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ASSOCIATION BETWEEN THE HYPOPLASIA OF THE MEDULLARY ARCUATE NUCLEUS AND HYPOPLASIA OF THE LUNG IN UNEXPECTED LATE FETAL DEATH (STILLBORN INFANTS)

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ABSTRACT - Stillbirth is defined as late fetal death before the complete expulsion or retraction of the fetus from the mother. It represents about half of the cases of perinatal mortality, with a prevalence of 5 to 12 per 1000 births

The pathologic investigations that have been carried in this field are unfortunately sporadic and incomplete. In particular, the studies on the pathology of the autonomic nervous system in fetuses are sadly lacking, despite the fact that abnormalities of these structures are often the main pathologic substrate for unexpected fetal death, as the hypoplasia of the arcuate nucleus, an important cardio-respiratory center of the ventral medullary surface, in SIDS.

This study attempts to assess the pathologic findings in 26 stillborn infants with a gestational age of 25 to 40 weeks. The brainstem and the lung were the particular focus of this study.

The brainstem was examined according to the protocol routinely followed in our Institute, available at the web-site <http://users.unimi.it/-patol/sids.html>. The pertinent nuclei in histological serial sections were outlined, namely the parabrachial/Kölliker-Fuse complex, the nucleus hypoglossus, the dorsal vagus motor nucleus, the tractus solitarius nucleus, the nucleus ambiguus, the trigeminal tractus and nucleus, the arcuate nucleus and the ventrolateral reticular formation.

As regards the lung examination, in each case the stage of development was evaluated on the basis of a macroscopic criterion used at autopsy, namely the correlation between lung weight and body weight (LW/BW), and according to microscopic criteria, that is, the presence of cartilaginous bronchi up to the distal peripheral level and the radial alveolar count (RAC). The normal reference values for the last three months of gestation correspond to > 0.022 for LW/BW and for RAC they range from 2.2 to 4.4.

In 17 cases (65%) pulmonary hypoplasia was observed, characterized by a decrease in volume and/or weight of the lungs, without lobulation anomalies or alteration of the indices of pulmonary development, with LW/BW value below 0.022, a RAC below 2.2 and the presence of cartilaginous bronchi up to the distal peripheral level.

In 9 cases (35%), microscopic examination of serial sections of the brainstem showed varying degrees of hypoplasia of the arcuate nucleus. Precisely, in 8 cases a marked bilateral hypoplasia was evident and in one, the nucleus was completely absent (agenesis). In 8 of these cases there was also hypoplasia of the reticular formation.

A significant correlation ($p < 0.05$) was observed between pulmonary hypoplasia and arcuate nucleus agenesis/hypoplasia. In fact, 8 cases (31%) were characterized by congenital hypodevelopment of both arcuate nucleus and lung. In all these cases chronic hypoxic signs were found.

These results suggest that in about a third of stillbirths the hypoplasia of the arcuate nucleus would exert a negative effect on respiratory movements in utero and therefore on lung development. In the cases where pulmonary hypoplasia is not accompanied by hypodevelopment of this nucleus the explanation could be a wrong physiological mechanism, more precisely a failure to block the inhibitory action of the pontine Kölliker-Fuse nucleus.

In conclusion, all the findings of our study confirm the hypothesis that functional or structural alterations of components of the vegetative nervous system which modulate fetal breathing, as the arcuate nucleus hypoplasia, may lead to disturbances in the development of the respiratory apparatus, in particular to pulmonary hypoplasia in stillbirth.

SUDDEN INFANT DEATH SYNDROME (SIDS): ASSOCIATED ALTERATIONS OF THE CARDIAC CONDUCTION SYSTEM AND BRAINSTEM

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The crib death or Sudden Infant Death Syndrome (SIDS) is one of the major social and health problems of today's medicine not yet resolved. Among a total of over 100 SIDS and 30 control cases, a combined morphologic post mortem study of the cardiac conduction system and brainstem was performed in 42 cases of SIDS and in 12 controls. In every case a complete autopsy was performed, according to the autopsy protocol usually followed at our Institute in cases of sudden death, including particularly the observation of the cardiac conduction system, and of central and peripheral autonomic nervous structures involved in the cardio-respiratory reflexogenesis. The cardiac conduction system was removed in two blocks cut serially at intervals of 40-mm and stained alternately with HE and azan. Transversal serial 5-mm sections were made through the entire brainstem were stained using alternately hematoxylin-eosin, Bielschowsky, and Klüver-Barrera stains. The volume of the arcuate nucleus was measured by 3D-reconstruction. The Mahaim fibers were observed in 16% of control and in 17% of SIDS cases with arcuate nucleus (ARCn) histologically well developed, and from 50% (severe bilateral hypoplasia) to 71% (monolateral hypoplasia) in SIDS cases with ARCn hypoplasia. The Mahaim fibers are statistically more frequent in SIDS with ARCn hypoplasia than in the cases with well developed ARCn (control and other SIDS cases) ($p < 0.005$). The resorptive degeneration, cartilaginous meta-hyperplasia, and the His bundle dispersion were statistically unrelated with the presence of ARCn hypoplasia. In order to better understand the morphologic lesions associated with crib death, we suggest that an accurate morphological and immunohistochemical approach and examination of the on serial sections of both cardiac conduction system and brainstem should be routinely employed in every case of sudden death in infancy. A disadvantage of the herein-described extensive serial section study would be the need of adequately specialized and equipped laboratory centers, with the study of more than one thousand of slides for each case.