UDC:616.23/.24–007.17–018–092–053.32
DOI: 10.24061/2413-4260.XIII.1.47.2023.6

MORPHOLOGICAL EVOLUTION AND DIAGNOSIS OF BRONCHOPULMONARY DYSPLASIA IN VERY PRETERM INFANTS

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Summary

Bronchopulmonary dysplasia (BPD) remains one of the most common and severe diseases in very preterm infants, which can cause death. Since the first description of BPD in 1967, not only understanding of the disease's nature, its definition, classification, epidemiology, features of the clinical course, diagnosis, prevention, treatment, and prognosis but the specific autopsy histopathological features have changed. The primarily reason for these is considered a change in the population of sick and dead infants as a result of improving clinical practice, increasing the survival rates of the most immature neonates, and reducing the incidence of severe BPD forms and the associated mortality.

The BPD form that has been described initially is now called "old" BPD and is characterized by significant lung injury. In the smallest neonates, who were treated with exogenous surfactant, the histopathological signs of the disease changed, determining the need to modify the theoretical concept of BPD. The leading feature of the new BPD form was the disorder of lung development and formation, not their injury. Morphologically, this was manifested by a reduced number and simplified structure of acini, changes in the capillary structure with less obvious fibrosis of the lungs. Such morphometric methods as the radial alveolar count and the count of mean number of alveoli intercepts can be used for the histopathological diagnosis of a simplified lung structure. The use of these techniques helps to objectively assess lung growth retardation. Although the number of cases of "new" BPD currently prevails, some autopsies are still characterized by histopathological changes typical for the "old" form of the disease. A combination of classic and new features is also possible. When establishing a pathological diagnosis of BPD, it is essential to consider all specific histopathological changes that may indicate the presence and severity of the disease, as well as its role in thanatogenesis. This is important not only for the correct postmortem diagnosis of BPD, but also for the studying of various disease phenotypes.

The article describes the main histopathological characteristic of various BPD forms, as well as methods of evaluating the simplified lung structure.

Keywords: *bronchopulmonary dysplasia; histopathology; preterm infants.*

Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease in preterm infants, which increases the frequency of negative long-term consequences [1,2,3]. It is known that clinical symptoms of BPD, primarily chronic oxygen dependence, are associated with certain histopathological changes in the affected lungs, which are found at autopsy in dead infants [4,5]. However, due to the polyetiological nature of the disease, the morphological changes in the lungs are different, which leads to the differences in the modern clinical phenotypes of BPD [6,7]. Accordingly, studying the pathomorphological features of different phenotypes of BPD is essential for understanding the differences in the mechanisms of lung damage that determine the course and prognosis of the disease [8].

In 1967, Northway et al. [9] first described BPD as a chronic lung disease that developed mainly in premature infants after severe respiratory distress syndrome (RDS), which required treatment with mechanical lung ventilation and high oxygen concentrations (≥ 80 %) for at least 24 hours. The authors presented clinical, radiological and histopathological data of 32 infants (19 of them died). The average gestational age and birth weight of the dead babies were 31 weeks and 1660 g, and those of the surviving babies were 34 weeks and 2234 g, respectively. Age at death ranged from 2 days to 11 months.

Typical histopathological changes that characterized the lungs of dead infants at the age of 10-20 days had significant injury and partial regeneration of the airway epithelium; widespread meta- and hyperplasia of mucosal cells in the bronchi and bronchioles; progressive fusion with the formation of spherically limited groups of emphysematous alveoli surrounded by areas of atelectasis; gross focal thickening of basement membranes and the presence of collagen in the interseptal spaces, as well as interstitial edema. After 30 days of life, in the lungs of infants who died of BPD, focal groups of emphysematous alveoli associated with bronchioles with obvious peribronchial smooth muscles hypertrophy were found; significant diversity of alveolar epithelium; widespread metaplasia with exfoliation of mucous membrane cells; generalized focal thickening of basement membranes with separation of capillaries from alveolar epithelium; vascular hypertensive changes; increasing reticulin, collagen fibrils and elastin fibers in the alveolar septa, as well as extensive fibrosis were described (Fig. 1). Macrophages and histiocytes were found in the airway exudate, and their quantity increased with the pathological process development [9].

