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Factors associated with neurodevelopmental impairment in preterm infants with bronchopulmonary dysplasia

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Abstract. – OBJECTIVE: Bronchopulmonary dysplasia (BPD) is a common and serious complication in preterm infants with very low birth weight and is known to lead to poor neurodevelopmental outcomes. This study aimed to identify factors associated with neurodevelopmental impairment (NDI) in patients with moderate to severe BPD.

SUBJECTS AND METHODS: A total of 83 preterm infants born between 24- and 29-weeks' gestation who were admitted to the neonatal intensive care unit and developed moderate/severe BPD between 2013 and 2017 were retrospectively evaluated. Developmental assessment was performed at 18 to 24 months of corrected age using the Bayley Scales of Infant Development II (BSID-II). Patients with NDI (n=41) and without NDI (n=42) were compared.

RESULTS: BSID-II Mental Development Index and Psychomotor Development Index scores were 87±11 and 83±8 in the non-NDI group and 57±12 and 52±8 in the NDI group, respectively (p<0.001). The NDI group had significantly lower birth weight (847±174 *vs.* 1012±192 g) and gestational age (26.1±1.3 and 27.6±1.6 weeks) compared to the non-NDI group (p<0.001). Intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity, exposure to steroids, duration of respiratory support, and length of hospital stay were significantly higher in the NDI group (p<0.001).

CONCLUSIONS: Many of the conditions in this study were found to be associated with poor neurodevelopmental outcomes in patients with BPD, such as prolonged respiratory support, prolonged hospitalization, intraventricular hemorrhage, retinopathy, and steroid therapy, can be avoided or prevented with strict protocols and prevention strategies. Appropriate management of comorbid risk factors may help prevent poor neurodevelopmental outcomes.

Key Words:
Bronchopulmonary dysplasia, Neurodevelopmental impairment, Prematurity.

Introduction

Bronchopulmonary dysplasia (BPD) is the most common chronic pulmonary disease of prematurity. Preventing and providing appropriate treatment for BPD are the main concern in neonatal intensive care units[1]. Advances in neonatal care such as ventilation strategies, antenatal glucocorticoid therapy, and exogenous surfactant administration have increased the likelihood of survival for infants with low birth weight (BW) and low gestational age (GA). However, BPD remains an important problem for 68% of preterm infants born between 22 and 28 weeks' gestation[2]. Although the incidence of BPD varies between centers, it occurs in approximately 40% of neonates born before 28 weeks and 80% of those born before 24 weeks' gestation[3]. Low BW, low GA, male sex, genetic predisposition, pre-/postnatal infection, and iatrogenic factors (oxygen damage, invasive mechanical ventilation, and blood transfusions) have been associated with the development of BPD[2]. Sixty-five percent of infants born at less than 1500 g receive respiratory support either in the delivery room or in the neonatal intensive care unit. Although invasive mechanical ventilation (MV) provides needed support, it can cause negative consequences such as BPD in the long term[4]. BPD may in turn lead to adverse neurodevelopmental outcomes due to its association with chronic inflammation and recurrent hypoxemia, which are both factors that adversely affect brain development and function[5].

Extremely preterm infants constitute a high-risk group for neurodevelopmental impairment (NDI), and the presence of BPD further increases the likelihood of NDI[6]. The present study aimed to evaluate neurodevelopmental outcomes in patients with moderate to severe BPD, identify fac-

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tors associated with NDI, and determine which of these factors are relevant during long-term follow-up.

Subjects and Methods

A total of 820 preterm infants born between 24^0 and 29^6 weeks of gestation who were admitted to our neonatal intensive care unit and developed moderate to severe BPD between 2013 and 2017 were retrospectively evaluated. Infants with major congenital anomalies or missing data were excluded.

Perinatal and natal data such as antenatal steroid treatment, mode of delivery, BW, and GA were recorded. Neonatal morbidities such as duration of MV, duration of noninvasive ventilation (NIV), duration of oxygen support, intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), periventricular leukomalacia (PVL), frequency of steroid treatment, and length of hospital stay were evaluated. The infants' need for oxygen was determined at postnatal day 28, postmenstrual week 36, and at discharge.

Developmental assessment was performed by a developmental pediatrician using the Bayley Scales of Infant Development II (BSID-II) at a corrected age of 18 to 24 months[7]. The Mental Development Index (MDI), Psychomotor Development Index (PDI), and visual and hearing impairment were evaluated. NDI was defined as having at least one of the following: MDI < 70, PDI < 70, bilateral deafness, bilateral blindness, and cerebral palsy (CP)[8]. The mean (±SD) BSID-II score for the MDI and PDI was 100±15. The characteristics of patients with NDI (n=41) and without NDI (n=42) were compared.

