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Persistent pulmonary abnormalities in newborns: The changing picture of bronchopulmonary dysplasia

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Abstract. Significant changes in the radiographic features of bronchopulmonary dysplasia (BPD) have accompanied recent advances in treatment of neonatal respiratory distress syndrome. Retrospective study of 709 newborns showed atypical radiographic findings in many patients with clinical BPD. While 12/20 infants with clinical BPD showed changes identical to Northway's stage 4 disease, the remaining 8 (40% of patients with significant respiratory dysfunction) had diffuse, fine infiltrates without emphysema. Radiographic progression from RDS through all Northway stages was observed in only 4 patients. Diagnosis of stage 2 BPD was complicated by the presence of PDA in 9/17 cases. Stage 3 BPD was identified with certainty in only 5 infants, but may have coexisted with PIE in as many as 22 cases. Nevertheless, there was close agreement between the radiographic findings and clinical severity of chronic lung disease. Mild (type 1) infiltrates following RDS may be distinguished from chronic pulmonary insufficiency of prematurity (CPIP) or "immature lung." In patients who require only short-term supplemental O_2, type 1 changes may reflect delayed resolution of RDS in an underdeveloped lung. These same findings in infants with prolonged O_2 dependence usually indicate a mild form of BPD. Coarse infiltrates and emphysema (type 2) are almost always associated with severe respiratory impairment.

Bronchopulmonary dysplasia (BPD) is a well-known complication of neonatal respiratory distress syndrome (RDS) [1-3]. Since its original description in 1967, BPD has steadily decreased in incidence, and significant changes have occurred in its clinical and radiographic presentation [4-7]. In addition, with improvements in medical management and increased survival of extremely premature and very low birth weight infants, new forms of neonatal chronic lung disease are being recognized [8-10].

Few recent reports have examined the prevalence and clinical significance of these changes. We conducted a 2-year retrospective study of all infants admitted to the University Hospital Newborn Intensive Care Unit (NICU), in order to (a) identify and categorize the radiographic patterns of chronic lung dis-

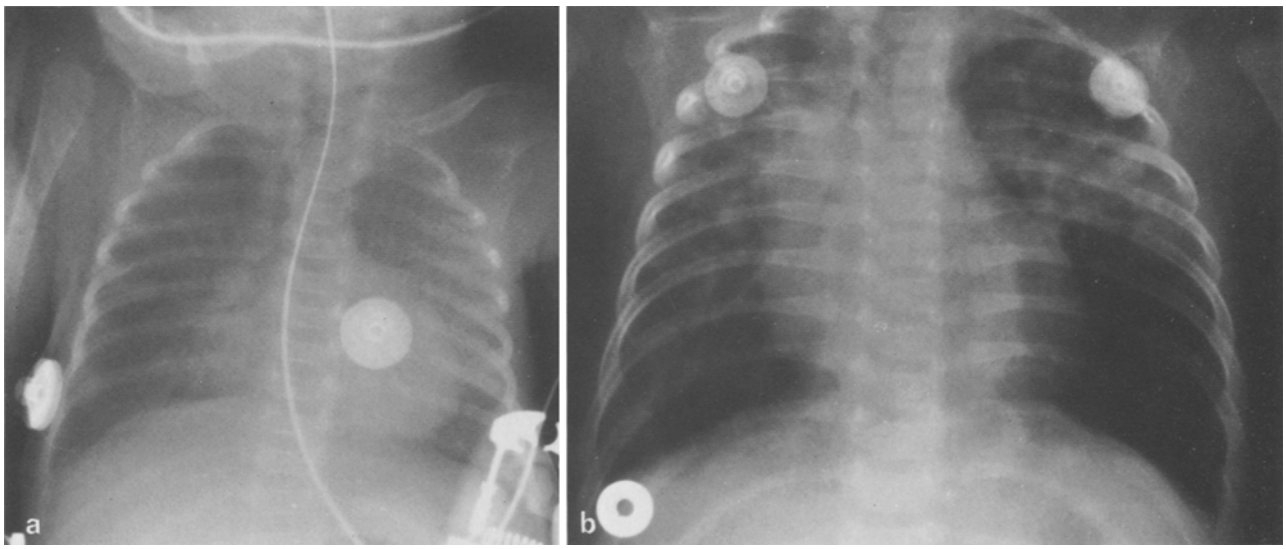

Fig. 1a, b. Radiographic types of persistent pulmonary disease: **a** type 1 disease, characterized by diffuse, streaky infiltrates and normal lung volume; **b** in type 2 disease, coarse infiltrates and regional emphysema are present, and the thoracic volume is markedly increased