The authors proposed to distinguish four stages of chronic lung disease - the acute period of RDS (the 1st

ISSN 2226-1230 (PRINT) ISSN 2413-4260 (ONLINE)

stage, which lasts 2-3 days), the regeneration period (the 2nd stage, 4-10 days), the period of transformation into chronic lung disease (the 3rd stage, 10-20 days) and the period of chronic lung disease (stage 4, later one month) [9]. A few decades later, Cherukupalli et al. similarly described the histopathology of the period of acute lung injury (RDS), as well as the proliferative, early, and late recovery phases in 48 infants who died from RDS or BPD [10].

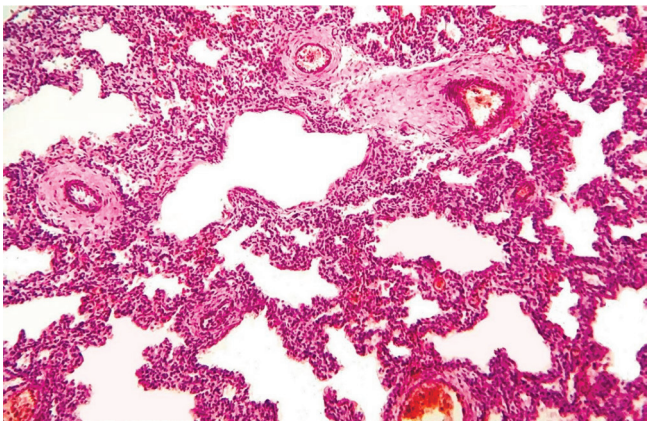

Figure 1. Lung tissue section from the infant with a gestational age of 31 weeks who died in 1 month and 10 days after birth. Fibrosis of interalveolar septa, changes in lung vessels (adventitous sclerosis, smooth muscle hyperplasia). Hematoxylin and eosin, x100

Numerous studies confirmed the described Northway et al. histopathological changes in the lungs of infants with BPD. However, most of them neither contained quantitative data nor analyzed the detected changes depending on the gestation age [4]. At the same time, as early as 1982, one of the publications described a critical decrease in the number of alveoli (10% of the norm) in a 33-month-old child who was born with a gestation age of 30 weeks and died of BPD [11].

As described by Northway et al. histopathological changes in the lungs of deceased infants are now called "old" BPD and are associated with lung injury caused by the harmful effects of endotracheal intubation, mechanical ventilation, and high oxygen concentrations. Death in such infants is mainly a consequence of severe respiratory failure in combination with a pulmonary heart [12].

The introduction of new methods of treatment and care of preterm infants, as well as more survival of the most immature babies, caused not only changes in the clinical course of the disease but also the morphological evolution of BPD. The infants described in the study by Northway et al. today die infrequently and survive mostly without chronic respiratory sequelae. Under the influence of the wider use of antenatal steroid prophylaxis, non-invasive respiratory support, and exogenous surfactant, as well as new safer methods of mechanical ventilation, the morphological signs of injury to immature lungs have changed. The change in the histological features of BPD in the post-surfactant era formed the concept of the "new" BPD [5]. Preterm birth during the canalicular and saccular stages of lung ontogenesis with the beginning of pulmonary gas exchange interrupts the normal development of the lungs, disrupting the processes of formation of alveoli and pulmonary vessels [13]. These changes are the main features of the "new" BPD, which can develop in extremely preterm babies who neither had severe RDS nor required mechanical ventilation after birth [5].

