IMMUNOHISTOCHEMICAL CHARACTERISTICS IN VARIOUS ESOPHAGEAL ANOMALIES

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Abstract. *In the study of various clinical and morphological forms of esophageal atresia—one of the developmental anomalies of the esophagus—immunohistochemical analysis plays a pivotal role. The chromogranin marker is used to identify neuroendocrine cells, specifically secretory neurons that indicate neuromuscular synapses, as well as to detect the ongoing synthesis of functional peptide bonds. Being a glycoprotein by nature, this marker allows for the assessment of the morpho-functional state of vesicles within the muscle layer by staining the components of neuromuscular synapses. Such analysis provides an essential foundation for planning appropriate treatment strategies based on the variant of esophageal atresia present.*

Keywords: *immunohistochemical analysis, esophageal atresia, neonates, morphology.*

Relevance of the problem. Esophageal developmental anomalies are pathological processes that stem from anatomical and histological disruptions during the embryonic development of the esophagus and its structures. Globally, this condition is found in approximately 40 out of every 100,000 newborns. In countries such as the United States and across Europe, early prenatal screening allows for timely diagnosis of such anomalies, often resulting in medical recommendations for pregnancy termination. The prevalence in these regions averages between 4 and 8 cases per 100,000 live births. In the Commonwealth of Independent States (CIS), including the Russian Federation, the incidence ranges from 20 to 25 cases per 100,000. In Uzbekistan, the rate is notably higher, averaging 8 to 10 cases per 1,000 newborns, with a mortality rate of 60–78% within the first month of life.

At present, this issue remains a critical concern for pediatricians and neonatologists, particularly given the increased risk-up to 2.5 times higher-among infants born to consanguineous parents, as confirmed by international literature and clinical data. Most concerning is the mortality rate exceeding 85% in cases involving combined tracheoesophageal fistulas, where newborns often succumb to aspiration pneumonia within the first days of the early neonatal period**.**

Materials and Methods. The research material consisted of autopsy specimens taken from newborns diagnosed with esophageal developmental anomalies who had died either following surgical intervention or without surgical treatment at the Republican Perinatal Center. Esophageal tissue samples from 18 such cases were selected for immunohistochemical examination.

Objective. To evaluate the significance of immunohistochemical studies in identifying the clinical and morphological types of esophageal developmental anomalies.

Discussion and Results. Subsequent immunohistochemical investigations demonstrated that the chromogranin marker is instrumental in identifying neuroendocrine cells, secretory neurons associated with neuromuscular synapses, and in confirming the synthesis of functional peptide bonds. As a glycoprotein, chromogranin enables evaluation of the morpho-functional condition of neuromuscular vesicles through targeted staining within the muscle layer.

Notably, even in minimal concentrations, this marker exhibits high sensitivity—making it possible to visualize APUD (Amine Precursor Uptake and Decarboxylation) cells and vesicles within the synaptic structures. Through chromogranin staining, one can determine the maturity of APUD cells within the mucosal layer of the esophageal wall, thereby assessing morpho-functional characteristics and predicting clinical-morphological outcomes. The partial preservation of neuromuscular synaptic control by APUD cells offers insight for both diagnostic and therapeutic planning in cases of esophageal atresia, including whether to pursue conservative or surgical treatment, and allows for a prospective evaluation of expected outcomes.

The chromogranin marker showed weak positive expression only in cases of isolated (Type I) esophageal atresia. In other subtypes, the expression was weak or entirely negative. This indicates that non-isolated forms of esophageal atresia, especially those combined with other developmental anomalies, are characterized by a more severe morphological presentation and a significant reduction in the number and functionality of APUD cells in the esophageal wall.

As a complex glycoprotein, this protein marker stains the membranes of neurosecretory cells and gives a positive reaction—typically appearing as a light yellow hue in functionally active tissues. However, if expression is seen in a dark brown hue, it may suggest a high concentration of chromogranin protein, indicating increased activity in neurosecretory cells, or even the presence of a neoplastic process. In our study, this marker showed moderate intensity specifically in the Type I cases.

The low expression of chromogranin is explained by the underdevelopment of neuromuscular synapses and the presence of increased numbers of fibroblasts and histiocytes surrounding these areas. This contributes to the formation of fibromuscular tissue complexes, further disrupting functional capacity. Such findings suggest that esophageal atresias require urgent diagnostic evaluation and timely treatment planning. Failure to act appropriately and promptly—particularly in the presence of pronounced clinical-morphological indicators—can lead to a high mortality rate, reportedly as high as 90%.

Conclusion. The low expression of the chromogranin marker reflects a deficiency in the biologically active substances produced by neuromuscular synapses and APUD cells. From a clinical and morphological standpoint, this highlights the necessity of introducing such

bioactive agents as part of therapeutic interventions. These findings confirm a fundamental developmental lag in the neuromuscular connectivity in various forms of esophageal atresia.Therefore, in proposing a treatment algorithm, special attention should be given to enhancing the excitability of neuromuscular synapses. Such an approach may offer a significant therapeutic advantage, with the potential to preserve life in approximately 50–92% of affected patients.

