### Status thymicolympathicus: real or fake?


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### Abstract

Sudden infant death syndrome (SIDS) is the sudden, unexpected death of an infant less than one year of age that remains unexplained after a full investigation. SIDS is the most frequent cause of death of infants between two weeks and one year of age, explaining 35% to 55% of all deaths in this age group. We report a newborn male who died soon after birth. The newborn was cyanotic, bradycardic at first, and then asystolic; without any vesicular murmur, apneic, low amplitude thorax movements, even under conditions of positive pressure ventilation on the endotracheal tube. The microscopic aspect thymus highlighted a corticomedullary ratio quite high in favor of the cortical, rich in lymphocyte population, with the dilated subcapsular sinuses. In this report, we considered that cardiorespiratory failure, which was the immediate cause of death, could have been caused by the thymus hypertrophy. This hypertrophy can be a complication of an intrapartum preexistent condition, most probably of hepatic nature.

**Keywords:** status thymicolympathicus, sudden death infant syndrome, thymus hypertrophy.

### Introduction

Sudden infant death syndrome (SIDS) is the sudden death of an infant less than one year of age that cannot be elucidated after a thorough investigation is carried out, including a complete autopsy, examination of the death, and an analysis of the clinical history. SIDS is the main cause of death among infants of one to 12 months old. It is uncertain whether SIDS happens during sleep itself or during the transitions between sleep and arousal that appear during the night, since such deaths are typically not observed. Many definitions of SIDS have been proposed, starting in 1969 with a “complex syndrome”, with a multiple etiological factors and continuing with the concept that SIDS is an exclusion diagnosis [1].

The frequency of SIDS seems to be higher between two and four months and can be associated with prematurity and some viral infections [2].

There are three categories of risk factors: environmental, such as low socioeconomic status, maternal risk factors – smoking, intrauterine hypoxia or infant risk factors – male gender, prone sleeping, siblings) [3]. When people was advised about the risk of sudden death and avoided the prone position of the infant, the prevalence of SIDS decreased from 1.2 to 0.546 per 1000 live births in 2006 (50%) [3].

SIDS still remains a problem for the pediatrics coroners and anatomopathologists. For over a century, status thymicolympathicus was considered responsible for the sudden death in children. The fact that sudden death occurs in association with lymphatic hyperplasia, including the thymus, is unquestionable, even though the causal connection of these lesions with death is not clear yet [4].

This case presentation proposes to highlight again that “status thymicolympathicus” is an outdate concept: the hypertrophic thymus hiding another preexistent pathological process, the thymus being the effect and not the cause of the thanato-regenerative process.

### Case presentation

We report a case of a newborn male, with birth weight (BW) 3400 g, birth length (BL) 52 cm, head circumference (HC) 35 cm, thoracic circumference (TC) 31 cm, normotensive anterior fontanelle (AF) 2/2 cm, spontaneously born in cephalic presentation, Apgar score 1/1 min, 2/5 min, 2/10 min, 2/15 min, resuscitated in the delivery room, undergoing all the neonatal resuscitation stages, without any success. He dies after 45 minutes since birth, when the resuscitation team stops the resuscitation procedures.

Delivery conditions: Spontaneous birth in cranial presentation, Apgar score 1/2/2 (primary apnea, generalized cyanosis, atonia, areflexia, bradycardia), requiring neonatal resuscitation procedures in the delivery room: intubation with the endotracheal tube of 3.5 Fr, up to a sign of 9.5 cm, on which there is ventilated a self-inflating balloon with positive pressure coordinated with an external cardiac massage for 60 seconds, characterized afterwards by the umbilical vein in low position, being administered Adrenalin in three doses and expanded volume: 34 mL of 0.9% sodium chloride, 6 mL of sodium bicarbonate, continuing the cardiac massage and positive pressure ventilation. There appears an inefficient cardiac activity, heart rate 90 beats/min, followed by persistent bradycardia (50 beats/min) and undetectable oxygen saturation. Although there continued the neonatal resuscitation procedures, with cardiac ventilation and massage, coordinated with...
drug administration, the newborn does not respond, remaining asystolic and in undetectable oxygen saturation.

Clinically, the newborn was cyanotic, bradycardic at first, and then asystolic; without any vesicular murmur, apneic, low amplitude thorax movements, even under conditions of positive pressure ventilation on the endotracheal tube; normally shaped mouth cavity, distended abdomen with no enlarged liver or spleen, atonia, areflexia. He dies 45 minutes after supported resuscitation procedures.