The histopathological features of the "new" BPD are mainly established on autopsies, biopsy data [14,15], as well as in experimental animal studies. Husain et al. [14] analyzed autopsy data from 22 BPD patients (14 surfactant-treated infants and 8 infants managed without surfactant administration), comparing them with data from 15 age-matched controls. The gestational age of most infants with BPD was less than 30 weeks. The authors described a smaller number of simplified alveoli, minor airway damage, a smaller number of dysmorphic capillaries in combination with less significant arterial changes, variable airway smooth muscle hyperplasia, and variable interstitial fibroproliferation. These changes were proposed as histopathological features of the “new” BPD. Alveolar septal fibrosis was significantly less and generally more diffuse in surfactant-treated infants. Instead, as a histopathological marker of new BPD, the authors proposed the presence of large alveoli with a small number of secondary septa in the distal acini of the lungs. In all lung samples obtained from patients with BPD at a postmenstrual age of more than 40 weeks the formation of alveoli was disturbed, which was confirmed by objective morphometric methods. The use of exogenous surfactant did not accelerate the formation of acini in the lungs of infants with BPD [14]. Simplification of distal lung acini and absence of alveolar septa were also the main changes in all lung biopsies studied by Coalson [15]. At the same time, the degree of cell infiltration and fibrosis in simplified alveolar structures was variable [15].

The main histopathological differences between "old" and "new" BPD were summarized by Coalson [15] and Hayes et al. [16] (Table 1).

In practice, several morphometric methods can be used to confirm a smaller number of alveoli in an infant's lungs. The method of radial counting of the number of alveoli (radial alveolar count, RAC) [17] determines the number of alveoli that are crossed by a perpendicular line drawn from the center of the respiratory bronchiole to the edge of the acinus (the nearest septal division or the edge of the pleura) (Fig. 2) [18]. This method provides determination of the reliable lung growth index during intrauterine, early and late postnatal development, as well as during childhood [19, 20]. It was established that counting in 40 fields of view is more accurate than counting in 10 fields [20]. However, regardless of the number of fields of view used, the same magnification must be applied and the average value calculated. Lung study using this method in a cohort of stillborn fetuses and dead newborn babies made it possible to determine the approximate normal number of alveoli for different age children groups (Table 2) [20].

Another morphometric method to assess the degree of lung alveolarization is the calculation of the average number of alveolar septa crossed by a standard ruler (mean linear intercept, MLI). This indicator, determining the size of the alveoli, also reflects the degree of the structure simplification, which is compensated by an increase in their size. It is determined by counting the number of alveolar septa that fall on a 1-mm ruler placed in the center of the field (Fig. 3). All fields of view should have the same

magnification [21]. The following formula is used [14]:

$$Lm = N \times L/m,$$

where Lm is the average number of alveolar septa crossed by a standard ruler, N is the number of fields of view, L is the length of the ruler (1 mm), and m is the number of alveolar septa.

Table 1

Evolution of the histopathological of BPD according to Coalson [15] in the modification of Hayes et al. [16]

Old BPD	New BPD
• Alternating areas of atelectasis and emphysema • Obvious airway epithelial lesions (hyperplasia and squamous cell metaplasia) • Reduction of the internal surface area and alveoli • Airway smooth muscles hyperplasia • Significant fibroproliferation • Obvious vascular hypertensive changes	• Reduced, large and simplified alveoli (alveolar hypoplasia, reduced acinar complexity) • Mild airway epithelium lesions • Variable airway smooth muscles hyperplasia • Variable interstitial fibroproliferation • Reduced number of dysmorphic capillaries • Milder arterial/arteriolar vessels lesions • Less alveolar septal fibrosis, but more diffuse

Table 1

Estimated number of alveoli, determined by radial counting, in different age groups of fetuses and infants [20]

Gestational age, weeks	The average number of alveoli in one field	Postnatal age, months	The average number of alveoli in one field	Gestational age, weeks	The average number of alveoli in one field	Postnatal age, months	The average number of alveoli in one field
18	1.5	1	6.7	32	3.4	80	11.1
19	1.6	2	7.4	33	3.6	90	11.2
20	1.7	3	7.8	34	3.8	100	11.3
21	1.8	4	8.1	35	4.0	110	11.4
22	1.9	5	8.3	36	4.3	120	11.5
23	2.0	6	8.5	37	4.5	130	11.6
24	2.1	8	8.8	38	4.8	140	11.7
25	2.3	10	9.0	39	5.1	150	11.7
26	2.4	20	9.7	40	5.4	160	11.8
27	2.5	30	10.1	41	5.7	170	11.9
28	2.7	40	10.4	42	6.0	180	11.9
29	2.8	50	10.6	43	6.4	190	12.0
30	3.0	60	10.8	44	6.75	200	12.0
31	3.2	70	11.0	44	6.75	200	12.0

The described morphometric methods should be used for the diagnosis of "new" BPD in cases without classic histopathological sign of this disease as alveolar septa fibrosis. If the infant's postmenstrual age exceeds 40 weeks, the ratio of the radial alveolar count (RAC) to the mean linear intercept (MLI) less than 30 is diagnostic for "new" BPD [14].