Cerebral palsy was identified based on muscle tone, movement, and postural disorders[9]. BPD was defined using the classification developed through a National Institutes of Health Workshop and reported by Jobe and Bancalari[10].

The decision to initiate MV or NIV was made based on the standard respiratory support protocol of our unit[11]. Postnatal steroid therapy was planned for patients who were still receiving MV support after 14 days[11,12].

Cranial ultrasound (US) was performed on days 1, 3, and 7; patients with signs of IVH or PVL were followed with cranial US weekly. IVH was graded according to the Papile classification, with IVH grade or III or higher defined as advanced[13]. Severe PVL was defined based on findings of cysts[14].

NEC was diagnosed according to laboratory, clinical, and radiological findings and was staged according to the modified Bell criteria[15]. PDA was diagnosed according to echocardiography performed between 24 and 72 hours (left atrium/aortic root > 1.5 and/or ductus diameter > 1.5 mm)[16] and was treated medically using ibuprofen or paracetamol therapy and surgically by ductal ligation in patients for whom medical treatment was contraindicated or did not induce PDA closure.

ROP was graded according to the International Classification of Retinopathy of Prematurity after examination by an ophthalmologist[17]. ROP stage III or higher and requiring laser treatment was classified as advanced[18].

Ethics committee approval was obtained for this study (29.05.2018-24).

Statistical Analysis

SPSS® for Windows version 22 software (IBM, Armonk, NY, USA) was used for data analyses. Categorical variables were compared using chi-square test; continuous data were summarized as mean and standard deviation and compared using Student's *t*-test. Mann-Whitney rank-sum test was used for nonparametric data. Results with *p*-values lower than 0.05 were considered significant.

Results

A total of 820 preterm infants born between 24^0 and 29^6 weeks of gestation who were admitted to our intensive care unit between 2013 and 2017 were retrospectively evaluated. Of these, 180 infants (21%) died. Among the survivors, 90 infants (14%) were diagnosed as having moderate to severe BPD. Infants with major congenital anomalies or missing data were excluded. As a result, data from 83 infants who underwent BSID-II were analyzed.

There were 41 patients in the NDI group and 42 patients in the non-NDI group. The NDI group had significantly lower BW (847±174 *vs*. 1012±192 g) and GA (26.1±1.3 and 27.6±1.6 weeks) compared to the non-NDI group ($p<0.001$). The prevalence of IVH, PVL, ROP, steroid therapy, respiratory support, and length of hospital stay were significantly higher in the NDI group ($p<0.001$, Table I). BSID-II MDI and PDI values were 87±11 and 83±8 in the non-NDI group and 57±12 and 52±8 in the NDI group, respectively ($p<0.001$). MDI

Table I. Demographic and clinical data of preterm infants with bronchopulmonary dysplasia according to the presence of neurodevelopmental impairment.

	Non-NDI (n=42)	NDI (n=41)	p
Gestational age, weeks*	27.6±1.6	26.1±1.3	<0.001
Birth weight, g*	1012±192	847±174	<0.001
Mode of birth (CS), n (%)	33 (78.4)	34 (82.9)	0.61
Antenatal steroid therapy, n (%)	28 (66.7)	21 (51.2)	0.38
MV duration, median, days¶	6 (0-36)	20 (0-69)	0.006
NIV duration, median, days¶	9 (1-37)	28 (6-45)	0.003
Supplemental Oxygen duration, median, days¶	31.5 (10-85)	28 (0-59)	0.108
Time to return room air, median, days¶	67 (45-112)	83 (59-116)	0.16
IVH, n (%)	24 (57.1)	38 (92.7)	<0.001
IVH Stage 3-4, n (%)	3 (7.1)	13 (31.7)	0.005
PVL, n (%)	5 (11.9)	19 (47.5)	<0.001
PDA, n (%)	28 (66.7)	31 (75.6)	0.36
PDA ligation, n (%)	2 (5.3)	5 (15.2)	0.23
NEC, n (%)	2 (4.8)	1 (2.4)	1
ROP Stages 3-4, n (%)	5 (13.2)	16 (48.5)	0.001
Laser therapy for ROP, n (%)	10 (25.6)	30 (75)	<0.001
Steroid therapy*	16 (38.1)	32 (78)	<0.001
Day of steroid initiation*	53.2±19.2	51.3±14.1	0.77
Time to return to birth weight, days*	13.6±4.4	15.2±3.9	0.13
Length of hospital stay, days*	81.8±16.1	105.4±13.3	<0.001

**t*-test, mean±SD
¶Mann Whitney U, median (min-max)
IVH, intraventricular hemorrhage; MV, mechanical ventilation; NEC, necrotizing enterocolitis; NIV, noninvasive ventilation; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

and PDI were lower than 70 in 45.8% and 47% of the patients, respectively. Cerebral palsy was detected in 16 patients (19.3%), blindness in 3 patients (3.6%), and deafness in 2 patients (2.4%).