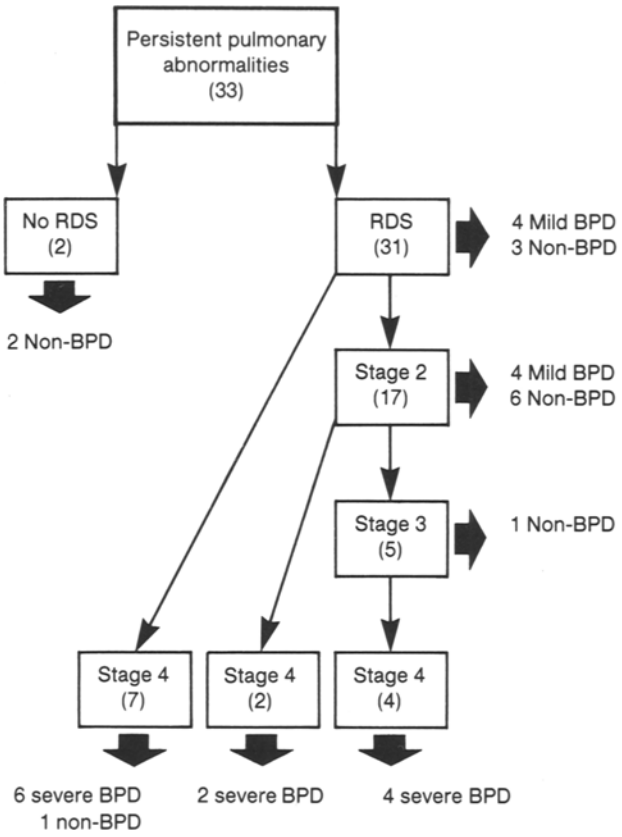

Fig. 2. Clinical and radiographic course of infants with persistent infiltrates. Chart showing development and progression of Northway stages, as well as incidence and severity of clinical BPD

Table 1. Persistent pulmonary abnormalities - BPD risk factors in infants with and without clinical BPD

	Type 1 - mild		Type 2 - severe	
	BPD	non-BPD	BPD	non-BPD
No. patients	8	12	12	1
Birth weight (grams)	1130.0	1344.0	1123.7	1580.0
Gestational age (weeks)	29.8	30.0	28.0	32.0
Peak inspiratory pressure (cm H_2O)	21.5	20.5	27.9	22.0
Days' mechanical ventilation	18.4	6.3	30.9	6
Maximum FIO_2	0.76	0.72	0.85	0.90
Days' supplemental O_2	45.6[a]	10.7	75.5[a]	7
Weight change (%) - 3 days	−11.2	−6.7	−11.0	−2.5
Weight change (%) - 10 days	−12.7	−7.8	−11.8	−10.8
RDS				
None	0	2	0	
Mild	4	4	3	
Moderate	0	5	3	
Severe	4[b]	1[b]	6	1
Clinically significant PDA	2	5	5	
Apgar scores				
1 min	4.4	4.3	4.6	8
5 min	7.6	6.0	6.7	9
Extra-alveolar air leak	4[c]	5	12[c]	1