Data on pregnancy: Unmonitored pregnancy; the mother stated that she consumed food in high quantities.

Case particularity: Despite the positive pressure ventilation on the endotracheal tube, the thorax trips were of low amplitude, inefficient ventilation, and inefficient resuscitation procedures.

**Pathological report**

At opening the thorax, there was observed a hypertrophied thymus, compressing both lungs. The liver was also oversized for a term delivery newborn. There were sampled fragments of organs, which were subject to the standard histological processing, by fixation in 10% neutral formalin and Hematoxylin–Eosin (HE) staining.

The microscopic aspect thymus highlighted a cortico-medullary ratio quite high in favor of the cortical, rich in lymphocyte population, with the dilated subcapsular sinuses. In the interlobular septa, there was already been observed frequent adipocytes, distributed in random nests on the surface down into the lobe depth (Figure 1). The medulla, which in the newborn is well differentiated from the surrounding cortical, was indistinct in this case: the corticomelllary limits were constituted only by the highly dilated veins, the medulla being densely populated with lymphocytes (Figure 2). The medullar characteristics are the thymic Hassall’s corpuscles, but they were also identified with difficulty, only in the high magnitude images, being in a low number and in first stages of organization (Figure 3). The general aspect was of a highly quantitative developed thymus, with a qualitative differentiation left from the gestational age.

The lungs were practically non-respiratory, with the bronchial mucosa epithelium plicatured and with areas of atelectasis. The presence of free acinary sacs may be interpreted in the context of the respiratory resuscitation procedures practiced for 45 minutes (Figure 4).

**Figure 1** – Thymus, general microscopic aspect: dilated subcapsular sinuses and high cortico-medullar ratio in favor of the cortical (HE staining, ×40).

**Figure 2** – Thymic lobule: indistinct cortico-medullar limit, suggested only by dilated veins, the medulla being densely populated by lymphocytes (HE staining, ×40).

**Figure 3** – Thymic medulla: immature Hassall’s corpuscles within a dense lymphocytic population (HE staining, ×200).

**Figure 4** – Partly-respiratory lung: bronchial mucosa plicatured and large acini alternatively distributed, with areas of atelectasis (HE staining, ×40).
The liver microscopically presented edema and periportal hyalinosis, accompanied by hepatocyte lesions, such as vacuolar and granular dystrophy, occasionally binucleate cells (Figure 5). The lymphocyte infiltrate was randomly distributed (periportal, mediolobular and centrilobular) under the form of pseudofollicular lymphocyte aggregates (Figure 6). All these lesions showed a long-lasting liver suffering.

![Figure 5](Liver: portal space and periportal zone with edema and hyalinosis (HE staining, ×40).)

![Figure 6](Liver: lymphocyte infiltrate randomly distributed (periportal, mediolobular and centrilobular). Inset: pseudofollicular lymphocyte aggregates (HE staining: ×40; inset, ×200).)

### Discussions

The concept of “hypertrophic thymus” has been a debate and discussion subject for more than a century [5]. At first, it had to be accepted the idea that a child is not a miniature adult: the normal parameters in a child differ from the ones in an adult. Thus, if we systematically find a relatively adult reduced sized thymus during autopsies, this does not mean that a small sized thymus is normal in children, as well. In fact, precisely this discrepancy that “the thymus is the childhood gland”. The thymus is not a gland; it is a main lymphatic organ. The thymosin intervenes in the late intrathymic maturation of lymphocytes, while the lymphocyte responsiveness are stimulated by the serum thymic factor, thymopoietin and thymic humoral factor so they are active biological substances that act locally or upon the immune system, at the most [6]. The thymus is not present only in children, its functions being exerted during the whole life time [7].

A source of confusion may be neglecting the fact that the thymus examination in adults is performed especially on corps of subjects that had suffered from consumptive chronic diseases, leading to thymus hypertrophy [8]. In contrast, in newborns and babies, the autopsies often highlight a “hypertrophic thymus”, which is, probably, either reactive to the pathological condition that led to death in the first place. Consequently, more useful would be the morphometric studies performed by screening with non-invasive imagistic methods. Such studies show a great variability within normality and with no significant differences between natural delivery or Caesarean (C)-section newborns [9]. Instead, there may be performed correlations with the “micro-environment” provided by the mother [10] or with the nourishment level [11].

The definition of status lymphaticus or thymicolymphaticus is the condition leading to sudden death, especially at very young age, being a main cause, a minor stress or, at the very most, a small shock [5].