This disease phenotype is also characterized by reduced secondary alveolar septation, which is a sign of alveoli structure simplification (Fig. 4).

In addition to determining the RAC and MLI, it is important to assess the presence and spread of fibrosis in the lung tissue. Fibrosis in the lungs can be focal, if it is limited to several separate acini, or diffuse, if it is present in all parts of the lungs (Fig. 5). It is also necessary to assess the presence or absence of necrotizing bronchiolitis, which is caused by the harmful effects of high oxygen concentrations and gas pressure during mechanical ventilation [14].

The concept of "new" BPD is mainly based on the "arrest of growth" of the lungs, and not on their injury [5,22]. However, there are currently signs that BPD is changing again. The number of infants requiring tracheostomy and mechanical ventilation is increasing due to the increased survival of extremely preterm with extremely low birth weight babies with complex medical problems [7]. In particular, the frequency of BPD in children with gestational age 23 weeks is about 78%, among which 58% is severe form of the disease [23]. Therefore, early mortality and survival with severe BPD remain a clinical challenge [6,24]. Differences in injury and repair patterns probably result from multiple lung dysmaturity phenotypes that are caused by antenatal and postnatal risk factors, as well as genetic background [25]. Thus, lung damage, which leads to the occurrence of BPD, is not uniform, and is manifested by various changes in lung structure. [26]. Therefore, during the histological examination, it is essential to consider morphological signs of both "old" and "new" BPD.

An important point is making the diagnosis of BPD, which remains controversial despite the established criteria, as they are not perfect [27,28]. Currently, the definition and classification of BPD of the US National Institutes of Health (2001) as modified by Walsh et al. are recommended for use (2003). Diagnosis according to this classification is made by the presence of at least 28 days of oxygen dependence after birth [29,30]. At the same time, some preterm babies with significant lung injury may die before reaching 28 days of life from severe respiratory failure caused by existing BPD. In such a situation, according to the current classification, there is formally no basis for making

ISSN 2226-1230 (PRINT) ISSN 2413-4260 (ONLINE)
KEY TITLE: NEONATOLOGIÂ, HÌRURGIÂ TA PERINATAL'NA MEDICINA (ONLINE)
ABBREVIATED KEY TITLE: NEONATOL. HÌR. PERINAT. MED. (ONLINE)

a clinical diagnosis of BPD, which may be the reason for discrepancies between clinical and pathological diagnoses. The National Institute of Child Health and Human Development (2016) proposed changes and clarifications to the classification and definition of BPD [31]. One of the new recommendations is the possibility to make a clinical diagnosis of BPD before preterm infant has reached 28 days of postnatal age in the case of death after 14 days of life due to persistent parenchymal lung disease and severe respiratory failure in the absence of other causes (e.g., necrotizing enterocolitis, intraventricular hemorrhage, episode of sepsis, etc.). However, this classification is not valid and is at the stage of discussion and testing. At the same time, an accurate pathological diagnosis of BPD, which takes into account all possible histopathological signs of this disease, is an important element of confirming the clinical diagnosis, as well as making the diagnosis when typical morphological changes in the lungs are already present, but the clinical criteria of the disease have not reached yet. On the other hand, the presence of histopathological changes in the lungs of a deceased infant, characteristic of BPD, does not automatically mean that BPD is the cause of the death of such a baby. In order to make such a conclusion, it is necessary to be sure that the infant really died from respiratory failure due to typical lung injury, and not because the other reasons mentioned above.