[a] $p < 0.001$ (revised results); [b] $p < 0.05$; [c] $p < 0.01$

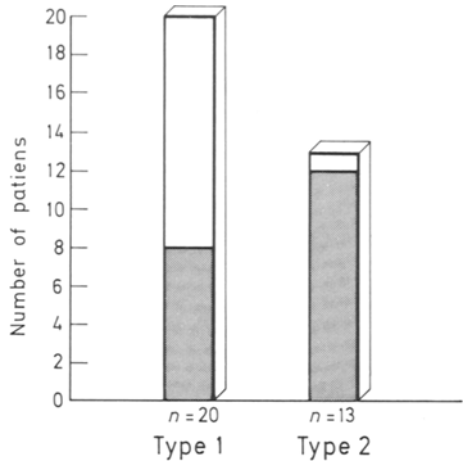

Fig. 3. Distribution of type 1 and type 2 abnormalities in BPD and non-BPD groups. Graph demonstrates a statistically significant association between type of radiographic abnormality and severity of respiratory dysfunction. Clinical BPD was more common in the type 2 group, while most patients with type 1 disease did not require long-term supplement O_2. ▨ BPD; □ non-BPD; $p < 0.01$

ease in this population, (b) determine the incidence of each specific pattern, and (c) examine the relationships between type of radiographic abnormalities, severity of respiratory dysfunction, and recognized BPD risk factors.

Patients and methods

The study population included all NICU admissions during calendar years 1982 and 1983, excluding infants with major lethal congenital anomalies and those who died or were discharged to the normal newborn nursery within the first 24 h of life. All patients with radiographic pulmonary abnormalities persisting beyond 2 weeks of age were designated as the study subgroup and selected for further analysis.

Chest radiographs were reviewed in the study subgroup to confirm the diagnosis of RDS and/or BPD. The presence or absence of extra-alveolar air leaks, segmental infiltrates, pleural effusions and cardiomegaly, was also recorded. Clinical data collected in the study subgroup included birth weight, gestational age, Apgar scores at 1 and 5 minutes, maximum ventilation rate, maximum inspiratory and expiratory pressure, duration of mechanical ventilation, maximum FIO_2, duration of supplemental 02, presence or absence of significant PDA, and fluid balance at 3 and 10 days of age as inferred by percent change in body weight from birth.

RDS was graded radiographically as mild, moderate or severe, as follows:

Mild - fine granular infiltrates confined predominantly to the lung bases; inconspicuous air bronchograms.

Moderate - diffuse fine granular infiltrates and air bronchograms; heart border and diaphragms indistinct but visible.

Severe - diffuse homogeneous opacification with prominent air bronchograms; heart border and diaphragms not visible.

Persistent pulmonary disease was staged radiographically according to Northway's criteria for BPD [1, 5] where appropriate, and was also described as [4]:

Mild (Type 1) - diffuse haziness, streaky infiltrates with small cystic areas, small or normal lung volume (Fig. 1 a).