The disease was described for the first time in Vienna, by A. Paltauf and it has rapidly become popular in the Western Europe [12]. Until the 50s, it was taught to British medical students, and in 1931, the American Surgeon-General’s Catalogue presented this condition in two columns. Actually, the status thymicolymphaticus was overrated, being a cover diagnosis in case of “white autopsias”, when the pathologist could not identify any lesion compatible with the infant death. As a treatment, there was suggested the surgical one, at first. Thymectomy, proposed by Rehn, in 1890, and extended as a rule by König, in 1906, had a mortality death of 1:3 surgeries, considered too high [13]. A lot more serious was the thymus irradiation, a treatment solution proposed by Friedländer, in 1907 [14] and supported by another great personality of medical pathology: Rudolf Virchow [15]. Because the thymus is situated close to the thyroid gland, the consequence was the dramatic increase of the thyroid cancer incidence. It was estimated that over 10 000 deaths were caused by this practice, so useless and devastating at the same time [16].

The first one denying the status thymicolymphaticus as a pathological entity and, implicitly, as a cause of sudden death in newborns, was the Hammar Swedish man, who dedicated lots of decades to the study of this mysterious and confuse organ at that time. In an extended overview, in 1923, he criticizes the lack of scientific rigor and he rejects the idea that the thymus may obstruct the airways [17]. This attitude was quickly adopted by the prestige publications and starting from the 60s, the condition of “status thymicolymphaticus” has started to disappear from the MEDLINE database.

Still, there exists a scientific basis of the thymico-
lymphaticus status motivated by the genetic studies on laboratory animals. Thus, the R420W mutation of the heart receptor gene for ryanodine (RyR2) may also manifest through the lymphatic organs hypertrophy, including the thymus [18]. As this mutation is mainly responsible for the arrhythmogenic right ventricular dysplasia cardio-myopathy [19] and of catecholaminergic polymorphic ventricular tachycardia [20]. Mutations in the cardiac ryanodine receptor gene (hRyR2) cause catecholaminergic polymorphic ventricular tachycardia. It is natural that the cardiac symptoms and signs should be the cause of these sudden deaths, while the lymphatic organ changes should be genetically motivated associations. The RyR2-encoding Ca\(^{2+}\) channel gene codifies not only the Ca\(^{2+}\) channels in the myocardium, but also from the lymphatic organs, including from the thymus, the altering of these channels leading to the accumulation of abnormally differentiated lymphocytes in the thymus, as Ca\(^{2+}\) is essential in the positive and negative selection of thymocytes [21]. Therefore, the same genetic mutation may determine lethal cardiac functional changes, and also associated thymic hypertrophy, with no causal connection to death [22].

The liver contributes to the immune system homeostasis by two major mechanisms: on the one side, by its strategic position in the way of intestinal absorption products it plays a part of immune surveillance; on the other side, it synthesizes essential soluble molecules for an effective immune response [23].

Immune surveillance exerts through more specialized cells in the detection and capture of pathogenic agents brought in by the portal blood flow. These are the resident antigen presenting cells, mainly represented by the Kupffer cells and by the sinusoidal endothelial cells, composing the liver reticuloendothelial system, as well as by the dendritic cells. These cells participate in the coordinated immune response that leads to the pathogenic agents’ identification, leukocyte recruitment and antigen presentation to the vascularization lymphocytes. In the end, the defense part should be regularly restrained in order to avoid an inappropriate immune response against the non-pathogenic exogenous molecules, such as the ones coming from alimentation. Due to this role of activation and tolerance balancing, the liver may be considered a first line immune system organ [24]. The liver, especially by its hepatocytes, is a major source of proteins involved in the inborn or adaptive immune response, especially by the synthesis of the soluble pathogen-recognition receptors and complement components [25]. The role played by the Kupffer cells is essential in the immunity mediated by the T-lymphocytes: not only it activates these lymphocytes, but it also inhibits the antigen-specific T-cell responses induced by other antigen-presenting cells (APCs) [26].

Conclusions

We may state that cardiorespiratory failure, which was the immediate cause of death, could have been caused by the thymus hypertrophy. Still, this hypertrophy cannot be considered as the initial cause, but more a complication of an intrapartum preexistent condition, most probably of hepatic nature. We should also take into consideration the possibility that the food add-on abuse may have caused fetal liver suffering, as well as the genetic tests for R420W mutation of the ryanodine RyR2 gene cardiac receptor may be useful in orienting the diagnosis towards a genetically determined heart condition.

Conflict of interests

The authors declare that they have no conflict of interests.

References


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