References:

1. Vorotnikova N.A., Chernenkov Yu.V., Eiberman A.S. Gastroesophageal reflux disease and bronchial obstructive syndrome in children – "a vicious circle" or comorbidity? // Experimental and Clinical Gastroenterology. – 2022. – No. 3 (199). – P. 26–36.
2. Sukalo A., Kozlovsky A. *Pediatric Gastroenterology and Dietetics.* – Litres, 2022.
3. Akhrarova F. *The influence of connective tissue dysplasia on the course of gastroenterological diseases in children* // Pediatrics. – 2023. – Vol. 1. – No. 1. – P. 380–386.
4. Soboleva M.K., Kinsht D.A. *Congenital defects and minor developmental anomalies in newborns depending on the type of infertility overcome and parental health* // Medical Council. – 2021. – No. 11. – P. 22–28.
5. Choi G, Je BK, Kim YJ. Gastrointestinal Emergency in Neonates and Infants: A Pictorial Essay. Korean J Radiol. 2022 Jan;23(1):124-138.
6. Madeleine A, Audrey N, Rony S, David S, Frédéric G. Long term digestive outcome of œsophageal atresia. //Best Pract Res Clin Gastroenterol. 2022 Feb-Mar;56-57
7. Sadreameli SC, McGrath-Morrow SA. Respiratory Care of Infants and Children with Congenital Tracheo-Oesophageal Fistula and Oesophageal Atresia. Paediatr Respir Rev. 2016 Jan17:16-23.
8. Boybeyi-Turer O, Iyigun I, Cagan M, Celik HT, Ozyuncu O, Soyer T. A rare congenital esophageal anomaly mimicking an isolated esophageal atresia: Kluth Type IV membranous esophageal atresia. Congenit Anom (Kyoto). 2021 Nov;61(6):208-211.
9. Ge Y, Xu B, Shi J, Tang W. Application value of high-frequency ultrasound combined with ultrasonography in the diagnosis of neonatal esophageal atresia. Afr Health Sci. 2023 Sep;23(3):547-553
10. Chernetsova E, Agarwal A, Weir A, Oltean I, Barkey J, Demellawy DE. Diagnostic Value of Mid-esophageal Biopsies in Pediatric Patients with Eosinophilic Esophagitis. Pediatr Dev Pathol. 2021 Jan-Feb;24(1):34-42.
11. Wechsler JB, Bolton SM, Gray E, Kim KY, Kagalwalla AF. Defining the Patchy Landscape of Esophageal Eosinophilia in Children with Eosinophilic Esophagitis. Clin Gastroenterol Hepatol. 2022 Sep;20(9):1971-1976.e2.
12. Rohanizadegan M, Tracy S, Galarreta CI, Poorvu T, Buchmiller TL, Bird LM, Estroff JA, Tan WH. Genetic diagnoses and associated anomalies in fetuses prenatally diagnosed with esophageal atresia. //Am J Med Genet A. 2020 Aug;182(8):1890-1895.

13. Best C, Sudel B, Foker JE, Krosch TC, Dietz C, Khan KM. Esophageal stenting in children: indications, application, effectiveness, and complications. //Gastrointest Endosc. 2009 Dec;70(6):1248-53
14. Schmedding A, Wittekindt B, Schloesser R, Hutter M, Rolle U. Outcome of esophageal atresia in Germany. //Dis Esophagus. 2021 Apr 7;34(4): doaa093.
15. Gayle JA, Gómez SL, Baluch A, Fox C, Lock S, Kaye AD. Anesthetic considerations for the neonate with tracheoesophageal fistula. Middle East J Anaesthesiol. 2008 Oct;19(6):1241-54
16. Pinheiro PF, Simões e Silva AC, Pereira RM. Current knowledge on esophageal atresia. //World J Gastroenterol. 2012 Jul 28;18(28):3662-72.
17. Nagappa S, Kalappa S, Vijayakumar HN, Nethra HN. Comparison of the effectiveness of intravenous fentanyl versus caudal epidural in neonates undergoing tracheoesophageal fistula surgeries. Saudi J Anaesth. 2022 Apr-Jun;16(2):182-187.
18. Paul M, Bamba C, Vinay V, Krishna B; Bharani Kumar B.1. Comparing Opioid with Opioid-free Anesthesia Technique in Neonates Undergoing Tracheoesophageal Fistula Repair. Oman Med J. 2023 Sep 28;38(5):e547.
19. Fukuta A, Kamimura T, Furuno W, Yamamoto J, Yokota C, Omura S. Abdominal esophageal banding for esophageal atresia with tracheoesophageal fistula in neonates with severe associated anomalies. Pediatr Surg Int. 2021 Feb;37(2):261-266.