

**PATHOMORPHOLOGICAL ASPECTS OF THE INTEGRATED RELATIONSHIP
BETWEEN THE ADRENAL GLAND AND THYMUS IN NEONATES WITH
ADVANCED RESPIRATORY DISTRESS SYNDROME**

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ABSTRACT

Background: Respiratory distress syndrome (RDS) in newborns is a life-threatening pulmonary condition characterized by surfactant deficiency, alveolar collapse, hypoxia, and systemic stress responses. While the pulmonary features of RDS have been extensively studied, less attention has been paid to the morphofunctional integration of the adrenal gland and thymus, two central organs in neonatal stress physiology and immune regulation. Their structural alterations may play an essential role in the disease course.

Objective: This study aims to describe the histological and pathomorphological changes of the adrenal gland and thymus in neonates diagnosed with advanced respiratory distress syndrome, and to analyze the integrative relationship between these organs.

Methods: A descriptive, morphologically oriented study was conducted using adrenal and thymus specimens obtained during neonatal autopsies. Tissues were fixed in buffered formalin, embedded in paraffin, sectioned at 4–5 μm , and stained using hematoxylin–eosin, Masson's trichrome, PAS, and immunohistochemical markers (ACTH-R, CD3, cytokeratin, Ki-67). Histological alterations were evaluated according to standard neonatal tissue morphology criteria.

Results: Advanced RDS produced marked structural alterations in both organs. The adrenal cortex demonstrated lipid depletion, cytoplasmic vacuolization, progressive cortical thinning, and focal hemorrhages, most prominent in the zona fasciculata. The adrenal medulla showed chromaffin cell swelling and reduced granularity. The thymus showed severe cortical atrophy, lymphocyte depletion, increased apoptosis, widening of medullary spaces, and prominent Hassall corpuscle degeneration. Parallel degenerative changes in both organs strongly reflected systemic stress and immune suppression.

Conclusion: Significant histopathological changes occur simultaneously in the adrenal gland and thymus during neonatal RDS, demonstrating their functional and structural interdependence. Understanding these integrative alterations provides important insights into neonatal adaptation mechanisms, immune dysfunction, and systemic stress responses in severe respiratory pathology.

Keywords

neonatal respiratory distress syndrome, adrenal gland, thymus, histology, pathomorphology, immune response, stress physiology.

INTRODUCTION



Respiratory distress syndrome (RDS) remains one of the most critical causes of morbidity and early neonatal mortality worldwide. It is primarily associated with surfactant deficiency, leading to alveolar collapse, inadequate gas exchange, hypoxemia, and systemic metabolic disturbances. In addition to its well-established pulmonary pathology, RDS triggers a cascade of endocrine and immune responses that may drastically alter the morphophysiology of vital neonatal organs. Among these, the adrenal gland and thymus play key roles in adaptation to extrauterine life.

The adrenal gland functions as the primary endocrine center of the neonatal stress axis, contributing to the synthesis of glucocorticoids, mineralocorticoids, and catecholamines. The immature neonatal adrenal gland is highly sensitive to hypoxia and systemic stress. Cortisol deficiency or dysregulation has been recognized as a major aggravating factor in neonatal respiratory distress, yet morphological evidence of adrenal involvement remains comparatively understudied.

Similarly, the thymus plays an essential role in shaping adaptive immunity during the neonatal period. It is well known that systemic stress, hypoxia, corticosteroid excess, and sepsis can induce rapid thymic involution. However, the specific histological patterns of thymic atrophy in the context of RDS and their relationship to adrenal gland alterations have not been sufficiently described in the literature.

The integrated functional relationship between these two organs—via the hypothalamic–pituitary–adrenal axis and glucocorticoid-mediated immune modulation—suggests that structural changes in one organ may be tightly associated with morphological alterations in the other.

Therefore, the aim of the present study is to conduct a detailed histological and pathomorphological analysis of the adrenal gland and thymus in neonates with advanced respiratory distress syndrome, emphasizing the structural correlates of their physiological integration.

MATERIALS AND METHODS

Study Design

This research is a descriptive, morphology-centered pathoanatomical study conducted on neonatal autopsy material. The study focuses on the adrenal glands and thymus of infants diagnosed clinically and histologically with advanced respiratory distress syndrome.

Sample Collection

Autopsy specimens were selected from newborns (gestational age 32–40 weeks) who succumbed within the first seven days of life due to RDS-related complications. Exclusion criteria included congenital adrenal hyperplasia, thymic dysplasia, severe congenital malformations, or maternal endocrine disorders. Organ samples collected: Adrenal glands (right and left). Thymus (whole organ or representative lobe segments)

Tissue Processing. Fixation: Samples were fixed in 10% neutral buffered formalin for 24–48 hours.

Embedding: Tissues were processed and embedded in paraffin blocks.