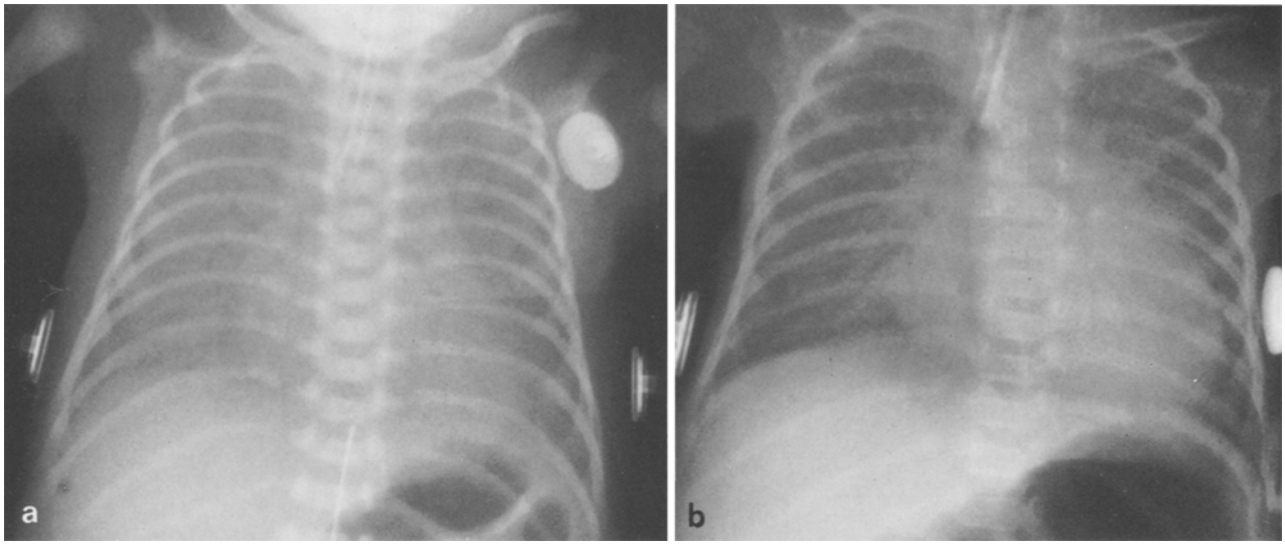

Fig. 4 a, b. Two infants with increasing lung opacification during the first 2 weeks of life: **a** homogeneous consolidation and perihilar air bronchograms in a patient with stage 2 BPD; **b** in a patient with pulmonary edema due to PDA, the infiltrates are identical to those of the exudative stage of BPD. The presence of cardiomegaly suggests the true diagnosis

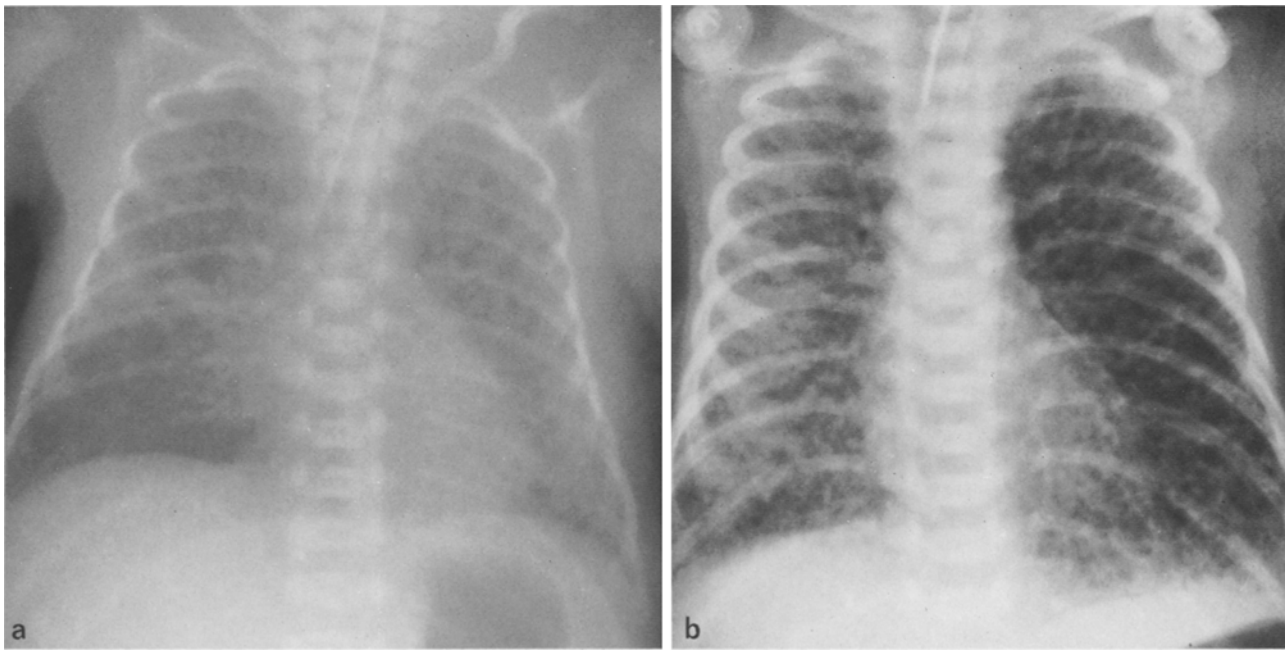

Fig. 5 a, b. Stage 3 BPD vs pulmonary interstitial emphysema (PIE): **a** stage 3 BPD – numerous small areas of focal emphysema; **b** bilateral PIE in premature infant treated with positive pressure ventilation. The chest is hyperexpanded, and the lungs have a "bubbly" appearance throughout, similar to stage 3 BPD

Severe (type 2) – radiolucent areas alternating with irregular densities, chest hyperexpanded (Fig. 1 b). The roentgen features of this entity are identical to those of Northway's stage 4 BPD.

