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ADRENAL CORTICAL IMMATURITY: A MORPHOLOGICAL KEY TO FATAL NEONATAL RDS

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Annotatsiya. Muddatidan oldin tug‘ilgan chaqaloqlarda buyrak usti bezining to‘liq shakllanmaganligi va timusning giperplaziya ko‘rinishida kattalashuvi, stressor omillarga ekstremal adaptatsiya reaksiyalarining pastligi bilan davom etib, o‘tkir respirator distress-sindromning og‘ir kechishi va chaqaloqlarda bevosita buyrak usti bezi gormoni — kortizolning yetishmasligi bilan namoyon bo‘lishini tasdiqlaydi. Bu esa, o‘z navbatida, o‘pkalarning kengayishi va surfaktantning to‘liq sintezi buzilishiga olib keladi. Buyrak usti bezida morfologik jihatdan yetilmaganlik koptokchalarning deyarli hali kurtak ko‘rinishida bo‘lishi, spongiotsitlarning mayda, yirik yadroli, sitoplazmasida lipidli kiritmalarning kamligi, to‘rsimon qavat epiteliylarining mayda yadroli, och sitoplazmali ko‘rinishda bo‘lishi bilan xarakterlanadi.
Kalit so‘zlar: muddatidan oldingi tug‘ruq, respirator distress-sindrom, buyrak usti bezi, morfologiya.
Аннотация. У недоношенных новорождённых неполное формирование надпочечников и увеличение тимуса в виде гиперплазии сопровождаются сниженной способностью к экстремальным адаптационным реакциям на стрессовые факторы. Это подтверждается тяжёлым течением острого респираторного дистресс-синдрома и недостаточностью гормона надпочечников — кортизола. Дефицит кортизола, в свою очередь, приводит к нарушению расширения лёгочной ткани и полноценного синтеза сурфактанта. Морфологически в надпочечниках выявляются признаки незрелости: клубочковая зона преимущественно сохраняется в виде зачатков, спонгиоциты мелкие, с крупными ядрами и скудными липидными включениями в цитоплазме, клетки сетчатого слоя характеризуются мелкими ядрами и светлой цитоплазмой.
Ключевые слова: преждевременные роды, респираторный дистресс-синдром, надпочечники, морфология.
Abstract. In preterm neonates, incomplete adrenal cortical development together with compensatory thymic enlargement is associated with a diminished capacity for adaptive responses to extreme stress. This is reflected clinically in the severe course of acute respiratory distress syndrome (RDS) and a direct deficiency of the adrenal hormone cortisol, which in turn impairs pulmonary expansion and complete surfactant synthesis. Morphological examination of the adrenal glands reveals characteristic signs of immaturity: glomerular zones remain largely in a primordial state, fascicular spongiocytes are small with large nuclei and scarce cytoplasmic lipid inclusions, and the epithelial cells of the reticular layer display small nuclei with pale cytoplasm.
Keywords: preterm birth, respiratory distress syndrome, adrenal glands, morphology.

Introduction.

Respiratory distress syndrome (RDS) remains one of the leading causes of neonatal morbidity and mortality worldwide, with hyaline membrane disease representing its most severe pathological form. According to World Health Organization data, RDS complicates approximately 750,000 of the 3 million premature births recorded annually, and survival among affected infants averages only 50%, falling to as low as 25% even under intensive care [1. 2024:B.101374; 6. 2025:B.235]. Mortality attributable to RDS varies considerably by region: reported rates range from 11–15 per 1,000 births in the United States and the European Union to 15–17 per 1,000 in Turkey, Canada, South Korea and Japan, 20–30 per 1,000 in the Russian Federation, and 30–50 per 1,000 across the Commonwealth of Independent States, occasionally exceeding 70 per 1,000 during the early neonatal period.

The severity of RDS is inseparable from the maturity of the hypothalamic–pituitary–adrenal (HPA) axis. Functional maturation of the adrenal cortex is not complete until approximately 30 weeks of gestation,

leaving infants born before this threshold transiently unable to mount an adequate cortisol response to the stress of extrauterine life [4. 2022:B.e328; 5. 2021:B.369]. This relative adrenal insufficiency of prematurity directly compromises terminal alveolar differentiation and surfactant phospholipid synthesis, linking adrenal hypofunction mechanistically, rather than coincidentally, to the severity of respiratory failure [7. 2023:B.1804]. The thymus, in turn, is highly sensitive to circulating glucocorticoids, and its compensatory enlargement in infants who die of RDS has been proposed as an indirect marker of an inadequate stress-adaptive response [2. 2022:B.714]. Antenatal corticosteroid administration remains the most effective intervention for accelerating fetal lung maturation, though its efficacy continues to be refined and appears to depend on the inflammatory context of the pregnancy [3. 2024:B.479; 8. 2020:B.e139452].