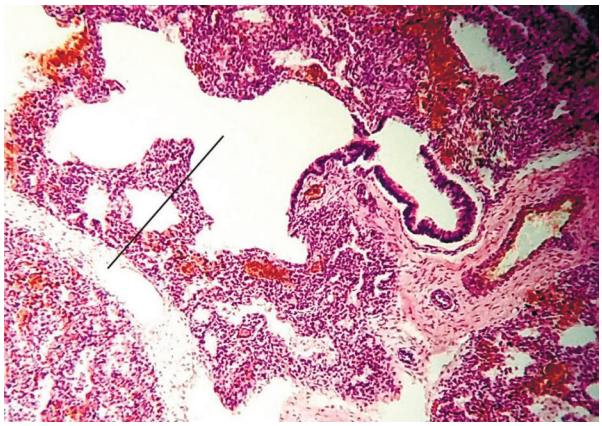

Figure 2. Lung tissue section from an infant with a gestational age of 27-28 weeks who died in 12 days after birth. Simplified alveolar structure of the lungs. The number of alveoli by radial count is 2. Hematoxylin and eosin, x100.

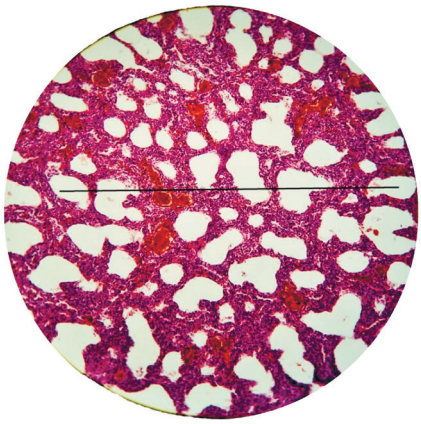

Figure 3. Lung tissue section from an infant with a gestational age of 27-28 weeks who died in 12 days after birth. Simplified alveolar structure of the lungs. Counting the number of alveolar septa crossed by a standard 1 mm ruler (description in the text). The number of alveolar septa is 5. Hematoxylin and eosin, x100.

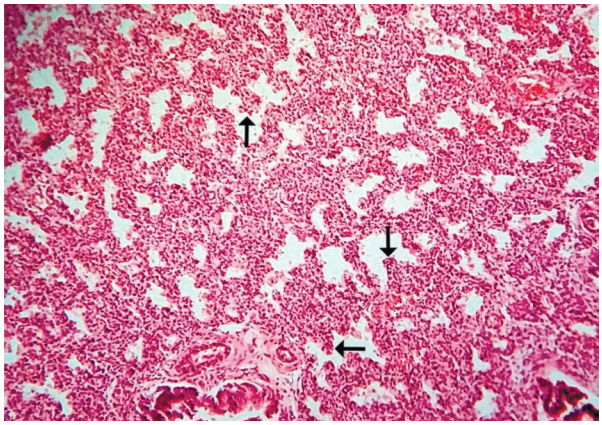

Figure 4. Lung tissue section from an infant with a gestational age of 26 weeks who died in 17 days after birth. Interalveolar septa are wide with increased cytosis, impaired formation of secondary alveolar septations (reduced number). Areas of formation of secondary septations are marked with arrows. Hematoxylin and eosin, x100.

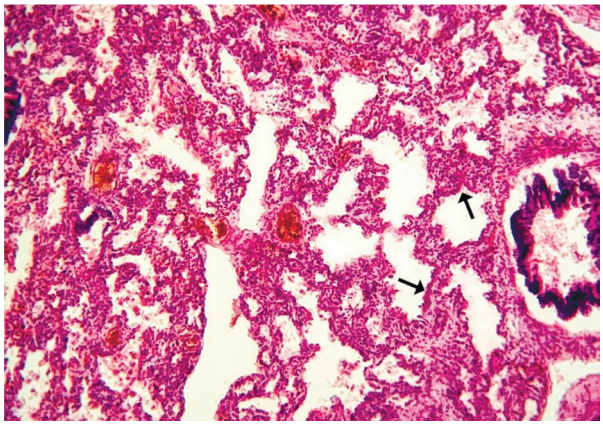

Figure 5. Lung tissue section from an infant with a gestational age of 31 weeks who died in 1 month and 10 days after birth. Widespread septal fibrosis in the lungs. Areas with the most obvious fibrosis are marked with arrows. Hematoxylin and eosin, x100.