Discussion

Bronchopulmonary dysplasia is associated with poor neurodevelopmental outcomes, with a direct link between the severity of BPD and neurological damage[1]. Long-term respiratory support, prolonged hospitalization, intraventricular hemorrhage, periventricular leukomalacia, retinopathy, and steroid therapy are risk factors for NDI.

BPD was first described by Northway[19] in 1967, with MV injury and oxidative stress shown to be responsible for the pathogenesis of classical BPD. Due to various preventive strategies, most cases of BPD observed today have a different etiology and pathogenesis. Pathological changes observed in BPD include damage to the alveolar structures, alveolar dysplasia, pulmonary microvascular dysplasia, and the development of pulmonary fibrosis during follow-up. These changes cause a delay in lung function improvement and reduced compliance[2]. Ongoing lung injury and healing over the course of months results in a chronic condition characterized by fibrosis, atelectasis, macro-/microcystic structures, and hyperinflation[3].

Although invasive MV is a life-saving intervention for infants with extremely low BW[3], limiting its use in preterm infants reduces the risk of mortality and NDI at 24 months[4,20]. In the present study, prolonged MV was found to increase the risk of NDI (Table I). Another study[4] of 404 preterm infants born before 30 weeks' gestation showed that restricted MV reduced the risk of mortality and NDI at 24 months. The adverse effects of MV should be prevented by providing NIV if needed in the delivery room and avoiding unnecessary intubation to prevent ventilator-associated lung injury[21]. The early use of NIV reduces the risk of BPD and mortality[3,22]. Fischer and Buhrer[23] reported in a study of preterm infants born before 30 weeks' gestation that a respiratory strategy that avoided MV and prioritized NIV resulted in lower rates of BPD and mortality. Each neonatal intensive care unit should aim to implement restricted MV by establishing a respiratory support protocol. In our study, we attributed the longer NIV duration in the NDI group compared to the non-NDI group with the prolonged MV duration in this group.

Prolonged hospitalization, noise and light exposure, reduced maternal contact, and invasive interventions have an adverse impact on normal brain development[2]. Bauer et al[6] found that prolonged hospital stay was an important risk factor for NDI at 24 months, similar to our study.

Prematurity and low BW have been reported as major risk factors for BPD in numerous studies[24,25]. BPD incidence rates reported in the literature also vary between centers. Although factors such as differences in practice, pre-/postnatal risk factors, and patient identification are involved, the main factor in the development of BPD is immaturity[26,27]. In the Canadian Neonatal Study Group, BPD was observed in 28.1% of infants born before 25 weeks' gestation, compared to 4% in those born between 29 and 32 weeks[24]. Lower GA and BW are associated with greater immaturity of the pulmonary and central nervous systems, making them more susceptible to organ damage. The need for respiratory support increases and the duration of MV/NIV support is longer, which leads to prolonged hospitalization[2,28]. The results of the present study showed an increase in the risk of NDI with lower BW and GA (Table I).

BPD and ROP are two important problems that arise due to abnormal vascular development in preterm infants[29,30]. Many growth factors, including vascular endothelial growth factor, are required for the normal development of the pulmonary vasculature and alveolar structures. Deficiency of these angiogenic factors disrupts pulmonary vascular development and alveolarization, resulting in BPD. Disordered angiogenesis is a common factor associated with both BPD and ROP[31]. Reiterer et al[32] determined that advanced ROP was more common in BPD patients (11.3%) than in a non-BPD group (13.6%, p=0.026), but comparison of neurodevelopmental outcomes in the BPD and non-BPD groups revealed no difference according to ROP. In our study, the prevalence of advanced ROP and laser therapy differed significantly between the NDI group compared to the non-NDI group (p=0.001, p<0.001) (Table I). Kaul et al[33] reported that advanced ROP was a risk factor for NDI at both 2.5 and 6.5 years of age. Bae et al[34] also identified advanced ROP as a risk factor for NDI (aOR: 5.669, 95% CI: 1.132-28.396).

Recurrent episodes of hypoxia, hypercapnia, and respiratory acidosis in infants in this group are associated with hypoxic brain injury[35]. Chronic hypoxia disrupts normal development in the central nervous system, leading to the irreversible development of immature brain tissue. In addition, growth retardation due to hypoxic ischemic encephalopathy, IVH, and immature organ function can cause neurological sequelae such as movement disorder, cognitive impairment, audiovisual dysfunction, language development disorder, and behavioral and psychological problems in preterm infants[2]. IVH is especially common in infants born before 32 weeks of gestation[36,37]. In a study of 122 preterm infants by Gilard et al[36], 18% had stage 2 IVH, 39.3% had stage 3-4 IVH, and 55.9% (n=43) had CP. Advanced IVH was associated with increased mortality and NDI. In another study[37], any degree of IVH or PVL increased the risk of CP (OR: 3.4, 95% CI: 1.6-7.22; OR: 19.12, 95% CI: 4.57-79.9, respectively) and PVL increased the risk of hearing and visual impairment. IVH and PVL were also found to increase the risk of NDI in the present study (p<0.001).