Despite this evidence base, the histomorphological substrate of adrenal insufficiency in infants who die with RDS remains insufficiently studied, particularly with regard to its integral relationship with thymic pathology in determining fatal outcome — a gap that defines the relevance of the present study.

Results and discussion.

Morphological examination of adrenal glands obtained from preterm infants of 26–32 weeks’ gestation who died with a clinical and morphological diagnosis of RDS revealed consistent signs of structural immaturity. The capsule was of irregular thickness, with anatomical zonation almost undefined and histoarchitecture resembling that of the embryonic period. The glomerular zone was predominantly in a primordial, bud-like state. Spongiocytes of the fascicular zone were small, with large nuclei and pale eosinophilic cytoplasm containing few or no lipid inclusions, while the reticular layer consisted of small, immature secretory epithelial cells with large nuclei and light cytoplasm. Venous plethora was present across all cortical zones; the medullary layer additionally showed foci of hemorrhage, a pronounced degree of catecholamine synthesis, interstitial stromal edema, and a high proportion of necrobiotic cells. In infants of 30–32 weeks, subcapsular hemorrhage and ingrowth of fibrous capsular tissue into the parenchyma were additionally observed, together with strangulated, scarred cortical foci, indicating a further decline in morphofunctional capacity superimposed on arrested embryonic development.

At the organ level, these histological changes were paralleled by measurable alterations in weight and clinical status. In neonates who died of RDS, adrenal gland weight averaged 1.6 g, while thymic weight exceeded the age-appropriate norm by approximately 30.5%, consistent with compensatory thymic hyperplasia in the setting of inadequate cortisol output. The combination of blunted stress-induced respiratory excitation and impaired surfactant production was associated with a marked increase in mortality, reaching 70–80% among affected neonates; clinically, these infants were assessed at 1–1a points on the Apgar scale. Pathophysiologically, the deficiency of cortisol required to adequately induce respiratory stimulation was reflected in pronounced plethora and diapedetic hemorrhage within small-caliber vessels of both the cortex and medulla, a marked reduction in lipid inclusions within fascicular spongiocytes, and interstitial edema — findings consistent with hemodynamic disturbance secondary to adrenal cortical insufficiency [2. 2022:B.714; 4. 2022:B.e328].

These findings are consistent with the broader clinical literature on relative adrenal insufficiency of prematurity, in which vasopressor-resistant hypotension and impaired cardiovascular adaptation in extremely preterm infants are frequently attributable to an adrenal gland structurally incapable of the demanded output [4. 2022:B.e328; 5. 2021:B.369]. The concurrent thymic enlargement observed in this study is a notable structural counterpart to adrenal hypofunction: because glucocorticoids are the principal negative regulator of thymic mass under stress, insufficient cortisol output may permit relative thymic hyperplasia rather than the involution ordinarily seen with an intact stress response [2. 2022:B.714]. This pattern parallels the elevated cortisol-precursor-to-cortisol signature described in preterm infants who go on to develop bronchopulmonary dysplasia, suggesting axis activation that fails to meet peripheral demand rather than simple axis quiescence [7. 2023:B.1804]. From a therapeutic standpoint, these morphological findings reinforce the rationale for antenatal corticosteroid administration to accelerate fetal lung and adrenal maturation, while underscoring that the effectiveness of such therapy depends on gestational timing and the inflammatory context of the pregnancy [3. 2024:B.479; 8. 2020:B.e139452].

Conclusion.

Preterm neonates who die with respiratory distress syndrome demonstrate a consistent pattern of adrenal cortical immaturity — undifferentiated glomerular zones, lipid-depleted spongiocytes, immature reticular epithelium, and venous plethora with hemorrhage — accompanied by compensatory thymic hyperplasia, reduced Apgar scores, and markedly elevated mortality. These results indicate that adrenal structural competence, rather than respiratory pathology in isolation, constitutes a key morphological

determinant of survival in extremely preterm infants, supporting the integration of morphological and endocrine assessment, together with timely antenatal corticosteroid therapy, into the management of neonates at risk of fatal RDS.

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