Sectioning: Sections were cut at 4–5 μm thickness using a microtome.



Staining Methods: Hematoxylin & Eosin (H&E) for general histology. Masson’s trichrome for connective tissue evaluation. Periodic acid–Schiff (PAS) for detecting carbohydrate-rich structures and basement membranes

Immunohistochemistry (IHC): ACTH-R (adrenocorticotrophic hormone receptor): adrenal cortical stress activity. Chromogranin A: identifying chromaffin cells in adrenal medulla. CD3 and CD4: thymocyte populations. Cytokeratin: epithelial reticular cells of thymic stroma. Ki-67: cell proliferation index

Microscopic Evaluation

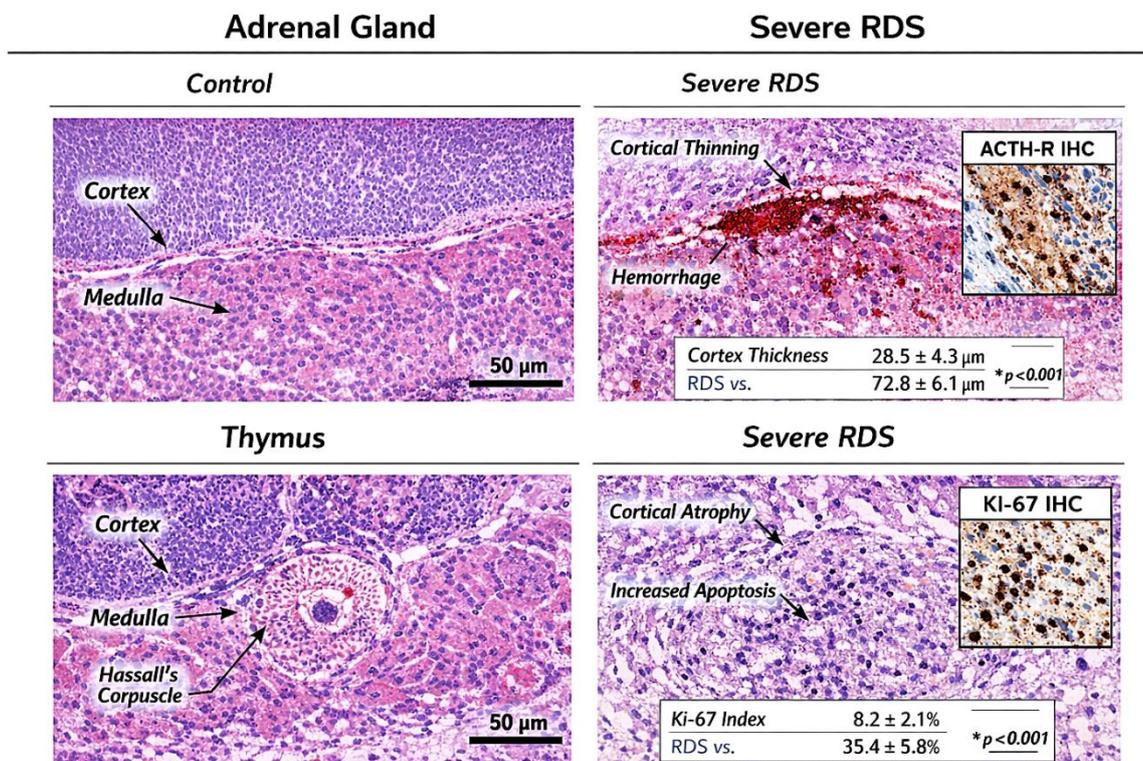
Histological examination focused on: In the adrenal gland: Zonal architecture (glomerulosa, fasciculata, reticularis). Lipid content and vacuolization. Cortical thickness. Vascular congestion and hemorrhage. Medullary chromaffin cell morphology. IHC-based endocrine stress markers.

In the thymus: Cortical-medullary demarcation. Thymocyte density. Reticuloepithelial cell morphology. Hassall corpuscle structure. Fibrous septa widening. Apoptotic bodies and degeneration. Proliferation indices (Ki-67).

Ethical Considerations. This study used anonymized postmortem material in accordance with institutional bioethical guidelines. No identifiable patient information was included.

RESULTS

Adrenal Gland Pathomorphology. Gross Morphology. Adrenal glands obtained from RDS cases appeared: Slightly reduced in overall mass. Pale yellow-gray on cut surface. Showing focal petechial hemorrhages, more pronounced in severe hypoxic cases.