Therefore, extremely premature infants who die today with "new" BPD show minimal fibrosis and injury of the respiratory tract against a background of striking reduction in the number of alveoli and impaired microvessel development. These histopathological findings demonstrate that processes which interrupt normal lung development rather than lung injury cause the "new" BPD. Accordingly, the correct description and assessment of histopathological changes in the lungs are important not only for the correct postmortem diagnosis of BPD, but also for the studying of various disease phenotypes.

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НЕОНАТОЛОГІЯ, ХІРУРГІЯ ТА ПЕРИНАТАЛЬНА МЕДИЦИНА Т. XIII, № 1(47), 2023
NEONATOLOGY, SURGERY AND PERINATAL MEDICINE VOL. XIII, № 1(47), 2023
KEY TITLE: NEONATOLOGIÂ, HÌRURGIÂ TA PERINATAL'NA MEDICINA (ONLINE)
ABBREVIATED KEY TITLE: NEONATOL. HÌR. PERINAT. MED. (ONLINE)
ISSN 2226-1230 (PRINT) ISSN 2413-4260 (ONLINE)

МОРФОЛОГІЧНІ ЕВОЛЮЦІЯ І ДІАГНОСТИКА БРОНХОЛЕГЕНЕВОЇ ДИСПЛАЗІЇ У ЗНАЧНО НЕДОНОШЕНИХ НЕМОВЛЯТ

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«Львівське обласне патологоанатомічне бюро» [2] (м.Львів, Україна)**

Резюме

Бронхолегенева дисплазія (БЛД) залишається одним з найпоширеніших і найтяжчих захворювань у значно недоношених немовлят, яке може бути причиною їх смерті. Від першого опису БЛД у 1967 р. змінились не лише розуміння природи цього захворювання, його визначення, класифікація, епідеміологія, особливості клінічного перебігу, діагностика, профілактика, лікування і прогноз, але і специфічні гістопатологічні ознаки, які виявляють на автопсії у померлих дітей. Це насамперед пов'язано зі зміною популяції хворих і померлих немовлят внаслідок удосконалення клінічної практики, покращення показників виживання найбільш незрілих дітей, зменшення частоти тяжких форм БЛД і пов'язаної з ними летальності. Форма БЛД, яка була описана початково, сьогодні має назву «старої» БЛД і характеризується значним ураженням легень. У найменших новонароджених дітей, яких лікували екзогенним сурфактантом, гістологічні ознаки захворювання змінились, визначаючи потребу модифікації теоретичної концепції БЛД. Провідною ознакою нової форми БЛД було порушення розвитку і формування легень, а не їх ураження. Морфологічно це виявлялось зменшеною кількістю та спрощеною будовою ацинусів, змінами у структурі капілярів з менш явним фіброзом легень. Для гістопатологічної діагностики спрощеної будови легень можна застосувати такі морфометричні методики як-от радіальний підрахунок кількості альвеол та підрахунок середньої кількості альвеолярних перегородок. Застосування цих методик допомагає об'єктивно оцінити затримку росту легень. Хоча кількість випадків «нової» БЛД на сьогодні переважає, частину автопсій все ще характеризують гістопатологічні зміни, характерні для «старої» форми захворювання. Можливим є також поєднання класичних і нових ознак. Встановлюючи патологоанатомічний діагноз БЛД, важливо враховувати усі специфічні гістопатологічні зміни, які можуть свідчити за наявність і тяжкість захворювання, а також його роль у танатогенезі. Це є важливими не лише для правильної посмертної діагностики БЛД, а і для вивчення різних фенотипів цього захворювання.

У статті описані основні гістопатологічні ознаки, характерні для різних форм БЛД, а також методи оцінки спрощеної будови легень.

Ключові слова: бронхолегенева дисплазія; гістопатологія; передчасно народжені немовлята.

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Received for editorial office on 12/01/2023
Signed for printing on 19/02/2023