Clinical BPD was diagnosed in any infant with persistent radiographic abnormalities beyond 2 weeks of age, who also had a history of pulmonary disease requiring mechanical ventilation during the first 24 h of life, and who required $FIO_2 > 0.21$ to maintain arterial $pO_2 > 50$ mmHg after 28 days of age.

Clinically significant PDA was diagnosed when there was radiographic and/or echocardiographic evidence of PDA with one or more of the following: fluid retention, systolic or continuous murmur, apnea, bradycardia, difficulty in weaning from mechanical ventilation, bounding peripheral pulse, and wide arterial pulse pressure.

The incidence and type of persistent pulmonary abnormalities were determined, and the presence or absence of Northway's stages 2–4 was noted. The relationships between these radiographic abnormalities, presence and severity of RDS, coexistence of PDA or extra-alveolar air leak, and development of clinical BPD were examined.

Measurement data were evaluated by the Student's t-test, and frequency data were analyzed by chi-square with Yate's continuity correction for small sample size.

Results

During 1982-1983, there were 709 admissions to the NICU. RDS was diagnosed in 148 infants. Thirty-three infants (4.7% of all admissions) showed radiographic lung abnormalities persisting beyond the first two weeks of life, and 20/33 (13.5% of all patients with RDS) met the diagnostic criteria for clinical BPD.

BPD stages 2-4 (Northway) - incidence, outcome, and complications

Radiographic findings consistent with Northway's stage 2 BPD were observed during the first 2 weeks of life in 17 patients. All 17 infants had a prior history of RDS, and 10 of these subsequently developed clinical BPD. Stage 3 was identified in 5 cases, 4 of whom developed radiographic stage 4 disease and clinical BPD. Stage 4 changes were seen in 13/33 patients with persistent radiographic abnormalities. All of these 13 infants had RDS initially, and 12 developed BPD by clinical criteria. Stage 4 followed RDS alone in 7 cases, and developed directly from stage 2 disease in 2 infants. Stepwise progression from RDS through each Northway stage was observed in only 4 patients. These findings are summarized in Figure 2.

PDA was diagnosed in 9/17 patients with stage 2 changes. No difference in incidence of PDA was observed between those infants who developed clinical BPD (5/10) and the remainder (4/7) with stage 2 abnormalities. Five infants with clinical BPD and stage 4 disease had significant PDA at some time in their hospital course (n.s.).

Extra-alveolar leaks (pneumothorax, pneumomediastinum, pneumopericardium) occured prior to 1 month of age in 22 patients. The incidence of this complication was not significantly different overall for infants with (16/20) and without (6/13) clinical BPD. However, all 13 patients with stage 4 abnormalities had a history of one or more air leaks in the first month of life ($p < 0.001$).

Persistent pulmonary abnormalities - relationship to BPD risk factors and severity of clinical respiratory disease

Mild (type 1) radiographic disease was present in 20 infants. RDS preceded type 1 disease in 18/20 patients, and was moderate or severe in 10. Eight newborns with mild persistent infiltrates following RDS had clinical BPD. Type 1 changes developed in the absence of Northway's radiographic stages in 9 infants, 5 of whom belonged to the non-BPD group. Severe (type 2) disease was observed in 13 infants. All had a history of RDS, which was moderate or severe in 9 cases. Only one patient with type 2 disease belonged to the non-BPD group ($p < 0.01$). This infant had severe RDS initially. These data are represented in Figures 2 and 3.

In patients with type 1 radiographic disease, there were no significant differences between the BPD and non-BPD groups with respect to birth weight, gestational age, peak inspiratory pressure, maximum FIO_2, % weight change at 3 and 10 days of age, and Apgar scores at 1 and 5 minutes. Half of the infants with clinical BPD had severe RDS, compared with only 8% in the non-BPD group ($p < 0.05$).