Histological Alterations of the Adrenal Cortex. Zona Glomerulosa. Relative preservation of the cell cords in early-stage RDS. Mild cytoplasmic eosinophilia. Occasional nuclear pyknosis. **Zona Fasciculata.** This zone exhibited the most profound changes: **Lipid depletion:** The normal foamy, lipid-rich cytoplasm of fasciculata cells appeared markedly reduced. **Vacuolization:** Cytoplasmic vacuoles ranged from fine microvesicular patterns to coarse macrovesicular changes. **Cortical thinning:** Measured reduction of up to 30–40% compared to age-matched controls. **Increased apoptotic bodies:** Detected by condensed nuclear fragments. **Zona Reticularis.** Loosely arranged cords with disrupted cellular organization. Hyperchromatic nuclei and increased stromal connective tissue. PAS staining showed decreased carbohydrate content.

Vascular and Hemorrhagic Changes. Marked congestion of sinusoidal vessels. Extravasation of erythrocytes forming micro-hemorrhagic foci. Edema separating cortical cell cords.

Adrenal Medulla Alterations. Chromaffin cells showed: Swelling and cytoplasmic pallor. Reduced chromogranin A positivity, indicating compromised catecholamine storage. Blurred cell boundaries and vacuolization.

Immunohistochemical Findings (Adrenal Gland)

Marker	Findings
ACTH-R	Moderate to strong surface staining, indicating overstimulation during systemic stress.
Ki-67	Low proliferation index, reflecting exhaustion of adrenal cortex growth potential.
Chromogranin A	Reduced staining in medulla; loss correlates with hypoxic injury.

2. Thymus Pathomorphology

Gross Features. Thymus size was reduced in most cases. Lobular architecture was preserved macroscopically but appeared shrunken. Cut surface revealed pale yellowish-gray zones and fibrous septation.

Histological Alterations in Thymus. Cortical Zone. Severe lymphocyte depletion, reducing cortical thickness by 40–60%. Loss of basophilic staining, normally dense due to lymphocyte richness. Numerous apoptotic thymocytes, visible as tingible body macrophages.

Medullary Zone. Widening of medullary spaces due to cortical collapse. Increased epithelial reticular cell prominence, with eosinophilic, spindle-shaped morphology.

Hassall Corpuscles. Changes included: Fragmentation and concentric keratin layer disintegration. Occasional cystic transformation. Accumulation of necrotic debris in central regions.

Stromal and Vascular Changes. Vascular congestion. Thickened connective tissue septa. Focal edema.

Immunohistochemical Findings (Thymus)

Marker	Findings
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CD3	Markedly decreased cortical positivity.
CD4	Reduced helper T-cell precursor density.
Cytokeratin	Highlighted expanded reticuloepithelial network.
Ki-67	Low proliferation index in cortical thymocytes (indicative of suppressed thymopoiesis).

DISCUSSION

The present study demonstrates that advanced neonatal RDS is accompanied by profound and parallel structural changes in the adrenal gland and thymus. These findings highlight the integrated nature of neonatal endocrine-immune interactions under severe physiological stress.

Adrenal–Thymus Integration in Neonatal Stress

Neonatal RDS induces systemic hypoxemia, leading to compensatory activation of the hypothalamic–pituitary–adrenal axis. Elevated ACTH stimulates cortisol production, placing a high metabolic demand on the adrenal cortex. Cortisol, in turn, directly impacts thymic lymphocyte turnover, promoting apoptosis and inhibiting T-cell maturation. This biological mechanism explains the simultaneous degenerative changes observed in both organs.

Interpretation of Adrenal Changes. The adrenal cortex, especially the zona fasciculata, exhibited marked lipid depletion, thinning, and apoptosis. These alterations reflect: Exhaustion of steroidogenic reserves. Impaired cortisol synthesis. Hypoxic injury at the cellular level. Medullary changes indicated reduced catecholamine storage, which may contribute to impaired cardiovascular adaptation in neonates.

Interpretation of Thymic Changes. Thymic atrophy in RDS is likely secondary to: Elevated endogenous corticosteroids. Direct hypoxic injury. Systemic inflammation. Lymphocyte depletion and Hassall corpuscle degeneration suggest a severe reduction in immune competence, leaving neonates vulnerable to infections and limiting adaptive immune development.

Functional Significance. The combined morphological deterioration of adrenal and thymic tissues highlights: A compromised stress response. Suppressed adaptive immunity. Disrupted homeostasis in severely ill newborns. These changes may partially explain why neonates with advanced RDS have poorer clinical outcomes.

CONCLUSION

This study provides detailed histopathological evidence that advanced neonatal respiratory distress syndrome induces significant structural changes in both the adrenal gland and thymus. The adrenal cortex undergoes lipid depletion, cortical thinning, and stress-induced degeneration, while the thymus exhibits profound cortical atrophy, lymphocyte depletion, and structural disorganization.

These parallel alterations reflect the functional integration of endocrine and immune systems during neonatal stress. Understanding these pathomorphological relationships is essential for



improving prognostic assessments, guiding hormonal therapy strategies, and enhancing neonatal care protocols in severe respiratory disease.

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