life.

2. Material and methods

We studied 85 stillbirths, aged from 25 to 40 gestational weeks, sent to the “Lino Rossi” research Center of the Milan University from hospitals and health Institutions of Italian regions, in accordance with the abovementioned national Law 31/2006.

The fetuses had previously been submitted to a complete autopsy, including examination of the placental disk, umbilical cord and membranes, but without identifying a possible death cause. So, they were classified as “unexplained stillbirths” or, more appropriately, “SIUDS”.

For each case, a complete clinical history, with particular reference to the maternal lifestyle, was given. None of the mothers of the 85 victims had any significant pathology. The mothers were also asked for information about a smoking habit before and during pregnancy. Forty-eight mothers (56%) claimed to be active smokers

before and during pregnancy, while 37 (44%) declared no history of cigarette smoking. Since, as is well known (Shipton et al., 2009), retrospective assessment of a mother’s smoking habit, mainly after the death of a child, is sometimes unavoidable, the negative self-reports were verified by testing for cotinine, the main metabolite of nicotine, that has a long half-life, in the hair of victims. In 4 stillbirths among the 37 mothers who denied a smoking habit the cotinine-test was positive, thereby leading to a total of 52 (61%) the cases with nicotine absorption in pregnancy and reducing the actual number of non-smoking mothers to 33 (39%).

For every case, the material to be sent to the “Lino Rossi” Center consists of the brain, heart (for the specific study of the cardiac conduction system), a lock of the victim’s hair and, when possible, lung samples to evaluate the pulmonary maturation stage. A group of 52 fetuses who died of known causes, selected from a wide set of cases previously collected at the “Lino Rossi” Research Center, were designated as “Controls”. The same material and information, including the smoking habit, required for unexplained stillbirths was sent for the control cases from the medical Institutions involved in application of Law 31, for the specific purpose of carrying out comparative analyses.

The Controls were matched with the unexplained stillbirths for gestational age, sex and area of origin. Table 1 summarizes the SIUDS/Control case study, indicating the age-ranges, sex distribution and the death diagnoses.

Consent- Parents of all the infants included in the study provided written informed consent to autopsy and related researches; study approval was granted by the institutional review board of the Milan University (Lino Rossi Research Center).

2.1. Protocol for the anatomopathological study of the brain

After fixation in 10% phosphate-buffered formalin, the brains were processed and embedded in paraffin. Target of this study was the in-depth microscopic study of the brainstem. Transverse serial sections of the midbrain, pons, medulla oblongata and spinal cord (rostral cervico-thoracic tract), where the main structures controlling the vital functions are located, were made at intervals of 60 μ m. For each level, six-seven 5 μ m sections were obtained, two of which were stained using hematoxylin-eosin and Klüver-Barrera for histological examination, while two sections were treated for immunohistochemical detection of the neuronal nuclear antigen (NeuN), a marker of neuronal functionality. The remaining sections were saved for further investigations and stained as deemed necessary.

The routine histological evaluation of the brainstem was performed on the locus coeruleus, Kölliker-Fuse nucleus, and median raphé nucleus in the rostral pons/mesencephalon; on the parafacial/parafacial complex, superior olivary complex, ambiguus, pre-Böttinger, inferior olivary, arcuate, obscurus, pallidus raphé nuclei and solitary tract complex in the medulla oblongata; the intermediolateral nucleus in the spinal cord junction with the brainstem.

Many of these nuclei (and precisely the Kölliker-Fuse nucleus, the facial/parafacial complex, the pre-Böttinger nucleus and the intermediolateral nucleus) are anatomically and functionally interconnected via interneuronal synapses, modulating one another, within a network extending from the rostral spinal cord through the medulla oblongata, pons, to the caudal pars of the midbrain. This nervous complex is defined as “respiratory network” (RN), given its primary involvement in the control of breathing (Cohen, 1979; Bianchi et al., 1995; Viemari et al., 2003).

Fig. 1 presents a scheme of the human breathing control mechanism in perinatal life, proposed by one of the Authors in a recent paper (Lavezzi, 2015), indicating the more representative

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