Although corticosteroid therapy reduces inflammation in the lungs, facilitates extubation, and shortens the duration of MV in patients with BPD, it has undesirable effects on long-term neurodevelopmental outcomes[38,39]. In the present study, the prevalence of NDI was higher in hydrocortisone-treated patients than in untreated patients (p<0.001). Ofman et al[40] treated infants born before 28 weeks' gestation with hydrocortisone for 10 days starting on day 1 and observed no neurodevelopmental differences at 22 months compared to a placebo group. In another study[41] of 173 infants with a BW of less than 1000 g, MDI and PDI values at 18 to 22 months were lower in those treated with dexamethasone between postnatal days 14 and 42. In our study, steroid was initiated at a mean of 51.3±14.1 days in the NDI group, which was comparable to the non-NDI group (p=0.77). Hydrocortisone initiated early and at a low dose was reported to not cause NDI at 22 months[42]. The short half-life of hydrocortisone and its different activity on the receptors in the central nervous system make it safer than dexamethasone in terms of neurodevelopment[38]. However, the optimal timing and agent with which to initiate steroid therapy remains unclear and requires further investigation.

In our study, MDI and PDI were 87±11 and 83±8 in the non-NDI group and 57±12 and 52±8 in the NDI group, respectively (p<0.001). Overall, MDI and PDI values were below the threshold of 70 in 45.8% and 47% of the patients, respectively. In another study, infants born between 24^0 and 28^6 weeks' gestation with BPD (n=44) and without BPD (n=44) were compared and there was no dif-

ference between the two groups in terms of NDI[33]. This result may be attributable to the low number of patients with severe BPD, advanced ROP, and advanced IVC/PVL in the study. The prevalence of CP is approximately 10-14% in infants born before 28 weeks' gestation and 14% among those born before 26 weeks' gestation[20]. Hintz et al[43] found CP to be associated with advanced IVH-PVL in their study of 839 infants born before 25 weeks' gestation (OR: 1.66, 95% CI: 1.01-2.74). CP was detected in 16 patients (19.3%) in our study. In a similar study by Bauer et al[6], CP was detected in 22 patients (15%) and 56% of the patients did not have NDI. MDI was above 80 in 18% of the patients; motor scale and communication scores were above 80 in 26% and 37% of the patients, respectively. The better scores in their study compared to ours may be related to the lower prevalence of IVH and the similar rates of IVH in their NDI and non-NDI groups (p=0.36). There was also no difference between the NDI and non-NDI groups in terms of steroid exposure in their study, whereas the steroid treatment rate was higher in the NDI group in our study. Postnatal steroid therapy to prevent or treat BPD poses a risk for motor dysfunction in premature infants[20]. In our study, blindness was detected in 3 patients (3.6%) and deafness in 2 patients (2.4%). A previous study[44] demonstrated that BPD was an independent neurosensorial risk factor (OR: 1.92; 95% CI: 1.24-2.99).

A limitation of our study is that it was retrospective and single-center. Other limitations are that the patients had no follow-up and neurodevelopmental evaluation until a later stage, and our data are based on the BSID-II because this was the scale used during the study period. In addition, other treatments for BPD were not included in the data, nor were parental education and other social factors. Cranial magnetic resonance imaging in patients with BPD plays an important role in the early diagnosis of central damage, regular follow-up of neurological development, and rehabilitation and neurological recovery. The use of cranial US for cranial imaging is another limitation of our study. Multicenter, prospective studies including larger BPD patient series are needed to identify the factors that should be considered during the follow-up of these patients. Clinical interventions that may affect prognosis should be analyzed.

The care of patients diagnosed with BPD should be undertaken with a multidisciplinary support team that includes a neonatologist, pulmonologist, nutritionist, physiotherapist, speech therapist, respiratory therapist, family support team, and pediatricians. Chronic patient care centers should be established for patients with BPD, and special rooms should be designated to facilitate family contact and care. This will also enhance the family's sense of confidence. A dietician should monitor patients' nutrition and growth, and patients should be provided with both visual and auditory stimuli[1].

Conclusions

Our study suggests that many conditions identified as factors associated with poor neurodevelopmental outcome in patients with BPD, such as prolonged respiratory support, prolonged hospital stay, intraventricular hemorrhage, retinopathy, and steroid therapy, may be preventable with the development of protocols and protection strategies.

Conflict of Interest

The authors declare that they have no conflict of interest.

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