Among the 20 infants with BPD, there was an increased incidence of extra-alveolar air leak in those with type 2 radiographic disease ($p < 0.01$). No significant difference was observed between type 1 and type 2 groups in any of the other clinical parameters studied. Because of the large variance in duration of O_2 therapy and mechanical ventilation produced by a few outlying results, the two infants with oxygen and ventilation requirements greater than 1 year were excluded and the data reanalyzed for these two factors. The revised results indicated no difference in duration of mechanical ventilation, but signifcantly longer treatment with supplemental oxygen in the type 2 group. The results are summarized in Table 1.

Discussion

The results of this study suggest that the radiographic features and evolution of clinical BPD often vary from Northway's original description. Generalized or regional emphysema and coarse, irregular densities developed in 8% of all infants with RDS, and were present in only 60% of patients who required long-term O_2 therapy. In addition, 16/20 infants with clinical BPD failed to show a clear progression through four discrete radiographic stages. Ten of these infants never manifested radiologic stage 2 disease, and stage 3 was clearly identified in only 4 cases.

Recognition of Northway's stages of BPD, particularly stages 2 and 3, may be difficult due to the coexistence of one or more complications with similar roentgen features [11]. In more than half of the patients with stage 2 changes, the distinction between pulmonary edema due to PDA and the exudative phase of BPD was unclear (Fig. 4). Stage 3 BPD may likewise have been obscured in many instances by the presence of pulmonary interstitial emphysema (PIE), which occurred in 22 neonates (Fig. 5). The ra-

diologic differential diagnosis of these conditions is often important for acute clinical management. However, the results of this study suggest that it is of limited value for prediction of ultimate pulmonary outcome.

Type 1 and type 2 changes appear to represent opposite extremes in the spectrum of neonatal chronic lung disease.

Except for the two cases of persistent infiltrates without initial RDS, which could represent "immature lung," radiographic type 1 disease can be distinguished from this entity and from chronic pulmonary insufficiency of prematurity [8–10]. In infants with mild-to-moderate RDS, the persistent fine infiltrates may simply represent a prolonged resolution phase in an underdeveloped lung. Patients with type 1 abnormalities and clinical BPD, the majority of whom have a history of severe RDS, are similar to Edwards' "mild BPD" [6]. The chronic lung disease in these patients tends to be less severe than in infants with type 2 disease, as inferred from duration of supplemental O_2 requirements. Nevertheless, the occurrence of clinical BPD in infants with relatively mild roentgen findings reflects the fact that the extent of structural lung damage often exceeds radiographic estimates [11, 12].

In patients with type 1 abnormalities, the single best predictor of pulmonary function was radiographic severity of the initial lung disease. This observation is in agreement with histologic studies, which suggest that the degree of pulmonary fibrosis is directly related to the amount of proteinaceous exudate organized and converted into collagen by interstitial fibroblasts [13]. We were unable to demonstrate any statistically significant association of type 1 radiographic disease with early gestational age and low birth weight [4], ventilation protocol, PDA, or extracellular fluid balance.

Infants with type 2 infiltrates can be considered synonomous in most instances with Northway's stage 4 disease. These patients almost uniformly have marked pulmonary insufficiency, requiring long-term supplemental oxygen and ventilatory support.

The pathogenesis of radiographic type 2 disease appears to be multifactorial, involving the interaction between the initial underlying disease, effects of subsequent complications and therapy on the immature lung, and individual differences in response to tissue injury. The increased incidence of air leaks in type 2 patients, which was unrelated to differences in peak ventilation pressure, may reflect a greater sensitivity to barotrauma in newborns with severe initial disease and/or alveolar underdevelopment. In the present study, type 2 infants had received supplemental O_2 for longer periods than their type 1 counterparts with BPD. This finding could not be explained simply by the severity of RDS or the presence of early complications, and suggests that pulmonary oxygen toxicity plays an independent role in the etiology of type 2 abnormalities [14].

The significance of type 2 changes in a single infant without clinical BPD is unknown. This patient was unremarkable with respect to BPD risk factors and treatment, and was lost to follow-up after discharge from NICU. A larger study population may contain sufficient similar cases to permit further definition of this entity.

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